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The Connection between Marijuana, Cigarette Smoking and Metabolic Syndrome among Adults in the United States

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My research concentrates on determinants of metabolic syndrome and factors associated with metabolic syndrome. The object is to add to literature on risk factors of metabolic syndrome that has not been studied extensively or discuss issues of germinating interest on cardiovascular health. Findings can advise the development of interventions to help improve cardiovascular health as well as prevent other chronic diseases associated with metabolic syndrome. In my research, biomarkers, issues of lifestyle including recreational substance use and tobacco use, racial/ethnic disparities, having health insurance and other socio-demographic influences on metabolic syndrome have gained attention as important factors of addressing metabolic health and cancer.

List of Publications

1. Yankey, Barbara. A., Rothenberg, Richard, Strasser Sheryl, Ramsey-White, Kim, and Okosun Ike S. “Relationship between Years of Marijuana Use and the Four Main Diagnostic Criteria for Metabolic Syndrome among United States Adults.” *J Addict Res Ther* S11: 017. doi: 10.4172/2155-6105.1000S11-017

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3. Tetteh, R. A., Yankey, B. A., Nartey, E. T., Lartey, M., Leufkens, H. G., & Dodoo, A. N. (2017). Pre-Exposure Prophylaxis for HIV Prevention: Safety Concerns. *Drug Safety*, 1-11.

4. Tetteh, R. A., Nartey, E. T., Lartey, M., Mantel-Teeuwisse, A. K., Leufkens, H. G., Yankey, B. A., & Dodoo, A. N. (2016). Association between the Occurrence of Adverse Drug Events and Modification of First-Line Highly Active Antiretroviral Therapy in Ghanaian HIV Patients. *Drug Safety*, *39*(11), 1139-1149.

5. Eliason, S., Baiden, F., Yankey, B. A., & Awusabo–Asare, K. (2014). Determinants of unintended pregnancies in rural Ghana. *BMC Pregnancy and Childbirth*, *14*(1), 1.

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ABSTRACT

THE CONNECTION BETWEEN MARIJUANA, CIGARETTE SMOKING AND METABOLIC SYNDROME AMONG ADULTS IN THE UNITED STATES

By

BARBARA A. YANKEY

MARCH 24, 2017

Under the direction of Ike S. Okosun, PhD

Background: Alcohol, marijuana and tobacco are the most common recreationally used substances in United States (US). However, unlike alcohol and tobacco, marijuana is an illicit substance. The increasing support for reclassification of marijuana as legal substance necessitates investigating its effect on health. These studies seek to examine the relationship of marijuana and tobacco with metabolic syndrome (a precursor of cardiovascular diseases - the primary cause of morbidities and mortalities).

Method: Data from 2011 public-use linked mortality file of the National Center for Health Statistics, Centers for Disease Control and Prevention, and 2005-2006 & 2011-2012 US National Health and Nutrition Examination Survey was used to estimate the effect of marijuana and tobacco on metabolic syndrome. Odds ratios from logistic regression analyses were determined using four main diagnostic criteria for metabolic syndrome. Odds ratios were compared using: National Cholesterol Education Program Adult Treatment Panel III, World Health Organization, European Group for the study of Insulin Resistance and International Diabetes Federation definitions of metabolic syndrome. Hazard ratios (HRs) for cardiovascular mortality were estimated using cox proportional hazard regression.

Results: Each year of marijuana use was associated with increased odds of metabolic syndrome [OR=1.05 (95% CI: 1.01, 1.09)] and hypertension [OR=1.04 (95% CI: 1.01, 1.07)]. Each additional year of cigarette smoking was associated with increased odds of hypertension [OR=1.03 (95% CI: 1.00, 1.06)] and hyperglycemia [OR=1.03 (95% CI: 1.01, 1.05)]. Adjusted HR for hypertension mortality for marijuana users compared to non-marijuana users was 3.42 (95% CI: 1.20, 9.79) and 1.04 (95% CI: 1.00, 1.07) for each year of marijuana use.

Conclusion: Prolonged years of marijuana use was associated with increased odds of metabolic syndrome and hypertension irrespective of the criteria used to define metabolic syndrome. Our results also indicate that marijuana use is associated with increased risk for hypertension mortality. The association between prolonged use of marijuana and risk of cardiovascular morbidities and mortalities requires further investigation whilst developing global public health policies regarding legalization of marijuana use.

THE CONNECTION BETWEEN MARIJUANA, CIGARETTE SMOKING AND METABOLIC SYNDROME AMONG ADULTS IN THE UNITED STATES

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APPROVAL PAGE

THE CONNECTION BETWEEN MARIJUANA, CIGARETTE SMOKING AND METABOLIC SYNDROME AMONG ADULTS IN THE UNITED STATES

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DEDICATION

The process and outcome of my doctoral effort has been under the inspiration and direction of the Lord God Almighty to Whom I offer my work.

This dissertation is dedicated to the precious memories of my: Father Joseph Kofi Yankey Snr, Foster-Father Col. Kaku Korsah, Grandmother Matilda Ama Bedu-Addo, Auntie Comfort Ama Eghan and Grandfather Very Rev. J. E. Peters, who I believe share my success in spirit.

I dedicate my dissertation to my virtuous mother Faustina Yankey whose prayers, support and love are immeasurable. To my precious son Theodore Kenley Tabiri-Martins who has been a good inspiration and motivation. To my dear siblings David Yankey, Susanna Yankey and Joseph Kofi Yankey Jnr, my wonderful Niece and Nephews, Family and Priests of the Sekondi Anglican Diocese, for the perpetual hope they invested in me, the love and spiritual support they showered on me.

I have waited for that singular moment to document the exceptional guidance, instruction, support and encouragement I received from my advisor, Dr. Ike S. Okosun, throughout my academic journey at Georgia State University. This opportunity to do so, is one I would not like to miss, and document now.

This dissertation is also dedicated to those who suffer from varied chronic illnesses especially cardiovascular diseases and to those who battle addictive behaviors - that science will show and support a path to their recovery.

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PREFACE

Initiation and continual use of recreational substances, is a complex process. Science continues to investigate, project, inform and protect the populace from the deleterious effects of substance use. The National Institute on Drug Abuse states that “In reality, drug addiction is a complex disease, and quitting usually takes more than good intentions or a strong will. Drugs change the brain in ways that make quitting hard, even for those who want to.”

Michael D. Lemonick in his article on the science of addiction opens with the statement, “For a species wired for survival, we have an odd habit of getting hooked on things that can kill us.”

My dissertation was inspired by the many scenes of struggle as I travelled each day to school. I could hear the cry for help, feel the need for health, the yearning for love, see the hand of disparities. The question on my mind was simple; Why? Is it the search for joy? Is it curiosity? Is it neglect? Is it the lack of knowledge or is it deception that drives initiation of substance use? I came to the conclusion that the power still lies in knowledge; knowing the truth about the effect of any substances on our system. The saying has been from of old: “For lack of knowledge, people perish”

I find the words of Pope Francisco powerful for anyone struggling with substance use and ill health. “You can have defects, be anxious and irritated sometimes. Live, but do not forget that your life is the biggest company in the world. Only you can prevent your life from going into decline. There are many who will appreciate, admire and love you. I would like you to remember that, being happy is to stop being a victim of the problems and rather become an actor of history itself. Use failure to sculpt serenity.”

“Quia non habuit scientiam gens pereat”

Author's Statement Page

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Barbara A. Yankey
Signature of
Author

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CHAPTER 1

Literature Review

Marijuana and Cigarette Smoking as Recreational Substances

Recreational substances are substances that have the potential to alter consciousness with a resultant pleasurable feeling. Reasons ascribed to the use of recreational substances span primarily from actual relieve of depressing symptoms to curiosity and social acceptance. Some recreational substances are commonly regarded as drugs because of their effect on the central nervous system. They are classified as legal, illegal or controlled depending on their psychoactive properties.

Tobacco (Nicotiana species) and Marijuana (Cannabis species) are two common recreational substances whose main route of administration is smoking. Currently in the United States, apart from alcohol, tobacco and marijuana are the most common substances of abuse especially among adolescents (Latimer & Zur, 2010). The use of marijuana in adults is also increasing especially among adults aged 25 years and above.

Smoking is a general term that describes the process whereby active substances are delivered into the bloodstream via the lungs after inhaling smoke from burnt dried leaves. Smoking is associated with certain cultures and practices and has been practiced way back in 5000 BC; it currently is a common route of recreational drug use.

Smoking is one of the leading causes of preventable death worldwide and a reversible and modifiable factor for several morbidities. Smoking induces several physiological responses that are not only carginogenic but cardiotoxic as well; research shows that smoking aggravates atherogenesis (McGill, 1988). Smoking seems to find a way of sustaining its popular social

practice despite evidence of its detrimental effects on health. Research conducted by Doll and Hill initiated evidence into the carcinogenic effects of tobacco smoking on the lungs (Doll & Hill, 1950) and ultimately the first surgeon's general report on smoking and health in 1964 (Smoking & Health, 1964).

Smoking is hazardous to every organ of the body and the benefits of smoking cessation interventions cannot be overstated (Anthonisen et al., 2005; Eriksen, Mackay, & Ross, 2013; Kottke, Battista, DeFriese, & Brekke, 1988; Lemmens, Oenema, Knut, & Brug, 2008; Prochaska, Delucchi, & Hall, 2004; West & Shahab, 2010). A review of the lung health study demonstrated that smoking cessation reduces mortality from both lung cancer and coronary heart disease (Anthonisen et al., 2005). Smoking cessation also improves lipid metabolism and cardiometabolic factors (Gastaldelli, Folli, & Maffei, 2010). Most of these studies assessed tobacco smoking, however research on the health effects of marijuana smoking is now evolving.

Recreational Substance Use in the United States

In the first century BC, the tobacco plant was used for medicinal, religious, and recreational purposes (Newton, 2010). After several years of use, the deleterious effect of tobacco on health and economic growth cannot be overstated and the impact of public health measures towards smoking cessation and successes cannot be understated. The current inclination towards legalization of marijuana questions the possibility of a replay of the journey with tobacco (Falkowski, 2014).

The CDC reports that 17.8% of adults in the US were current smokers in 2013 with a greater prevalence among men (20.5%) than women (15.3%). The highest current smoking rates

were among non-Hispanic Multi-racials (26.8%) and non-Hispanic American Indians/Alaska Natives (26.1%) with lowest rates among non-Hispanic Asians (9.6%).

Marijuana is classified as a Schedule I controlled substance under Federal law (Digest, 2014). Schedule I substances under the Federal Controlled Substances Act (CSA) are considered as having a high potential for abuse and not having any currently accepted medical use in treatment, consequently its use is reserved for very limited circumstances. Notwithstanding, several States approve medical marijuana use and two States have legalized marijuana for recreational use.

The World Health Organization (WHO) reports that the worldwide annual prevalence of cannabis use is about 2.5%. The National Institute on Drug Abuse (NIDA) estimates that in the US prevalence of current cannabis users aged 12 years and older, rose up to 7.3% in 2012 from 5.8% in 2007. This escalation is attributed to the current trend towards legalization of marijuana.

As at 2013, 18 US states and the District of Columbia permitted medical use of marijuana, with Colorado and Washington permitting its recreational use. Contributing factors to the current move to legalize marijuana include the medical use of marijuana (Hoffmann & Weber, 2010). Additionally, some research support the argument that decriminalization of cannabis has the potential to make law enforcement resources available to control certain trafficking activities without increasing cannabis abuses (Single, E. et al., 2000). Research on the effects of chronic use of marijuana is exigent if marijuana will universally be used recreationally.

Tobacco

Tobacco use is a very important modifiable lifestyle associated with preventable ill health and premature mortality. Tobacco smoking is a major risk factor for many chronic diseases that affect primarily the heart, liver and lungs. Tobacco is obtained mainly from the leaves o the plant Nicotiana tobacum, though there are over 70 species of the plant. There are many formulations of tobacco; common ones are cigarettes, cigar, snuff and kreteks to name a few.

The main active ingredient in tobacco is nicotine which is a stimulant. The primary mode of administration is smoking. Nicotine binds to cholinergic nicotinic receptors and promotes the release of several neurotransmitters. Nicotine is addictive and induces tolerance (Benowitz, 1998); this plays a factor in its chronic and incremental use among some people. This could also play a competitive role with individual smoking cessation volition. Nicotine's stimulant activity on the sympathetic nervous system leads to increase in blood pressure and heart rate. High doses can also lead to hypotension.

The popularity and spread of tobacco use was facilitated by major tobacco companies who used several marketing strategies to make tobacco use especially smoking enticing and even acceptable among women (for whom smoking was frowned upon). Smoking rates in the US rose up to about 42% in the 1960's and dropped starting 1965 after the first surgeon general's report on smoking and health to about 20.6% in 2008 (Dube, Asman, Malarcher, & Carabollo, 2009) and about 19.3% among adults aged 18 years and above (Control & Prevention, 2011).

The WHO estimates that in the early 1990's about 1.1 billion people aged 15 years and above worldwide smoked; equivalent to a third of the global population. The gender rates were about 47% of males and 12% of females. It was estimated that the number of smokers may

increase to about 1.64 billion by 2030 with a resultant increase in factors of poor health as well as mortalities if no measures were taken to discourage smoking. Smoking cessation programs have contributed greatly in reducing smoking prevalence rates. Overall global smoking prevalence among people aged 15 years and above fell to 29% in 1995 (Jha, Ranson, Nguyen, & Yach, 2002). In 2012, the estimated worldwide age-standardized prevalence of smoking among this cohort was 31% for men and 6.2% for women, however there are regional disparities in these smoking rates (Ng et al., 2014).

Doll and Hill demonstrated associations between smoking and lung cancer (Doll & Hill, 1950), several other studies which ensued confirmed similar findings. A 34 year follow up of Framingham cohorts who were 30-62 years when they entered the study demonstrated that cigarette smoking was associated with lung and cardiovascular disease: lung cancer, stroke, ischemic heart attack etc. (Freund, Belanger, D'Agostino, & Kannel, 1993). It is an established fact that smoking is associated with several health hazards (Eriksen et al., 2013; Slama, 2012). Smoking is also characterized by premature and high mortality and cessation reverses ill health (Jha et al., 2013).

Across all studies the benefits of smoking cessation is emphasized. Smoking cessation has immediate and important benefits to all who stop smoking even after a short time, leads to longer life span, decrease the risk for lung cancer and cardiovascular diseases (Critichley & Capewell, 2007; General, 1990; Jha et al., 2013; Taylor Jr, Hasselblad, Henley, Thun, & Sloan, 2002).

There is evidence that tobacco use is associated with weight reduction and this has the potential of discouraging smoking cessation among people who seek to fight or prevent obesity.

Smoking may increase basal metabolism or reduce appetite and consequently may result in reduced intake of food (Louis-Sylvestre, 1993). Weight gain and obesity are however not just a direct cause of food or increased caloric intake. Obesity has multifactorial components and more research is needed in this area to fully elucidate the effect of tobacco use not only on weight but on the classification of obesity and among different populations.

Results of research on tobacco and weight distribution or classification are actually not conclusive; some report that smoking increases abdominal obesity (Chiolero, Faeh, Paccaud, & Cornuz, 2008) others that it decreases weight (Klesges, Meyers, Klesges, & LaVasque, 1989) and others report the associations are weight definition dependent (Potter, Pederson, Chan, Aubut, & Koval, 2004). Since body weight shares integrate properties with metabolic syndrome and several chronic diseases, one area of interest is the effect of tobacco use (which is also connected to several diseases and controversial with weight) on the metabolic syndrome.

Much as this is an understudied area for tobacco, available literature shows that smoking has nonlinear relationships with factors of metabolic syndrome especially among moderate smokers, but heavy smoking of 20 cigarettes or more daily leads to adverse levels of metabolic factors which approach linearity (Fontes, Moshammer, & Elmadfa, 2012). Research shows that smoking and even levels of serum cotinine consistent with environmental tobacco smoking is associated with metabolic syndrome (Sun, Liu, & Ning, 2012; Weitzman et al., 2005). Tobacco smoking is also associated with the lipid components of the metabolic syndrome; hypertriglycerideamia (Oh et al., 2005; Reynolds et al., 2011), low HDL (Chen et al., 2008; Oh et al., 2005).

Smoking causes inflammation; it increases the production of pro-cytokines, reduces levels of anti-inflammatory cytokines (Arnson, Shoenfeld, & Amital, 2010) and increases pathologic levels of inflammation-sensitive proteins like alpa1-antitripson,fibrinogen etc. which are associated with cardiovascular problems (Lind et al., 2004). Inflammation is a precursor to several factors of the metabolic syndrome.

Smoking also reduces glucose tolerance and plasma insulin levels and demonstrates a dose dependent relationship (Janzon, Berntorp, Hanson, Lindell, & Trell, 1983). A large cohort study conducted by Will J. C. et al., and other prospective studies show that smoking is associated with the incidence of diabetes and this was likely dose dependent as well (Kawakami, Takatsuka, Shimizu, & Ishibashi, 1997; E. B. Rimm et al., 1993; Eric B Rimm, Chan, Stampfer, Colditz, & Willett, 1995; Will, Galuska, Ford, Mokdad, & Calle, 2001).

Even though the relationship between smoking and body weight is complex, tobacco smoking is most likely associated with increasing rates of metabolic syndrome. The NCEP ATP III has emphasized that with increasing rates of obesity, metabolic syndrome is likely to have a greater attributable impact than tobacco on premature death from coronary artery diseases (E. S. Ford, Giles, & Dietz, 2002; S. Grundy et al., 2002; Program, 2001). This makes smoking and metabolic syndrome very important subjects for public health if global health goals must be achieved.

Marijuana and Medical Marijuana

Marijuana or cannabis is a leafy flowering plant that embraces three species; Cannabis sativa, Cannabis indica and Cannabis ruderalis. Though cannabis is used orally, common route of

administration is smoking after which it is readily absorbed in the lungs. Cannabis has psychoactive properties and is a popular recreational substance because it induces relaxation and euphoria to some extent.

Cannabis is also used medically in some settings; it has been used to relieve chronic and neuropathic pain as well as nausea where conventional medications fail to provide relieve of symptoms. Dronabinol and nabinol are medications of cannabis indicated for chemotherapy associated nausea and vomiting. They are also used to manage anorexia associated with weight loss in patients who have acquired immune deficiency syndrome. The use of cannabis is however also associated with psychotropic and other adverse health effects.

The active ingredients of cannabis are known as cannabinoids; the major psychoactive ingredient is Delta-9 tetrahydrocannabinol (THC). Cannabis exerts its effect on the endocannabinoid system where they act on cannabinoid receptors. Cannabinoid receptors are stimulated by endocannabinoids which are endogenous ligands. Cannabinoid receptors 1 (CB1) and 2 (CB2) were discovered during the 1990's and this has since increased interest in research of cannabinoids. Apart from the brain, cannabinoid receptors and endocannabinoids are present in peripheral tissues.

Absorption of cannabis can be erratic and differs in individuals. The plasma half-life of cannabis is 20-30 hours. Cannabis can be detected in the urine for up to two months in a heavy user but a few days in a rare user. In up to moderate doses, cannabis increases sympathetic activity leading to tachycardia and increased cardiac output. At high dosage, cannabis increases parasympathetic activity resulting in bradycardia and hypotension. Both the sympathetic and

parasympathetic effects of cannabis can be life-threatening especially among people who have underlying cardiac problems (Ghuran & Nolan, 2000; Olson, Anderson, & Benowitz, 2007).

Both CB1 and CB2 are involved in regulation of energy balance, appetite, insulin sensitivity and lipid metabolism (Blüher et al., 2006; Engeli & Jordan, 2006; Pagotto, Marsicano, Cota, Lutz, & Pasquali, 2006). Research support that the endocannabinoid system as well as chronic smoking of cannabis are associated with metabolic irregularities like abdominal obesity and insulin resistance (Blüher et al., 2006; Di Marzo, 2008; Kunos, 2007; Muniyappa et al., 2013) as well as cardiovascular function (Cota, 2007; Pacher & Steffens, 2009).

Upon stimulation of CB1 receptors, the liver and adipose tissues respond through lipogenesis, lipid accumulation and impairs insulin secretion and function or induces pancreatic beta cell death (Kim et al., 2012; Sarker & Maruyama, 2003). Apart from endocannabinoids, the psychoactive agent in cannabis, THC also stimulates CB1 and can induce glucose intolerance.

Cannabinoid receptors are important targets in pharmacology for managing obesity (Bellocchio, Mancini, Vicennati, Pasquali, & Pagotto, 2006). Stimulation of CB1 receptors increases appetite; the principle of managing obesity by using the pharmacologic agent Rimonabant which is a CB1 receptor antagonist. Rimonabant is however central acting and causes neuropsychological effects, thereby preventing its approval in the US and subsequent withdrawal from several markets. CB2 receptors are also involved in metabolic changes associated with diet, however stimulation of CB2 receptors improve glucose tolerance (Bermudez-Silva et al., 2007) and seem to work in the reverse of CB1 stimulation.

Chronic use of cannabis no doubt is associated with metabolic health. A major problem with the use of medical cannabis is standardization of the dose as well as an acceptable

formulation. There are about 60 cannabinoids in cannabis aside so many other active substances that have not been studied. Absorption of the active ingredients in cannabis is erratic and specific to an individual's physiologic make up which can lead to overdosing and poisoning. Also the effect of the active ingredients in cannabis can be contradicting and unpredictable.

The endocannabioid system is involved in metabolic regulation, is a major target of interest for managing obesity and indiscriminate use can lead to chronic detrimental health. It is important to consider the long term effect of chronic and liberal use of marijuana on metabolic and cardiovascular health among populations.

Metabolic Syndrome and its Genesis

Metabolic syndrome is the co-existence of delineated clinical and biochemical risk factors that increases the propensity of having a cardiovascular disease or event by about three fold (Isomaa et al., 2001). The genesis of work on factors associated with metabolic syndrome dates back. It is noteworthy that the masterpiece of the Father of pathology, Joannes Baptista Morgagni - 'De sedibus et causis morborum per anatomen indagata' published in 1765, initiated the description of correlation between visceral obesity, high blood pressure and cardiovascular disorders (Morgani, 1765). In 1947 the French physician Dr. Jean Vague published his work on the finding that abdominal obesity is associated with diabetes and cardiovascular diseases (Vague, 1947). He introduced the terminology android obesity to describe this condition.

During the late 1960s through 1970s, advances in technology and availability of epidemiologic data permitted varied research on the metabolic syndrome. Several terminology were used to describe the co-existence of its risk factors; metabolic trisyndrome and notable

among them plurimetabolic syndrome. In 1988 Dr. Gerald Reaven described the common clustering of dyslipidemia, hypertension and hyperglycemia as Syndrome X (Reaven, 1988). He noted that Syndrome X was a multiple risk factor for cardiovascular diseases and implicated the role of insulin resistance in Syndrome X, hence the term insulin resistance syndrome.

Metabolic Syndrome and Criteria for Research

The risk factors for metabolic syndrome are extensively documented, however a unifying definition remains a challenge. The risk factors, its combinations or cut of points are varied for different deliberative bodies; World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), National Cholesterol Examination Program, Adult Treatment Panel III (NCEP ATPIII) and recently criteria by the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF). The new IDF definition for metabolic syndrome is the presence of central obesity (ethnic specific waist circumference values) and any two values of the following: hypertriglyceridemia, elevated blood pressure, raised fasting plasma glucose or reduced levels of high density cholesterol. A previous diagnosis of diabetes or medications for any of the listed conditions is also included. The definition by NCEP ATPIII is commonly used in clinical practice because the factors are more practical to measure.

Metabolic Syndrome, Epidemiology and Risk Factors

The worldwide prevalence of metabolic syndrome ranges from 10% to about 84% depending on the definition used for metabolic syndrome or demographic composition of the

population (Desroches & Lamarche, 2007; Kolovou, Anagnostopoulou, Salpea, & Mikhailidis, 2007). The National Health and Statistics Report shows that during 2003 to 2006, based on NCEP/ATPIII guidelines, the prevalence of MetS in the United States was about 34% among adults aged 20 years and above. In the general US population, the age adjusted prevalence of MetS was estimated to have reduced from 25.5% in 1999 to 22.9% in 2010, however this pattern of decrease is not evident in the prevalence of risk factors of the individual components of MetS (Beltrán-Sánchez, Harhay, Harhay, & McElligott, 2013).

Obesity especially abdominal obesity is a major risk factor for metabolic syndrome, and consequently a component of metabolic syndrome (Bray, 2007; Despres & Lemieux, 2006). Obesity induces neuroendocrine abnormalities which affects various metabolic activities leading to diabetes and cardiovascular diseases (Björntorp, 1992). Surging rates of obesity among populations are associated with increasing MetS prevalence and incidence of chronic diseases (Eckel, Grundy, & Zimmet, 2005; James, Rigby, & Leach, 2004).

Dyslipidemia, insulin dysfunction, and high blood pressure are the other determinants of metabolic syndrome. Apart from increases in waist circumference, elevations in triglycerides and blood pressure and are most attributable to increase in rates of metabolic syndrome especially among adults (Earl S Ford, Giles, & Mokdad, 2004). Dyslipidemia promotes atherogenesis, which is a major path to aberrations in cardiovascular integrity (S. M. Grundy, 1997). The role of insulin dysfunction and hypertension in metabolic syndrome is demonstrated through their actions on the sympathetic nervous system, leading to endothelial abnormalities and poor cardiovascular function (Mendizábal, Llorens, & Nava, 2013).

Among demographic characteristics, increasing age also predisposes one to a higher tendency for metabolic syndrome. Progress in age is associated with several pathological processes in the human system (S. M. Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004) including changes in tissue energy metabolism that could lead to lower resting metabolic rate with advanced age (Fukagawa, Bandini, & Young, 1990).

Several studies show that MetS is more prevalent among men than women and this is attributed to android or central obesity (Regitz-Zagrosek, Lehmkuhl, & Weickert, 2006), which is more of a fat distribution pattern among men. Compared to gynoid obesity, android obesity leads to cardiovascular diseases. The anti-atherosclerotic property of estrogen also plays a protective role in the lower rates of MetS among women. This is evident in that fact that rates of MetS increase among post-menopausal women in whom estrogen levels are low (Regitz-Zagrosek, Lehmkuhl, & Mahmoodzadeh, 2007; Tong et al., 2005). Yet, among those with MetS, men still carry higher prevalence of cardiovascular diseases and mortality from other causes irrespective of underlying diagnosis of diabetes or cardiovascular disorder (Kurl et al., 2006; Lakka et al., 2002).

Social economic factors like education and income can change the relation between MetS and gender (Loucks, Rehkopf, Thurston, & Kawachi, 2007). Education and increased income generally acts favorably on metabolic factors. Among women those who are educated are generally less likely than those who are not, to have the MetS; however this pattern is not necessary so among men. This also applies to increased income; low income to poverty ratio is associated with high MetS rates among women (Loucks et al., 2007). The impact of other factors like marriage and place of birth on MetS are of research interest.

Racial and gender specific differences exist with respect to MetS (Ervin, 2009; E. S. Ford et al., 2002). Non-Hispanic White females are less likely than non-Hispanic Black and Mexican American females to have MetS, whereas non-Hispanic White males are generally more likely than non-Hispanic Black males to have MetS (Ervin, 2009). Ethnic differences in MetS rates, has partly been explained by diet (Beydoun et al., 2008), socioeconomic and lifestyle factors which contribute to obesity (Cossrow & Falkner, 2004) as well as genetic factors (Firmann et al., 2008) or an integration of the environment with genetic factors (Benyamin et al., 2007). Other physiologic factors like insulin resistance seem more prevalent among Hispanics, leading to a higher rate of MetS among them (Li et al., 2006).

Among lifestyle factors, whereas reduced physical activity and fatty diet are evidently associated with a higher risk for metabolic syndrome, the effects of alcohol and tobacco on MetS are not conclusive (Lee, Jung, Park, Rhee, & Kim, 2005; Mayer, Newman, Quesenberry, Friedman, & Selby, 1993; Eric B Rimm et al., 1995; Sacco et al., 1999; Santos, Ebrahim, & Barros, 2007). Yoon et al. however, conclude that heavy alcohol consumption is actually associated with increased likelihood of having metabolic syndrome as a whole or some factors of the MetS especially central obesity and hypertension (Y. S. Yoon, Oh, Baik, Park, & Kim, 2004).

Cigarette Smoking, Marijuana Use and Metabolic Syndrome

Although tobacco use has declined substantially in the United States, it remains the second-leading cause of total deaths and disability. The perception of lower risk associated with varied forms of substance use, can potentially lead to re-engagement or encourage initiation of substance use. For example flavored cigarettes enticed adolescents to initiate smoking. The

wrong notion that e-cigarettes are less harmful also encourages cigarette smoking. Legalization of marijuana backed by information, that marijuana is beneficial or not associated with certain diseases, or conditions that carry grave consequences on morbidity, disability and mortality like metabolic syndrome, could potentially threaten public health gains, if ultimately it is demonstrated not to be so. The scientific community, has the responsibility to protect the health of the public, through sharing evidence-based information, or at least in the absence of evidence exercise restraint in divulging information that could potentially be harmful in the long term. It is still important to document and support tested evidence of any benefits of substance use.

Because recreational substances affect the brain and have psychoactive properties, if it must be prescribed for ailments, monitoring must be available. It is necessary to invest resources to investigate and address any benefits or harms associated with substance use. If marijuana must be permitted for recreational use, the health system must be in readiness for the varied aspects of the consequences of liberal recreational use of a substance that is psychoactive, has erratic distributions and effects among different individuals and is comparatively understudied in contemporary times. It is important to invest in investigations on marijuana use and the primary cause of disabilities, morbidities and death, in the interest of sustaining public health gains in cardiovascular disease prevention among the population and achieving sustainable health for the populace.

Cardiovascular Morbidities and Mortalities

Cardiovascular disease (CVD) and stroke continue to be responsible for huge health and economic burdens both in the US and globally, irrespective of the declining rates of mortalities from CVDs. The American Heart Association report that a decline of 28.8% was observed in the

US from 2003 to 2013. The 2013 overall rate of death attributable to CVD was 222.9 per 100,000 Americans with gender and racial-ethnic differences (Mozaffarian, Benjamin, Go, Arnett, Blaha, Cushman, Das, de Ferranti, Després, & Fullerton, 2016). Non-Hispanic black males had the highest death rates (356.7 per 100,000) compared to 246.6 per 100,000 for non-Hispanic Black females. Generally, males had a higher death rate than females. The death rates were 269.8 for males and 184.8 for females (Mozaffarian, Benjamin, Go, Arnett, Blaha, Cushman, Das, de Ferranti, Després, & Fullerton, 2016).

The decline in CVD deaths are attributed to clinical and behavioral interventions especially increase in physical activity, good diet and smoking cessation as well as surveillance on cardiovascular health and its associated risk factors. Generally current cigarette smoking rates among adults have declined. In 2014, the prevalence of adult current smokers was 16.9% compared to 24.1% in 1998. Irrespective of the declining rates of cigarette smoking, CVD deaths due to tobacco use are still ranked high; together smoking and exposure to secondhand smoke are attributable for about one third of coronary heart disease mortalities (Mozaffarian, Benjamin, Go, Arnett, Blaha, Cushman, Das, de Ferranti, Després, Fullerton, et al., 2016).

Hypertension is a major risk factor for cardiovascular, cerebrovascular and renal diseases. Hypertension is an underlying factor for most cardiovascular and cerebrovascular mortalities as well as disabilities and as such poses a major health burden. Hypertension is attributable for almost 50% of all global deaths from stroke. Hypertension prevalence is expected to increase by about 60% on the global level by 2025 if no measures are taken to prevent the demographic expansion of hypertension among populations (Kearney et al., 2005). Interventions leading to controlled blood pressure is thus important. It is noteworthy that about 17.3% of all

hypertension cases are undiagnosed, and this carries grave consequences for those affected. Apart from smoking cessation, the decline in stroke mortality is also a result of controlling diabetes mellitus, hypercholesterolemia and hypertension.

Economic costs of cardiovascular disease and substance use

The American Heart Association (AHA) report that, estimated annual cost for CVD and stroke during 2011-2012 was $316.6 billion, including $193.1 billion in direct costs (hospital services, physicians and other professionals, prescribed medications, home health care, and other medical durables). During this period, indirect cost associated with lost future productivity due to premature deaths from cardiovascular diseases and stroke was $123.5 billion, the heaviest economic burden compared to all other diseases (the estimated direct cost for all cancer was $88·7 billion in 2011). The cost associated with addressing substance use in the US is estimated at $600 billion dollars annually (Abuse, 2015)

Theoretical Basis of Substance Use and Prevention

Substance Abuse and Mental health Services Administration (SAMHSA) report that in 2014, about 10.2% of Americans used an illicit substance in the past 30 days. They were aged 12 years and above. This percentage was higher than that observed each year from 2002 to 2013. Marijuana use is adjudged the main driver of the increased prevalence of illicit substance use, 22.2 million of the total 27.0 million people used an illicit substance in the past 30 days (adjudged current users).

Bandura's social cognitive theory (Bandura, 1999) explains the initiation and maintenance of a given behavior and has been used to explain smoking and drug related behaviors, as well as incorporated in plans to assist prevention or cessation of substance use. By this theory, cognitive, environmental and behavioral factors interplay to define substance use.

Cognitive factors explain how the individual's mental capability and disposition allows him/her to understand the effect of substance use on his/her system. The emotional coping responses to the effect of substance use, the individuals behavioral capacity under the influence of substance use as well as self-efficacy. Overall, outcome expectancies play a role in substance use. If the individual expects beneficial outcomes from substance use, they are likely to start or continue using substances. If the individual expects to have cure of an ailment from using substances, he/she is likely to use it. Medical marijuana proponents attest to the fact that they benefit from using marijuana, for example in treating severe vomiting or pain, that responds to no other analgesics. People may smoke cigarettes because they find that it relieves their stress. At the same time, people do abstain from tobacco or drugs after experiencing very bad effects of substances. For example someone who suffers a cardiac arrest after substance use, and would likely not want to use the substance again, having come to face the reality of possible death in connection to substance use. For some self-efficacy plays a major role in deciding strongly to abstain and giving up to the detrimental effects of the substance. The mental capability plays a major factor. At times genetic dispositions can explain cognitive behaviors with regard to substance use, whether an individual's use of substances is predominantly because of dictates ingrained in the genes.

The environment is a major determinant of substance use. Environmental factors may enhance or prevent substance use. Living in an environment where substance use is prevalent or is the norm can support the use of substances. Generally people who live in environments where substance use is prohibited or where laws prevent the use of substances are not likely to initiate or continue the use of substances. Peer use of illicit substances or recreational substances can be a major environmental factor. Policies that allow or disallow the use of substances can also be a factor for substance use. For example, banning smoking in public areas, prevents smoking in those areas even if an individual is a heavy smoker. He/she will have to look for the right environment to smoke. Alternately, bars that allow smoking for example will attract not only smokers, but continuation of smoking activity which an individual may have stopped for some time because of enabling environment.

Behavioral factors considers the individuals reactions to conditions in the environment or inputs from the environments. The individual is likely to use available information on marijuana use to make decisions whether to use marijuana or not. Information and education play very important roles in the choices we make. The duty of health professional is to make evidence based information available in a way to help individuals make informed decisions on their health. If marijuana use is beneficial like food, the information must be made available, if the use of marijuana is detrimental the information must be made available. Underlying each of these factors are constructs of the socio cognitive theory. The idea that marijuana use is safe seems to be assimilated well by a majority of the public and in some cases even among health-care professionals. This has contributed to the support for legalization of marijuana use not only medicinally but recreationally.

Constructs of the socio cognitive theory are behavioral capability, reciprocal determinism, emotional coping responses, outcome expectations, self-efficacy, collective efficacy, observational learning, incentive motivation, facilitation, self-regulation and moral disengagement.

Behavioral capability considers the basic knowledge an individual has on substance use and the skills necessary to avoid substance use initiation or quit substance use. For example knowledge on the biological effects of marijuana on the human system, knowledge about the nature of marijuana and other substances, its use and adverse effects, helps individuals to make decisions on its use. Skills necessary indulging or avoiding marijuana use depends on the knowledge. To a large extent, health professionals must make information on substance use available to target groups and the populace in general to help control substance use.

Reciprocal determinism, considers the interaction between individuals' behavior and the environment. Whilst the social environment affects individuals'' behavior, the individual's behavior or actions also affects the environment in which he/she operates or chooses to live. Whether people choose to live in environments that support marijuana use or live in environments that do not support marijuana use depends on this interplay. Is it likely that states that legalize recreational marijuana use will attract people who are prefer to use marijuana or is it likely that people who live in states that legalize recreational marijuana are likely to accept and adopt the use as well as put in more measures to sustain policies that support marijuana use and protect people who use marijuana?

Emotional coping responses address the responses to environmental and emotional stimulations or stressors. Coping responses are targeted towards achieving a mental wellbeing or

physical wellbeing, however, these responses can be negative or positive depending on the individual's cognitive functions. An individual who is addicted to substances is likely to become confrontative if he/she is denied access to substances. Dependence on addictive substances is a major problem for health systems but has been capitalized by the respective companies as a sales strategy because it ensures the continuous use of these products irrespective of the adverse effects. Yet others harmed by substance use seek social support and enroll in rehabilitation programs. Others are self-controlling enough in the face of being temptation to avoid substance use, or control its use. Several coping mechanisms like distancing and positive reappraisal have been described (Sudraba et al., 2015).

Outcome expectations describes an important factor in substance use behavior. Generally when people expect to have health benefits from a product, they are more likely to support its use and use it. Marijuana has been described as harmless in some publications, and people who expect not to be harmed by using marijuana will most likely use marijuana for some purpose. Medical marijuana is another reason why proponent s of marijuana use support its legalization. The outcome expectations of marijuana use is a major subject of contemporary debate. Yet others may use substances as an escape from reality. People who expect harms from the use of substances are likely to avoid using them. If business entities expect gains from sales of marijuana, they are likely to support its legalization and promote its sale. If state legislators expect to curtail illegal sales of marijuana and reduced criminal activities with marijuana legalization, they are likely to legalize marijuana use.

Self-efficacy is the confidence or belief an individual has in performing certain activities to achieve an expected outcome. This is a very relevant construct of substance use abstinence,

initiation, continuation or cessation. The level of self-efficacy determines the amount of energy or resources an individual or system will invest in performing an activity to achieve a set outcome.

Self-regulation is an individual's ability to perform an activity. An individual may strongly to decide quitting smoking or not use marijuana or any substances. Self-regulation involves how an individual plans to attain health or benefits from an action either through avoiding situations that may promote substance use, or staying strong and avoiding substance use even when it's available. Strategies used in self-regulation include goal setting, self-monitoring, self-reward, self-instruction, social support enlistment and feedback or evaluation.

Incentive motivation is the strategic use of rewards for achieving a set goal for example for not smoking for ten days, and punishments like withdrawal of some privileges for non-achievement of set goals. Motivational incentives have been used to assist people continue cessation programs, for example by awarding them prices for attending programs or not using substances or presenting urine samples for investigation to affirm abstinence from substance use (Stitzer, Petry, & Peirce, 2010).

Observational learning includes involves role modelling, observing the outcomes of the behavior of others and making informed decisions to abstain from a detrimental activity based on positive role modelling. Cues can be used in observational modelling to reinforce behavior or prevent certain behaviors. For example explicit pictures of harms associated with tobacco use on cigarette packages prevents people from smoking.

Facilitation involves the provision of resources and tools to assist in positive behavior. Public health educators and other health care professionals play an important role in facilitation.

Availability of rehabilitation centers and medications to help manage and prevent substance abuse are important facilitators. The environment can also serve as a positive or negative facilitator. Environments that promote or support substance use can be negative facilitators.

Collective efficacy is the combined force of a group to help each other achieve goals. Alcoholic Anonymous (AA) is a social group aimed at helping those who use alcohol heavily to stay sober or avoid heavy drinking through character building and spiritual support (Hunt & Azrin, 1973). When communities build solid trust, social capital and share healthy expectations, they can avoid crimes and unhealthy behaviors (Farmer, 2014).

Moral disengagement concerns a way of action which ignores the harm that can be caused to others through substance use. For example, individuals may neglect the effect of second hand smoking by smoking in public places. They may neglect the harm they can cause to others by using psychoactive substances and driving. Moral disengagement can be challenging force in substance use, especially considering the harm it can cause others who do not engage in unhealthy lifestyles. Not educating people on the harms of substance use, and supporting the use of substances that could potentially be harmful to people, especially those are not self-efficacious can be classified moral disengagement.

Constructs of the theoretical basis of substance use, is strongly tied to the socio-ecological model of health: individual, interpersonal, organizational, community and policy levels (Sallis, Owen, & Fisher, 2008). Each level of the socio-ecological model plays an important role in substance use and in the prevention of substance use. Science, the health community and social community must consider the health risks associated with recreational cannabis use and implement measures to protect the health of society.

Current evidence supports strategies to improve cardiovascular health. A three pronged strategy to improve cardiovascular health, include a) individual –focused approach which target lifestyle changes and treatment approaches, b) healthcare systems approach, which involves resources to improve health behaviors and health care as well as encouragement, facilitation and rewards for efforts by healthcare providers and patients towards health improvement and c) population approach which target lifestyle and treatment among various populations.

Limitations in Research

Research on marijuana use and in combination with metabolic syndrome is evolving. Data on marijuana use among all relevant age groups is scarce especially among the youth and elderly; this limits the population coverage that can be investigated for marijuana use and its effect on health.

Most research find no significant associations between marijuana use and metabolic syndrome, whilst others present results showing that marijuana use is associated with reduced values of some components of metabolic syndrome like blood glucose (Penner, Buettner, & Mittleman, 2013).

While these studies have stated some limitations others have questioned the design of the studies. Most studies on marijuana and metabolic syndrome are cross-sectional because the interest in this relationship is now evolving and data availability is limited. Longitudinal research on the relationship between marijuana and metabolic syndrome is scarce.

A major challenge with assessing marijuana use is the definition of marijuana use. Some studies use reported marijuana use as ever use of marijuana, use of marijuana in the past 30

days. The NHANES has variables that describe marijuana use based on having ever used marijuana, marijuana use in past 30 days, number of joints of marijuana used, age at first use of marijuana, and more recently (2011-2012), whether one has used marijuana regularly for the past year. Unlike cigarette smoking, the status of marijuana use has not been explicitly defined in literature. Also, information on cotinine, the active metabolite of nicotine from tobacco is publicly available for analysis, but that of marijuana is not. This poses limitations in quantifying marijuana use in research.

In assessing metabolic syndrome, definitions vary widely in literature because different deliberative bodies have different criteria for metabolic syndrome. This poses a challenge even in interpreting surveillance reports. The reported prevalence of metabolic syndrome is varies depending on the definition used. Cutt-off points for components of metabolic syndrome are also not unified.

Cardiovascular effects of marijuana is based principally on experiments with delta tetrahydrocannabinol (THC) the active ingredients of marijuana. This is principally on animal models and administered by other routes instead of smoking, unlike tobacco which has been studied extensively in real like situations among human subjects.

Marijuana is known to have a chemical variability has not been studied extensively. The chemical variability of marijuana, coupled with individual variations in smoking behavior, poses challenges in presenting firm conclusions on results from studies on marijuana that have used uncontrolled smoking observations (Jones, 2002). High potency marijuana is becoming readily available and experiments on their effects with respect to health is limited.

Studies on the effect of acute and chronic use of marijuana on specific biologic functions including cardiovascular processes for example, atherosclerosis, lipid metabolism, endothelial function, clotting function, and its sequelae are limited. Studies on cardiovascular effects of marijuana among older people with existing cardiovascular or cerebrovascular disease are limited. Generally, there is a need for studies on mortalities associated with marijuana use among the populace as its recreational use becomes legalized.

Statement of Purpose

The use of recreational substances carries both health and economic consequences which if not addressed could ultimately challenge global health developmental efforts. It is integral for public health to investigate the varied health effects of the use of substances that gain legal and liberal use. Tobacco and marijuana are two recreational substances used commonly in the United States. Like tobacco, marijuana use could potentially gain global acceptance with time. Tobacco remains a legal substance even though its detrimental health effects have been proven extensively. Public health has undoubtedly achieved a lot in the area of smoking cessation by improve the health of individuals who smoke as well as those exposed to second hand smoking.

According to the US Federal Law, The Controlled Substance Act of 1970; there is a penalty for any act of possessing, dispensing, and prescribing marijuana. However in 1996, some 14 States (California, Alaska, Oregon, Washington, Maine, Hawaii, Colorado, Nevada, Vermont, Montana, Rhode Island, New Mexico, Michigan, and New Jersey) had an amendment to their state laws that allowed people who had been diagnosed by certified licensed physicians as

having debilitating medical conditions to use of marijuana as supportive therapy. Gradually marijuana is gaining support for legalization of its recreational use.

A journey back in history recounts how research by Doll and Hill in 1950 found the association between smoking, lung cancer and heart disease (Doll, R. and Hill, A. B., 1950) after massive support for tobacco smoking. With great public health effort, research and legal battle, this ultimately led to the Tobacco Master Settlement Agreement (MSA) in 1998 to address tobacco related health-care costs. The current trend towards recreational use of marijuana could possibly be another journey down the trend. Research on possible adverse health effects of marijuana use is exigent.

Our research seeks to add to the geminating interest in research on metabolic syndrome and substance use as an illuminating pathway to addressing recreational substance use and factors associated with cardio-metabolic diseases, a major cause of morbidity and mortality. The cardio-metabolic association with recreational substance use especially marijuana has not been studied extensively, and this will be an exploratory study to add to emerging literature on marijuana use.

We used data from National Health and Nutrition Examination Survey (NHANES); a program purposed to evaluate the health and nutritional status of the United States population. We conducted bivariate and multivariate analysis to estimate the relationship between tobacco smoking and marijuana use and factors of/and the metabolic syndrome. Definition of metabolic syndrome has varying criteria by different deliberative bodies. We also assessed effect of using varying criteria to define metabolic syndrome on the relationship with tobacco smoking and marijuana use.

Our aim is to investigate the relationship between:

A) Tobacco and Marijuana use and factors of/and metabolic syndrome: Very few studies have looked at especially the relationship between marijuana use and metabolic syndrome. With the burgeoning interest in marijuana use, empirical studies on its impact with metabolic activity can be a pathway for describing chronic disease concerns related to its use.

B) Tobacco and marijuana use with metabolic syndrome using the different criteria for metabolic syndrome: Identifying a unified criterion for metabolic syndrome is still a challenge. Different authorities in health give different criteria and cut-offs for metabolic syndrome which could affect conclusions from studies. We plan to investigate the relationship of tobacco and marijuana smoking under the different criteria for metabolic syndrome and describe any differences in conclusion that may surface.

C) Marijuana use and cardiovascular health: The detrimental effects of tobacco on cardiovascular health are well studied, however that of marijuana is currently scarce. We will examine the relationship between marijuana use and mortality from cardiovascular diseases using the NHANES public-linked mortality data.

Research Question/Hypothesis

Our research question of interest is: a) is recreational substance use (Tobacco or Marijuana) associated with the metabolic syndrome? b) Using the different criteria for metabolic syndrome, are there significant differences in diagnosis of metabolic risk between people who engage in use of these recreational substances and people who do not? c) Do the additional criteria for metabolic syndrome proposed by the International Diabetes Federation (IDF) tell a

different story among those who use recreational substance and those who do not? d) Is the use of marijuana associated with mortality from a cardiovascular disease?

For the purpose of this study, we assume the hypotheses that: a) those who use/smoke tobacco and/or marijuana have increased odds for having risk factors of the metabolic syndrome than those who do not, b) the different criteria for metabolic syndrome equally predict metabolic risk factors among people who smoke tobacco or marijuana without significant differences, and c) marijuana use like tobacco use is associated with high risks of mortality from a cardiovascular disease.

Data

National Health and Nutrition Examination Survey (NHANES)

National Health and Nutrition Examination Survey (NHANES) started in 1960 and is a major program of the National Center for Health Statistics (NCHS), under the Centers for Disease Control and Prevention (CDC). The aim of the survey is to assess the health and nutritional status of civilian noninstitutionalized US population. Since 1999, NHANES is a continuous program which uses interviews and physical examinations for its purposes to assess the health and lifestyle indicators of a nationally representative sample of about 5000 US adults and children. After modifying the sampling technique employed for several iterations of data collection, NHANES adopted a continuous “rolling” sample approach in 1999; selection is done through complex, multistage probability sampling. Each year, the survey is conducted in 15 counties across the US. Interviews are conducted by physicians and other healthcare professionals in participant’s homes and examinations conducted in a mobile center.

National Health and Nutrition Examination Survey (NHANES III) Linked Mortality File – Public-use File

The NCHS has a mortality linkage to NHANES III. This linkage is with the death certificate data from the National Death Index (NDI). The linked mortality file provides information on mortality among NHANES III participants from 1988 to 2006. The mortality information is based on probabilistic match between NHANES III and NDI death certificate records. The linked mortality file has a public-use and a restricted-use file. The public-use file provides information on a limited set of mortality variables for adults of the NHANES III survey, whilst the restricted-use file has more detailed mortality information and mortality follow-up for children.

The public-use linked mortality file has information on the mortality status of adult participants (CDC, 2015). Mortality information on participants is obtained from death certificates or probabilistic matching from the National death index (NDI). The NHANES coded causes of death occurring in the US before 1999 are based on the 9th revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-9) guidelines and cause of death occurring since 1999 on the 10th (ICD-10) revision. Causes of deaths occurring before 1999 were subsequently recoded into comparable ICD-10 rubrics. All deaths are classified as due to diseases of the heart (001), malignant neoplasms (002), chronic lower respiratory disease (003), accidents-unintentional injuries (004), cerebrovascular diseases (005), Alzheimer's diseases (006), diabetes mellitus (007), influenza and pneumonia (008), nephritis, nephrotic syndrome and nephrosis (009) and all other causes (010). Those assumed alive, ineligible for follow up, aged below 18 years or have no cause of death available are left blank and un-coded.

Independent Variables

Our main independent variables are a) marijuana use and b) tobacco use. Tobacco use is assessed under smoking-cigarette use whilst marijuana use is assessed under drug use by NHANES.

For smoking, all participants aged 12 years and above are eligible. Participants aged 12 -19 years answered the questions at a mobile examination center using the Audio Computer-Assisted Self-Interviewing

(ACASI) system in English and Spanish. Participants aged 20 years and above answered the questions at home. They were interviewed by trained interviewers using the Computer-Assisted Personal Interviewing (CAPI) system. The ACASI and CAPI have built in consistency checks to reduce data entry errors.

Participants who are aged 12 to 69 years are eligible to be asked about their lifetime or current drug use. The participants administer a drug use questionnaire during an interview at a mobile examination center (MEC). In the publicly available data file, only information from participants aged 18-69 years are included. Adults aged 18 years and above self-administer the questions using Audio computer-assisted self-interviewing (ACASI) system. The ACASI system allows respondents to listen to and answer questions at their own speed. If an answer is entered that is programmed to be an error in the system, the respondent is prompted by the system to correct the response before proceeding. Participants are reminded that their answers are strictly confidential.

Smoking or Tobacco Use

For smoking/tobacco use, participants were asked a) "have you smoked at least 100 cigarettes your entire life?" Answers given yes or no will be used for analysis, b) age at regular smoking, "How old were you when you first started to smoke cigarettes fairly regularly?" Answers in range of years. Those who have never smoked are coded as zero. Those who refused to answer or did not know were not included in the analysis, c) current and continued use of cigarettes, "do you now smoke cigarettes?" We will include the answers every day, some days or not at all. Current smokers are those who have smoked at least 100 cigarettes in their life time and still smoke either every day or some days.

Marijuana Use

For marijuana use, participants are introduced to the description of marijuana and asked about their use of marijuana. "Marijuana is also called pot or grass. Marijuana is usually smoked, either in cigarettes, called joints or in a pipe. It is sometimes cooked in food. Hashish is a form marijuana that is also called 'hash.' It is usually smoked in a pipe. Another form of hashish is hash oil. Have you ever even once used marijuana or hashish?" We will only include participants who answered yes or no. Participants who refused to answer, or

said they did not know or any missing information will be excluded from the analysis.

Other questions on marijuana use include a) age at first use of marijuana; “how old were you when you the first time you used marijuana or hashish?” Answers in range of values in years, b) regular use of marijuana; “have you smoked marijuana or hashish at least once a month for more than once a year?” Answered as yes or no, c) age at regular use of marijuana; “how old were you when you started smoking marijuana or hashish at least once a month for more than one year?” Answers in range of values in years, d) frequency of marijuana use; “during the time that you smoked marijuana or hashish, how often would you usually use it?” Answers are categorized as once a month, 2-3 times a month, 4-8 time a month, 9-24 times a month, or 25-30 times a month, d) number of days they used marijuana in a month; “during the past 30 days, on how many days did you use marijuana or hashish?” Answered as a range of values, from 1 to a maximum of 30, e) number of pipes or joints smoked daily; “during the time that you smoked marijuana or hashish, how many joints or pipes would you usually smoke in a day?” Answered as 1per day, 2 per day, 3-5 per day, or 6 or more per day.

Control Variables

In our model, we controlled for demographic and lifestyle variables that confound the relationship between our main independent variables and dependent variable. One drug question of interest is whether a participant had ever used any other illicit/recreational drug, since these could be used jointly with marijuana; “Have you ever used cocaine, crack cocaine, heroin or methamphetamine?” The answers were yes or no. We used this as a control variable, where it was found to be confounding in the relationship between marijuana and metabolic syndrome.

Questions on demographic indicators are asked by trained interviewers at home using the CAPI system. Unlike those under16 years, who may need a proxy, participants who are 16 years and older are interviewed directly. They chose the language of preference, either English or Spanish.

Age

Age is related to cardiovascular health and no doubt metabolic syndrome as well as substance use. Some age categories highlight this relationship. We used age as a dichotomous variable because of the effect of age transition on substance use and metabolic health based on literature. In the NHANES, participants are asked to give their age in years at the time of survey.

Gender

Gender differences affect cardiovascular health as well as smoking and substance use. Males generally are more likely to use recreational substances than women do. Hormonal factors affect the cardiovascular health of men and women differently. Participants stated their gender as males or females.

Education

Education is related to metabolic syndrome factors and substance use. Generally, more educated people can afford healthier choices which positively affect cardiovascular health and this could be a confounder in our model. In NHANES, participants are asked "what is the highest grade or level of school you have completed or the highest degree you have received?" the answers are ranked as a) less than 9^{th} grade, b) 9^{th}-11^{th} grade (as well as 12^{th} grade with no diploma), c) High school grade or GED or equivalent, d) some college or AA degree and e) college graduate or above. We included education at an in interval level to control for the effect of each level rise in education in the model.

Race and Ethnicity

In NHANES, participants are asked to identify themselves with the race/ethnicity they belong. They are listed as Non-Hispanic Whites, Black, Asians, Mexican Americans, Other Hispanics and Multiracials/or people of Other-Race. We used race as dummy variables with Non-Hispanic Whites as the reference.

Country of Birth

We controlled for country of birth. This is dichotomized as born in USA or other. In the survey, participants are asked; "In what country were you born?" The responses are a) born in any of the 50 states of the USA or Washington DC and b) other (born in another country). Place of birth may be associated with

cardiovascular health, through the effectiveness of healthcare systems available that target, investigate or control these conditions at an earlier stage in life. Generally, rates of obesity are also higher among people born in US and this impacts metabolic syndrome rates. With respect to smoking, epidemiologic data shows that the prevalence of smoking is quite high in the USA, even though it is dropping due to smoking cessation interventions. Also, prevalence of marijuana use is high in the USA. We include country of birth as a confounder with respect to cardiovascular and metabolic health.

Income to Poverty Ratio

We controlled for the ratio of family income to poverty (PIR). Income is a major factor for cardiovascular health and as well as substance use. Generally, having a higher PIR is associated to better cardiovascular health, because of affordability for healthcare services and healthier lifestyle choices including dietary choices. Also, people who have a low PIR may engage more in substance use than those with a high PIR. Several explanations have been given for this relationship and could be the vice versa; drug use leads to poverty people may lose their jobs, alternatively, people who find themselves living in poor environments are often surrounded by drug users and may easily obtain drugs on the streets and become substance users themselves for several reasons. In the NHANES, PIR is recorded as a range of values from 0-4.9 and 5 for those whose PIR are either 5 and above. Respondents report the total annual income for the entire family in dollars. With this information, the PIR is calculated using the Department of Health and Human Services (DHHS) poverty guidelines. No ratios are computed if income data is missing. We will use variable as a continuous variable and assess the effect of each point rise in PIR or interval variable of: 0 to 1.0, 1.1 to 2.0, 2.1 to 3.0, 3.1 to 4.0, 4.1 to 4.9, and 5.0 and above.

For lifestyle factors, we controlled for alcohol use, physical activity and diet including other drug use.

Alcohol Use

Participants are asked about their lifetime and past 12 months' alcohol use, irrespective of the type of alcohol use. They are asked how often they had an alcoholic beverage in the past 12 months. We computed number of alcohol drinks per week and assessed on a continuous level.

Physical Activity

Participants are assessed for physical activity based on the Global Physical Activity Questionnaire (GPAQ). Participants are asked if apart from work and transportation activities, they engage in at least ten minutes of continuous a) vigorous or b) moderate recreational physical activity in a typical day. Those who respond no to moderate physical activity were classified as not physically active and those who respond yes as physically active.

Statistical Analysis

We conducted statistical analysis using SPSS and STATA packages.

To estimate the relationship between factors of/metabolic syndrome and recreational substance use. We conducted bivariate and multivariate analysis. We estimated the odds ratios for having unhealthy levels for any factor of /the metabolic syndrome among those who smoke tobacco, marijuana or both.

Model of bivariate analysis:

$$Y_{\text{component of MetS}} = b_0 + b_1(\text{cigarette smoking})$$

$$Y_{\text{component of MetS}} = b_0 + b_1(\text{marijuana use})$$

$$Y_{\text{component of MetS}} = b_0 + b_1(\text{cigarette smoking + marijuana use})$$

$$Y_{\text{MetS}} = b_0 + b_1(iv_1)$$

Model of multivariate analysis:

$$Y_{\text{component of MetS}} = b_0 + b_1(iv_1) + b_2(iv_2) + \ldots\ldots + b_k(iv_k)$$

$$Y_{\text{MetS}} = b_0 + b_1(iv_1) + b_2(iv_2) + \ldots\ldots + b_k(iv_k)$$

Note: iv = independent variable

For analysis by different criteria for metabolic syndrome, we assessed how the different criteria alters our diagnosis of metabolic syndrome. We estimated the odds ratios for having metabolic syndrome among those who smoke marijuana or tobacco compared to those who do not and assessed if there are any differences based on the different criteria.

Model for bivariate analysis by metabolic syndrome criteria:

$$Y_{MetS(ATPIII)} = b_0 + b_1(iv)$$

$$Y_{MetS(WHO)} = b_0 + b_1(iv)$$

$$Y_{MetS(EGIR)} = b_0 + b_1(iv)$$

$$Y_{MetS(IDF)} = b_0 + b_1(iv)$$

Model for multivariate analysis by metabolic syndrome criteria:

$$Y_{MetS(criteria)} = b_0 + b_1(iv) + b_2(iv_2) + \ldots\ldots + b_k(iv_k)$$

To estimate mortality from a cardiovascular disease attributable to marijuana or tobacco use. We used Cox proportional hazard regression to estimate the effect of marijuana use on cardiovascular mortality. We estimated hazard ratios to describe the relative risk of having a cardiovascular associated mortality. We used Nelson-Aalen curves to describe findings.

Model for survival analysis:

$$H(t) = H_0(t) \times \exp(b_1(iv_1))$$

$$H(t) = H_0(t) \times \exp(b_1(iv_1) + b_2(iv_2) + \ldots. + b_k(iv_k))$$

CHAPTER 2

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Original Article

A cross-sectional analysis of the association between marijuana and cigarette smoking with metabolic syndrome among adults in the United States

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ABSTRACT

Aim: To assess the relationship between marijuana use, cigarette smoking and metabolic syndrome among adults in the United States who reported they use marijuana or cigarettes in comparison to non-marijuana and non-cigarette users.
Method: We conducted multiple logistic regression analyses using data from the 2011–2012 United States National Health and Nutrition Examination Survey to estimate relationships between cardio- metabolic risk factors and increasing years of smoking cigarette or marijuana use. Statistical adjustments were made for both demographic and endogenous factors related to recreational substance use.
Results: Each year increase in marijuana use was significantly associated with increased odds of metabolic syndrome (OR = 1.05; 95% CI: 1.01, 1.09), and hypertension (OR = 1.04; 95% CI: 1.01, 1.07) adjusting for both demographic and endogenous factors related to recreational substance use. Each year increase in cigarette smoking was significantly associated with increased odds of hypertension (OR = 1.03; 95% CI: 1.00, 1.06) and hyperglycemia (OR = 1.03; 95% CI: 1.01, 1.05) after adjusting for confounders.
Conclusion: The results of this investigation suggest that increased years of marijuana or cigarette use are important factors in metabolic health; and consequently calls for the need to consider the potential negative effects of marijuana or cigarette for metabolic syndrome and its associated cardio-metabolic risk components.

1. Introduction

Cigarette smoking and marijuana (cannabis) use are two common recreational drug behaviors in many societies including the United States (US). While cigarette smoking is a modifiable risk behavior that is often linked to several chronic diseases [1], little is known about the true relationship between marijuana use and chronic disease conditions [2]. In the US, public opinion for marijuana seems to be changing to legalization with respect to its use for recreational purposes [3,4]. The use of marijuana for medical reasons [5–7] has elevated public support for its decriminalization. It is of importance to public health that the burgeoning support for marijuana legalization as a recreational substance be supported by evidence and research. Indeed, the increase in support for recreational use of marijuana in the US calls for an understanding and proper documentation of the nature of the association between marijuana use and conditions associated with diseases that have high rates of morbidity and mortality, including metabolic syndrome (MetS).

Metabolic syndrome is a complex disorder defined by a cluster of interrelated factors that increase the risk of cardiovascular, atherosclerotic diseases and type 2 diabetes. Described originally by Hanefeld and Leonhardt [8] and popularized by Reaven [9], MetS remains a subject of considerable curiosity because of the complexity of the pathophysiology. The main components of MetS are abdominal obesity, elevated arterial blood pressure, dysregulated glucose homeostasis, and dyslipidemia [10].

In this study we examined the relationship of recreational substance use, specifically cigarette and marijuana with MetS.

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While some research exist on the effect of cigarette use on MetS [11,12], very little exist on the relationship between marijuana use and MetS, including its components. An underlying reason for investigating the connection between marijuana and metabolic syndrome is that cannabinoid receptors (the cell membrane receptor for active constituent of marijuana) and endocannabinoids (endogenous ligands) are present in the peripheral tissues that are involved in energy regulation and homeostasis [13– 15]. Importantly, Delta-9-tetrahydrocannabinol (THC), the main active constituent of marijuana, acts on these cannabinoid receptors [16]. If an important relationship between cannabis and metabolic syndrome exists, its explication may help to lessen the future burden of cardiovascular diseases.

2. Data and method

2.1. Data source

This study used data from the National Health and Nutrition Examination Survey (NHANES). The NHANES is a major program of the National Center for Health Statistics (NCHS), under the Centers for Disease Control and Prevention (CDC) that assesses the health and nutritional status of the US population. Since 1999, NHANES enrolls approximately 5000 persons from 15 counties across the US yearly for interview and examination. The enrollment is based on a continuous nationally representative and complex sampling method.

2.2. Inclusion criteria

This study was restricted to participants of 2011–2012 NHANES. Only subjects aged 20 years and above who responded to the question on our main independent variable, "Have you ever even once used marijuana or hashish?" were eligible for this study.

2.3. Dependent variables

Our main dependent variable is metabolic syndrome (MetS). We also analyzed each of the individual components of MetS separately. We classified MetS using definitions by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III) 2004 modification, which adapts the International Diabetes Federation (IDF) definition for hypertension and diabetes. Participants considered as having hypertension had an average blood pressure above 130/85 mmHg or were on antihypertensive medication. We used an average of the recorded blood pressure readings as the value of an individual's blood pressure for the purpose of our study. Details on blood pressure measurement are described (http://www.cdc.gov/nchs/nhanes/nhanes2009-2010/current_nhanes_09_10.htm). Participants with fasting plasma glucose of 100 mg/dl or on some antidiabetic treatment including insulin were coded as having diabetes. The NHANES has a detailed description of laboratory and examination procedures listed on (http://www.cdc.gov/nchs/nhanes/nhanes2011-2012/manuals11_12.htm). Abdominal obesity was coded as yes for females with waist circumference of more than 88.0 cm and yes for males with waist circumference of more than 102.0 cm. Females with plasma High Density Lipoprotein Cholesterol (HDL-C) of less than 50 mg/dl and males with less than 40 mg/dl were coded as having low HDL-C. Hypertriglyceridemia was coded yes for all participants with plasma triglycerides of 150 mg/dl and above. Participants with three or more of the components of metabolic syndrome (abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia and low HDL-C) were coded as having metabolic syndrome.

2.4. Main independent variables

Participants who answered no to the question "have you ever used marijuana?" were categorized as never marijuana users. Those who answered yes (had ever used marijuana), and answered no to the question, "have you smoked marijuana or hashish at least once a month for more than a year?" were categorized as non-regular marijuana users and those who answered yes as regular marijuana users. Other questions on marijuana use include: Age at first use of marijuana ("how old were you the first time you used marijuana or hashish?") and Age at regular use of marijuana ("how old were you when you started smoking marijuana or hashish at least once a month for more than one year?"). We calculated years of marijuana use by subtracting age at regular marijuana use from the current age of participants. Participants who were non-regular or never users had zero for the number of years of marijuana used. For quantity of marijuana smoked, participants answered the question: "during the time that you smoked marijuana or hashish, how many joints or pipes would you usually smoke in a day?" The answers were 1 per day, 2 per day, 3–5 per day, or 6+ per day. We used this as the quantity of marijuana used per day and assigned never users or non-regular users "zero" use per day.

Our other independent variable of interest is cigarette smoking. Participants were asked, "Have you smoked at least 100 cigarettes your entire life?" We coded those who answered no as non-smokers. For current use of cigarettes, participants who said they have smoked at least 100 cigarettes in their entire life, were asked "do you now smoke cigarettes?" We coded those who said not at all as past smokers and those who said every day or some days as current smokers (current smokers are those who have smoked at least 100 cigarettes in their life time and still smoke either every day or some days). To know the age at regular smoking, participants were asked, "How old were you when you first started to smoke cigarettes fairly regularly?" We coded years of smoking cigarettes for those who have never smoked as zero and did the subtraction for current smokers. Those who refused to answer or did not know were not included in the analysis.

2.5. Control variables

For our control variables, we dichotomized age as above 25 years or below and compared with those above 25 years. This is based on the effect of this age transition on metabolic syndrome, specifically, aging and oxygen uptake during physical activity. Research shows that from age 25 years to age 65 years, the maximal intake of oxygen reduces by almost 5 ml per kg per min [17]. In analyzing the effect of our main independent variables on metabolic syndrome and its factors, we found it important to consider this factor. Gender was categorized as male and female. We compared other racial ethnic groups (Non-Hispanic Blacks, Mexican Americans, other Hispanics, Asians and other Races) with non-Hispanic Whites. We included education on an increasing level as laid down by NHANES (Tables 1a and 1b). We dichotomized physical activity as participation in at least moderate physical activity (at least 10 min of continuous daily recreational activity apart from all other activities) or not.

2.6. Control variables endogenous to recreational substance use

Married participants were compared to all other participants in other marital categories listed in NHANES. Poverty to income ratio was classified on an increasing level (Table 1a). Weekly frequency of alcohol intake as reported by participants was estimated and included in the model on an increasing level. Response to the

Table 1a
Demographic characteristics of participants by cigarette smoking and marijuana use status.

Variable	Sample size, (%)	Cigarette smoking Status, %			Marijuana use Status, %		
		Current	Past	Never	Regular	Non-regular	Never
Gender							
Male	1499 (50.87)	28.88	14.54	52.29	32.11	25.77	39.65
Female	1552 (49.13)	19.01	18.83	66.44	20.03	28.44	54.21
Race							
Non-Hispanic Whites	1113 (36.46)	31.09	20.49	48.43	32.70	33.51	33.78
Non-Hispanic Blacks	793 (25.99)	25.00	11.74	63.26	31.48	25.66	42.86
Mexican Americans	329 (10.78)	16.72	19.15	64.13	15.81	23.10	61.09
Other Hispanics	281 (9.21)	18.15	19.22	62.63	19.57	21.71	58.72
Asians	427 (14.00)	11.94	13.11	74.94	7.96	18.74	73.30
Other Race	108 (3.54)	29.63	14.81	55.56	40.74	28.70	30.56
Marital status							
Married	1371 (44.94)	18.67	19.91	61.42	20.00	27.52	52.48
Never married	920 (30.15)	23.18	11.64	65.18	28.48	28.26	43.26
Widowed	42 (1.38)	35.71	23.81	40.48	35.71	23.81	40.48
Divorced	275 (9.01)	33.09	22.18	44.73	33.45	29.82	36.73
Separated	123 (4.03)	33.33	10.57	56.10	22.76	25.30	52.03
Living with partner	320 (10.49)	36.56	14.37	49.06	39.81	20.06	40.13
Country of birth							
USA	2154 (70.65)	28.84	16.77	54.39	34.06	31.88	34.06
Other countries	895 (29.35)	12.51	16.54	70.95	7.26	15.31	77.43
Education							
<9th grade	149 (4.88)	22.82	22.15	55.03	12.75	8.72	78.52
9th to 11th grade	403 (13.21)	42.43	18.11	39.45	35.82	19.90	44.28
High school graduate	620 (20.32)	33.28	16.64	50.08	33.12	21.65	45.23
Some college/AA degree	1008 (33.04)	24.90	15.97	59.13	29.07	30.85	40.08
:::College graduate	871 (28.55)	8.15	16.07	75.77	15.73	32.84	51.44
Age groups (years)							
20–25	543 (17.80)	20.85	6.64	72.51	29.83	28.55	41.62
26–35	758 (24.84)	26.25	15.17	58.58	29.50	28.04	42.46
36–49	1015 (33.37)	24.14	16.85	59.01	22.76	26.80	50.44
50–60	735 (24.09)	23.95	25.58	50.48	24.76	25.17	50.07
PIR							
<1.00	753 (26.39)	34.79	13.94	51.26	32.49	24.10	43.41
1.00–2.99	1048 (36.73)	27.79	17.19	55.01	28.91	24.24	46.85
3.00–4.99	555 (19.45)	15.32	17.48	67.21	19.28	33.51	47.21
>5.00	497 (17.42)	10.06	19.72	70.22	20.52	33.80	45.67

Percentages are row percentages. Chi square tests (*p*-values not included in table) showed significant differences among the various groups by smoking and marijuana use status. PIR = Family income to poverty ratio.

Table 1b
Clinical and laboratory characteristics of participants by cigarette smoking and marijuana use.

Variable	Sample size	Overall percentage	Current smoking Status, %			Marijuana use Status, %		
			Current	Past	Never	Regular	Non-regular	Never
Clinical examination								
High WC	2996	49.80	22.65	18.57	58.78*	25.49	26.43	48.09
High blood pressure	3051	33.53	26.00	20.33	53.67***	26.13	26.03	47.85
Laboratory investigation								
High FPG	3051	20.88	24.96	20.57	54.47**	25.47	25.63	48.90
High Serum Triglycerides	3051	18.32	26.65	21.47	51.88***	26.12	28.09	45.80
Low Plasma HDLC	3051	39.63	27.79	16.46	55.75***	24.75	26.66	48.59
Components of MetS		Average ± SE						
Waist circumference, cm	1338	97.8 ± 0.8	98.4 ± 0.9	99.8 ± 1.8	97.1 ± 0.8***	98.5 ± 1.4	97.7 ± 1.1	97.5 ± 0.8*
SBP, mm Hg	1325	118.6 ± 0.8	121.7 ± 1.7	119.9 ± 1.6	117.0 ± 0.9***	120.3 ± 1.6	117.3 ± 0.9	118.2 ± 0.9*
DBP, mm Hg	1325	71.9 ± 0.6	71.8 ± 1.0	73.9 ± 1.0	71.2 ± 0.7***	72.0 ± 0.8	72.3 ± 0.8	71.5 ± 0.8
FPG, mg/dl	1355	101.6 ± 1.1	102.2 ± 1.4	104.6 ± 3.3	100.6 ± 1.4	102.6 ± 2.9	101.5 ± 1.5	101.01 ± 1.2
Serum triglycerides, mm/dl	1341	132.2 ± 6.4	149.1 ± 6.6	135.2 ± 9.8	124.8 ± 6.4***	139.2 ± 8.1	124.2 ± 8.2	133.0 ± 9.1
HDL cholesterol, mm/dl	1342	51.7 ± 0.6	49.8 ± 1.3	52.3 ± 1.1	52.3 ± 0.5**	50.9 ± 1.2	52.1 ± 0.9	52.1 ± 0.6

Tests of significance for row percentages are based on chi-square tests, for continuous variables are *F*-tests and averages shown are weighted averages. WC, waist circumference; FPG, fasting plasma glucose; HDCL, high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; *Significance at <0.05; **Significance at <0.01; ***Significance at <0.001 for row differences.

question "have you ever even once used (a) cocaine, (b) heroin or (c) methamphetamine?" was dichotomized as yes, for a positive answer to use of any one of them or no, if none of them has ever been used. Participants were also asked: have you ever had rehabilitation? We included the response on a dichotomized level as yes or no (Table 1a). Those who responded yes to the question (do you have health insurance?) were compared to those who said no for analysis in the multivariate model.

2.7. Statistical methods

We downloaded data using SPSS and analyzed with Stata/MP 11.2 software package. We compared basic demographic and clinical variables by cigarette smoking and marijuana use status. Unadjusted and multivariate logistic regression analysis was used to determine the association between cigarette smoking and marijuana use with metabolic syndrome and its compo- nents. Emphasis was placed on the duration (years) of smoking cigarette and/or marijuana use. We applied the appropriate weights in both our bivariate and multivariate analysis. The model, adjusted for age, gender, education, poverty to income ratio, participation in at least moderate physical activity, weekly alcohol use, other illicit drug use (methamphetamine, heroin or cocaine), having had rehabilitation, marital status and having health insurance. We considered p-value below 0.05 as statistically significant.

3. Results

3.1. Demographic and clinical characteristics

The total sample consisted of 3051 participants, 50.9% men and 49.1% women with an average age of 38.7 ± 11.7 years (average weighted age was 39.6 ± 0.7, not shown in table) ranging from 20 to 59 years. Overall 59.3% of study participants were nonsmokers, 24.0% were current smokers and 16.7% were former smokers. Approximately 47.0% of study participants were regular marijuana users, 26.2% have never used marijuana while 27.0% were non-regular users of marijuana. Among those who were regular marijuana users, 47.7% were current cigarette smokers as well, 25.7% were past cigarette smokers and 26.6% have no history of tobacco use (not shown in table). The demographic distribution by cigarette smoking or marijuana use status is shown in Table 1a. The prevalence and weighted averages of the components of metabolic syndrome are shown in Table 1b. Apart from fasting glucose, there are significant differences in these factors by cigarette smoking status. Stratifying by marijuana use status shows significant differences for systolic blood pressure and waist circumference. The prevalence of metabolic syndrome among all the study participants is 23.5%.

3.2. Unadjusted results

Unadjusted logistic regression shows that current smokers have an odds ratio of 1.43 (95% CI: 1.13, 1.81) for having high blood pressure, and 1.61 (95% CI: 1.01, 2.55) for having high triglyceride levels than nonsmokers (Table 2). The unadjusted model for marijuana use shows that each year of using marijuana is associated with an odds ratio of 1.02 (1.00, 1.04) of having metabolic syndrome. A significant increased odds with each year of cigarette smoking is observed for hypertension (OR: 1.03, 95% CI: 1.02, 1.03), hypertriglyceridemia (OR: 1.03, 95% CI: 1.02, 1.04) and hyperglycemia (OR: 1.02, 95% CI: 1.00, 1.03). Each year increase in marijuana use is also associated with a significant increase in odds for hypertension (OR: 1.01, 95% CI: 1.00, 1.02), hypertriglyceridemia (OR: 1.01, 95% CI: 1.00, 1.03) and hyperglycemia (OR: 1.02, 95% CI: 1.00, 1.03) (Table 2).

3.3. Adjusted results

Multivariate logistic regression analysis adjusted for age, gender, education, participation in at least moderate physical activity, weekly alcohol use, income to poverty ratio, having health insurance, marital status, other illicit drug use and having had rehabilitation. Controlling for these factors, the odds ratio for each year increase of using marijuana is 1.05 (95% CI: 1.01, 1.09) for metabolic syndrome and 1.04 (95% CI: 1.01, 1.07) for hypertension (Table 3a). In this same model, each year of smoking cigarettes is associated with an odds ratio of 1.03 (95% CI: 1.00, 1.06) for hypertension as well as 1.03 (95% CI: 1.01, 1.05) for hyperglycemia. By marijuana use status, the results show significant reduced odds for MetS (OR 0.23; 95% CI: 0.06, 0.90), hypertension (OR 0.31; 95% CI: 0.13, 0.70) and hypertriglyceridemia (OR 0.70; 95% CI 0.50, 0.99) among regular marijuana users compared to non-users (Table 3a). We did not find significant associations between smoking cigarettes or marijuana use and low levels of HDL in this analysis. Table 3b shows results for multivariate analysis separately among cigarette smokers and separately for marijuana users.

4. Discussion

Research supports the science that the endocannabinoid system as well as chronic smoking of cannabis is associated with

Table 2
Unadjusted analysis of having metabolic syndrome or risky levels of components of metabolic syndrome.

Variable	Cigarette, odds ratio (95% CI)			Marijuana, odds ratio (95% CI)		
	A. Years of smoking		B. Smoking status	C. Years of use		D. Use status
Metabolic syndrome						
	1.00 (0.99, 1.02)	Current	1.51 (0.80, 2.87)	1.02 (1.00, 1.04)	Regular	1.01 (0.56, 1.84)
		Past	1.64 (0.97, 2.79)		Non-regular	0.87 (0.67, 1.14)
Abdominal obesity						
	1.01 (0.09, 1.01)	Current	0.92 (0.66, 1.28)	1.01 (0.99, 1.02)	Regular	0.81 (0.59, 1.11)
		Past	1.11 (0.74, 1.66)		Non-regular	0.89 (0.70, 1.11)
Hypertension						
	1.03 (1.02, 1.03)	Current	1.43 (1.13, 1.81)	1.01 (1.00, 1.02)	Regular	1.82 (0.57, 1.19)
		Past	1.53 (0.94, 2.50)		Non-regular	0.94 (0.72, 1.23)
Hyperglycemia						
	1.02 (1.00, 1.03)	Current	1.46 (0.86, 2.48)	1.01 (1.00, 1.03)	Regular	1.10 (0.52, 1.34)
		Past	1.22 (0.69, 2.16)		Non-regular	1.01 (0.56, 1.41)
Hypertriglyceridemia						
	1.03 (1.02, 1.04)	Current	1.61 (1.01, 2.55)	1.02 (1.00, 1.03)	Regular	1.21 (0.71, 2.07)
		Past	1.40 (0.93, 2.11)		Non-regular	1.21 (0.80, 1.82)
Low HDL cholesterolemia						
	1.00 (0.09, 1.00)	Current	1.28 (0.93, 1.75)	1.01 (0.99, 1.02)	Regular	0.97 (0.65, 1.45)
		Past	0.95 (0.63, 1.43)		Non-regular	0.88 (0.61, 1.27)

A, The relationship between each year increase in cigarette smoking with the listed variables; B, The relationship between current smoker or past smoker compared to non-smokers and the listed variables; C, The relationship between each year increase in marijuana use and the listed variables; D, The relationship between regular marijuana users or non-regular marijuana users and the listed variables.

Table 3a
Multivariate analysis of metabolic syndrome/components with years of cigarette and MJ use controlling for other risk factors.

	Metabolic SYN	AO	HPT	HYPGLY	HYPTRIG	Low HDLC
Marijuana use[1]	1.05 (1.01, 1.09)	1.03 (0.99, 1.07)	1.04 (1.01, 1.07)	1.01 (0.97, 1.05)	1.02 (0.99, 1.04)	1.03 (0.99, 1.06)
Cigarette smoking[1]	1.00 (0.09, 1.00)	1.00 (0.09, 1.01)	1.03 (1.00, 1.06)	1.03 (1.01, 1.05)	0.99 (0.18, 5.45)	1.00 (0.09, 1.00)
Regular MJ user	0.23 (0.06, 0.90)	0.45 (0.14, 1.43)	0.31 (0.13, 0.70)	0.61 (0.18, 2.08)	0.70 (0.50, 0.99)	0.53 (0.19, 1.44)
Cigarette smoker	1.24 (0.96, 1.59)	0.93 (0.74, 1.17)	0.81 (0.49, 1.36)	0.74 (0.52, 1.04)	0.68 (0.33, 1.40)	0.97 (0.77, 1.23)
MJ Quantity[2]	1.25 (0.80, 1.95)	1.05 (0.77, 1.41)	0.98 (0.75, 1.28)	1.17 (0.82, 1.67)	1.03 (1.01, 1.05)	1.07 (0.80, 1.43)
Cigarette Quantity[2]	0.99 (0.90, 1.02)	0.98 (0.96, 1.00)	1.00 (0.97, 1.02)	0.99 (0.97, 1.02)	0.99 (0.96, 1.02)	1.01 (0.98, 1.03)
Age 25+	2.70 (1.60, 4.54)	2.75 (1.10, 6.84)	3.95 (2.06, 7.57)	2.68 (1.45, 4.97)	2.05 (1.01, 4.15)	1.41 (0.73, 2.73)
Males	0.94 (0.58, 1.50)	0.28 (0.19, 0.42)	1.29 (0.87, 1.91)	1.81 (1.20, 2.72)	1.60 (1.06, 2.41)	0.84 (0.55, 1.26)
Whites	1.08 (0.67, 1.73)	1.42 (0.99, 2.04)	1.08 (0.81, 1.45)	0.98 (0.72, 1.33)	1.16 (0.82, 1.65)	1.07 (0.70, 1.62)
Education	0.83 (0.72, 0.94)	0.82 (0.67, 1.00)	0.93 (0.79, 1.11)	0.89 (0.76, 1.04)	1.06 (0.88, 1.28)	0.95 (0.76, 1.19)
PIR[3]	0.87 (0.76, 1.01)	0.91 (0.84, 0.99)	0.92 (0.82, 1.03)	1.01 (0.90, 1.14)	0.95 (0.85, 1.06)	0.91 (0.78, 1.05)
Insured	1.33 (0.76, 2.35)	1.07 (0.73, 1.58)	1.77 (1.02, 3.07)	1.22 (0.91, 1.63)	1.00 (0.60, 1.66)	1.40 (0.93, 2.10)
Married	1.50 (0.87, 2.57)	1.12 (0.74, 1.69)	0.99 (0.60, 1.64)	1.03 (0.71, 1.47)	1.33 (0.89, 1.98)	1.31 (1.01, 1.70)
Moderate PA[4]	0.82 (0.46, 1.46)	0.94 (0.65, 1.36)	1.05 (0.84, 1.32)	0.75 (0.54, 1.04)	0.94 (0.61, 1.47)	0.82 (0.59, 1.14)
Alcohol Intake[5]	1.10 (0.61, 1.98)	1.47 (0.95, 2.25)	1.82 (1.07, 3.08)	0.83 (0.44, 1.57)	1.45 (0.90, 2.34)	1.06 (0.76, 1.49)
Other drug use	1.48 (0.86, 2.58)	1.16 (0.52, 2.58)	0.63 (0.40, 0.99)	0.88 (0.61, 1.26)	1.02 (0.99, 1.04)	1.21 (0.78, 1.87)
Rehabilitation	0.83 (0.37, 1.86)	0.67 (0.36, 1.25)	1.04 (0.54, 2.00)	0.94 (0.44, 2.01)	0.99 (0.18, 5.45)	0.67 (0.36, 1.27)

[1]Each year increase in use/smoking; [2]Number of joints/cigarettes; [3]Family Income-to-Poverty Ratio; [4]At least moderate physical activity (recreational); [5]Weekly. Bold values indicate significance at alpha ::; 0.05. MJ, marijuana; SYN, syndrome; AO, abdominal obesity; HPT, hypertension; HYPGLY, hyperglycemia; HYPTRIG, hypertriglyceridemia; HDL, high density lipoprotein cholesterol.
All odds ratios with 95% CI starting from 1 and not in bold are due to rounding and have p-values above 0.05.

Table 3b
Adjusted analysis for metabolic syndrome and components separately for cigarette smoking and marijuana use.

Variable	Cigarette use Odds ratio (95% CI)		Marijuana use Odds ratio (95% CI)	
	(A) Years of smoking	(B) Current	(A) Years of use	(B) Regular user
Metabolic syndrome	1.00 (0.09, 1.00)	1.17 (0.90,1.52)	1.05 (1.01, 1.09)	0.25 (0.06, 1.02)
Abdominal obesity	1.01 (0.99, 1.03)	0.84 (0.55, 1.29)	1.03 (0.99, 1.07)	0.42 (0.13, 1.36)
Hypertension	1.04 (1.01, 1.07)	0.67 (0.40, 1.11)	1.05 (1.02, 1.09)	0.26 (0.10, 0.67)
Hyperglycemia	1.03 (1.01, 1.05)	0.71 (0.43, 1.08)	1.02 (0.98, 1.06)	0.50 (0.13, 1.89)
Hypertriglyceridemia	1.04 (1.02, 1.06)	0.62 (0.46, 0.85)	1.03 (1.01, 1.06)	0.76 (0.15, 3.97)
Low HDL cholesterolemia	1.00 (0.09, 1.00)	0.96 (0.77, 1.20)	1.02 (0.99, 1.05)	0.54 (0.18, 1.55)

CI, confidence interval; adjusted analysis is based on the model in Table 3a and shows only the odds ratios for respective dependent variables in the table for: Each year increase in smoking cigarette. Current smoker compared to non-smoker or former smoker. Each year increase in marijuana use. Regular marijuana user compared to non-regular or non-user.

metabolic irregularities including abdominal obesity and insulin resistance [18–21]. In our research, basic examination characteristics show that, among the study participants, regular marijuana users had an average waist circumference higher (98.5 ± 1.4) than that for the general participants (97.8 ± 0.8). Research also shows that cigarette smoking causes inflammation which is a precursor for metabolic syndrome. Smoking increases the production of pro-cytokines, reduces levels of anti-inflammatory cytokines [22] and increases pathologic levels of inflammation-sensitive proteins like alpa1-antitripson, fibrinogen, etc. [23]. In our study, by status, unadjusted analysis showed no significant increase in odds for MetS among those who smoke cigarettes or those who use marijuana when compared to those who do not (Table 2). Current cigarette smokers, however, had 43.0% increase in odds for high blood pressure and 61.0% increase for high serum triglycerides compared to nonsmokers.

The relationship between metabolic syndrome and marijuana use or cigarette smoking appears to be associated with the years of use/smoking. Our results show significant associations between years of marijuana use or cigarette smoking and metabolic syndrome as well as some of its components. This finding needs further investigation with respect to the duration of use or cutoff point that is likely to put one at the most disadvantage for metabolic abnormalities. In multivariate analysis, even though by cigarette smoking or marijuana use status the relationship may seem protective, we find otherwise by duration of use. Each year of marijuana use was associated with a significant 5.0% increase in odds of having metabolic syndrome and 4.0% increase in odds of having hypertension (Table 3a). Each year increase in smoking cigarette also increases the odds of having hypertension by 3.0% as well as hyperglycemia by 3.0%. Separate models that concentrated on smoking alone or marijuana use alone yielded results that were similar (Table 3b).

With respect to findings in existing research, marijuana users and cigarette smokers may be showing better metabolic profiles by status. However, the relationship between duration of use in this study draws our attention to a possible long-term adverse effect. For example in our model, marijuana users are 77.0% less likely to have metabolic syndrome, 69.0% less likely to have hypertension and 30.0% less likely have hypertriglyceridemia compared to non-users, however considering years of use, the relationship shows a higher odds for MetS and some of its components. This finding suggests that, the duration of marijuana use or smoking is an important factor in assessing metabolic health and that with prolonged years of use, the effects on metabolic health may be unfavorable. It is worth noting that we considered the effect of age transition on metabolic factor as well.

Although the harmful effect of cigarette smoking on cardiovascular health is well known [24–27], the effect on some metabolic health factors is not definite [11,12] neither is that for marijuana use. Universal findings on this effect can have important implications for public health and chronic disease management.

With respect to factors of metabolic syndrome, some research show that marijuana use is associated with lower insulin levels [28] as well as less prevalence of diabetes among users and that it needs to be investigated in the management of diabetes [29]. Marijuana (cannabis) exerts its effect on the endocannabinoid

system by acting on cannabinoid receptors. Cannabinoid receptors are stimulated by endocannabinoids that are endogenous ligands. Both cannabinoid receptor 1 (CB1) and receptor 2 (CB2) are involved in regulation of energy balance, appetite, insulin sensitivity and lipid metabolism [15,21,30,31]. Research on marijuana and metabolic syndrome is still geminating and without definite results. Research conducted by Penner et al. [28] based on a multiple linear regression model concluded that marijuana use was associated with lower levels of fasting insulin and lower waist circumference, with the inference that marijuana users may have a good glycemic profile. A cross-sectional study by Muniyappa et al. [20] on the chronic effect of marijuana smoking on metabolic syndrome showed that those who smoke marijuana had a higher percent abdominal visceral fat, lower plasma HDL cholesterol, lower adipocyte insulin resistance index and lower percent free fatty acid (FFA) suppression during an oral glucose tolerance test (OGTT). A study by Thompson and Hay [32,33] questions the use of a linear regression in estimating this association and consequently recommend other analysis and models that consider factors endogenous to marijuana use. In our study we used logistic regression analysis and controlled for some factors endogenous to recreational substance like other drug use, rehabilitation, marriage, alcohol use, health insurance and income to poverty ratio. Available literature on smoking also shows that smoking has nonlinear relationships with factors of metabolic syndrome especially among moderate smokers, but heavy smoking of 20 cigarettes or more daily leads to adverse levels of metabolic factors [11]. In this exploratory study we controlled for increasing quantity of cigarette or marijuana used. A near significant reduction in abdominal obesity was found with increased quantity smoked. This relationship between smoking and weight or abdominal obesity has been demonstrated in some studies with varying results as well [34]. Even though reported bias may play a role, it is of interest to examine the effect of quantity of marijuana smoked in subsequent models because there is a biological basis between smoking and weight. Whilst considering years of marijuana use or cigarette smoking, the use of biological markers for smoking and marijuana use with cut offs might also be of importance in future studies to assess the causal effects of recreational substance use on metabolic health using longitudinal data.

4.1. Strengths and limitations

A major strength of the study is the use of NHANES data. The NHANES has extensive and quality assured demographic, lifestyle, clinical and laboratory data for our purposes. The survey also embraces a large nationally representative sample. Our major limitation is the use of cross-sectional data as well as reported information which may be subject to recall or reporting bias. Also cross-sectional data ideally estimate associations and not causal relationships. However, for our exploratory purpose, the NHANES data is appropriate. Another main factor to consider in research on MetS is diet; however, we were unable to do so because the data were unavailable at the time of this study. As a proxy we included PIR, health insurance and education as a means of controlling for nutrition and health practices since income and education are highly associated with diet and healthy choices. It is worth noting that we assigned both past smokers and non-regular users a duration of zero recreational substance use. A way to quantify the years of use among past smokers and non-regular marijuana users would also help to better assess the association between duration of recreational substance use and metabolic syndrome. Another important factor could be the use of biological markers of recreational substance use. For example, Delta-9-tetrahydrocannabinol (THC) is a marker of marijuana use; however even though NHANES has data on cotinine as a marker for cigarette smoking, laboratory results on THC is yet to be available.

5. Conclusion

Increased years of marijuana use or cigarette smoking are associated with unhealthy levels of the components of metabolic syndrome among adults in the US. With the inclination for recreational marijuana use, this relationship may be considered critically to avert future metabolic complications. The duration of marijuana use or cigarette smoking is potentially an important factor in assessing metabolic health. With prolonged years of use, the effects on metabolic health might be unfavorable. We also found that marijuana use like cigarette smoking is also associated with hypertension. Our research seeks to add to the geminating interest in research on metabolic syndrome and marijuana use and cigarette smoking as an illuminating pathway to addressing recreational substance use and factors associated with cardiometabolic diseases, a major cause of morbidity and mortality.

Conflict of interest

The authors have none to declare.

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CHAPTER 3

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Relationship between Years of Marijuana Use and the Four Main Diagnostic Criteria for Metabolic Syndrome among United States Adults

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Abstract

Objective: Research on marijuana use suggests a protective effect on metabolic syndrome. National Cholesterol Education Program, Adult Treatment Panel III, World Health Organization, European Group for the study of Insulin Resistance and International Diabetes Federation have different criteria for metabolic syndrome. Definitions of both marijuana use and criteria for metabolic syndrome may influence the observed effects. We examine the relationship of years of marijuana use with the four common definitions of metabolic syndrome.

Method: This is a cross-sectional study of 3051 adults aged ≥ 20 years who participated in the National Health and Nutrition Examination Survey 2011-2012. Only participants who responded to the question, "Have you ever even once used marijuana or hashish?" were enrolled. Using multivariate logistic regression, we estimated odds ratios for metabolic syndrome with each year of marijuana use.

Results: Adjusted odds ratios (AOR) for having metabolic syndrome with each increase in year of marijuana use was 1.05 (95% CI: 1.02, 1.08) using National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria. Respective AOR using International Diabetes Federation (IDF) was 1.08 (95% CI: 1.04, 1.13) and 1.05 (95% CI: 1.04, 1.13) using World Health Organization (WHO) or European Group for the study of Insulin Resistance (EGIR) criteria. Using ATP III or IDF criteria, the adjusted odds ratio of having hypertension (AOR Hyp) for each year of marijuana use was 1.07 (95% CI: 1.03, 1.12). Using WHO criteria, AOR Hyp was 1.05 (95% CI: 1.01, 1.09) and 1.08 (95% CI: 1.03, 1.12) using EGIR. All the applicable criteria show increased odds for abdominal obesity: AOR 1.06 (95% CI: 1.00, 1.11) (ATP III), 1.09 (95% CI: 1.05, 1.14) (EGIR) or 1.07 (95% CI: 1.01, 1.13) (IDF). Adjusted odds ratio for having high oral glucose tolerance test levels was 1.12 (95% CI: 1.07, 1.18) using WHO and EGIR criteria.

Conclusion: Irrespective of the criteria for metabolic syndrome, each year of marijuana use showed increased odds of having metabolic syndrome, hypertension or high oral glucose tolerance test levels. This increased odd is in contrast to most findings in literature. The small, yet consistent increase in odds for hypertension was slightly higher than that observed with cigarette smoking. Recreational marijuana use may be detrimental to cardiovascular health. A standardized definition of marijuana use will be relevant for further investigation.

Keywords: Cannabis; Cardiovascular disease; Cigarette; Marijuana; Metabolic syndrome; Tobacco

Introduction

Marijuana is a psychoactive substance that induces relaxation and euphoria. Marijuana is classified as a schedule 1 drug by the drug enforcement administration (DEA) and is an illicit compound under federal law. However, by the end of election 2016, 28 states had legalized medical marijuana. Eight states and Washington DC also permit adult recreational marijuana use. Support for legalization of marijuana is on ascendancy [1]. Like cigarette, the main route of administration of marijuana is smoking and whereas the detrimental effect of tobacco/cigarette on cardiovascular health is established, that of marijuana is unknown.

Metabolic syndrome (MetS) is a constellation of cardiovascular risk factors and is a condition associated with detrimental cardiovascular prognosis. Because cardiovascular disease (CVD) is a leading cause of mortality worldwide [2], the prevalence of metabolic syndrome may be an important determinant of the health status of a nation. The prevalence of metabolic syndrome generally increases with age. During the period 2003 to 2012, metabolic syndrome prevalence in the United States (US) was about 18.0% among adults aged 20-39 years, 35.0% among adults aged 40-59 years and 46.7% among adults aged 60 years and above [3]. In 2012, an estimated 31.0% of all global deaths were due to CVDs [4]. Studies on tobacco and marijuana are inconclusive

on their associations with metabolic syndrome and its components [2,5]. Metabolic syndrome has varying criteria. National Cholesterol Education Program, Adult Treatment Panel III (ATP), World Health Organization (WHO), European Group for the study of Insulin Resistance (EGIR) and International Diabetes Federation (IDF) have different criteria for metabolic syndrome. Definitions of both marijuana use and criteria for metabolic syndrome may influence the observed effects. We examine the relationship of years of marijuana use with the four common definitions of metabolic syndrome. Our hypothesis is that the definition used for metabolic syndrome may change the estimates of the associations between marijuana use and metabolic syndrome.

Variable	Sample Size (%)	Race					
		NHW	NHB	MA	OHISP	ASIANS	ORACE
Marijuana Use[***]							
Never	1427 (46.80)	33.78	42.86	61.09	58.72	73.30	33.56
Non-regular	824 (27.03)	33.51	25.66	23.10	21.71	18.74	28.70
Regular	798 (26.17)	32.7	31.48	15.81	19.57	7.60	40.74
Cigarette smoking[***]							
Never	1807 (59.25)	48.43	63.26	64.13	62.63	74.94	55.56
Past	510 (16.72)	20.49	11.74	19.15	19.22	13.11	14.81
Current	733 (24.03)	31.09	25.00	16.72	18.15	11.94	29.63
Gender[*]							
Male	1552 (50.87)	52.02	46.66	54.71	48.04	53.40	55.56
Female	1499 (49.13)	47.98	53.34	45.29	51.96	46.60	44.44
Marital Status[***]							
Married	1371 (44.94)	49.15	31.65	52.28	41.28	56.91	38.89
Other	1680 (55.06)	50.85	68.35	47.72	58.72	43.09	61.11
Country of Birth[***]							
USA	2154 (70.65)	95.06	89.91	41.77	26.79	19.67	80.56
Other Countries	895 (29.35)	4.94	10.09	58.23	73.21	80.33	19.44
Education[***]							
≤ High School Graduate	1172 (38.41)	33.42	38.97	69.6	52.31	19.44	29.63
≥ Some College	1879 (61.59)	68.58	61.03	30.6	47.69	80.56	70.37
Age groups (Years)[**]							
20-25	543 (17.80)	15.09	20.43	15.50	17.08	19.44	28.70
Above 25	2508 (82.20)	84.91	79.57	84.50	82.92	80.56	71.30
PIR[***]							
<1.00	753 (26.39)	24.91	31.12	30.95	30.15	15.56	27.18
1.00 to 2.99	1048 (36.73)	36.02	36.93	42.52	43.13	29.16	38.83
3.00 to 4.99	555 (19.45)	19.26	19.09	18.03	17.94	24.04	14.56
>5.00	497 (17.42)	19.81	12.86	8.50	8.78	31.20	19.42
Other Drug Use[***]							
No	2504 (82.23)	74.41	87.01	80.49	87.14	94.6	71.30
Yes	541 (17.77)	25.59	12.99	19.51	12.86	5.40	28.70

Ever had rehabilitation[***]							
No	2877 (94.30)	92.54	92.18	97.57	96.44	99.30	92.59
Yes	174 (5.70)	7.46	7.82	2.43	3.56	0.70	7.41

Table 1a: Proportions of recreational substance use and demographic characteristics of participants stratified by race, Percentages are column percentages. Chi square tests ([*]P<0.05, [**]P<0.01, [***]P<0.001) show significant differences among the various racial ethnic groups. MA: Mexican Americans; NHW: Non-Hispanic Whites; NHB: Non-Hispanic Blacks; OHISP: Other Hispanics; ORACE: Other Race or Multiracial; PIR: Family Income to Poverty Ratio.

Literature Review

Metabolic syndrome is a co-occurrence of hypertension, hyperlipidemia, hyperglycemia and visceral obesity. Metabolic syndrome is associated with cardiometabolic pathology [6]. There is no unified definition [7,8] for MetS, however, the definition by the National Cholesterol Education Program, Adult Treatment Panel III (ATP III) is widely adopted because of its clinical applicability [8]. In accordance with ATP III, MetS is a co-occurrence of any three of the following: Hypertension, hyperglycemia, abdominal obesity, reduced high density lipoprotein cholesterol (HDL-C) or hypertriglyceridemia. By WHO standard, MetS is a diagnosis of diabetes or increased two hour oral glucose tolerance test (OGTT) or fasting insulin levels plus any two or more of the following: hypertension, obesity, high plasma triglycerides, low plasma HDL-C or albumin creatinine ratio ≥ 30. By EGIR criteria, MetS consists of fasting insulin level above 75th percentile of cohorts, and two or more of the following: hypertension, abdominal obesity, hypertriglyceridemia or low HDL-C. The IDF criteria require increases in ethnicity-specific waist circumference and any two or more of the following: hypertension, hypertriglyceridemia, low plasma HDL-C and high fasting plasma glucose or diagnosis of diabetes [8].

Results from research on marijuana use and MetS suggest a protective effect of marijuana use for MetS and some of its components [5,9]. Although some therapeutic effects of extracts of cannabis (marijuana plant) can be anticipated [10], these benefits may not apply to recreational use of marijuana. In the US, tobacco and marijuana are the most common substances of abuse after alcohol [11]. Statistics from the 2014 National Survey of Drug Use and Health, under the Substance Abuse and Mental Health Services Administration, show that among US adults aged 18-25 years, the lifetime prevalence of alcohol, cigarette and marijuana use were 83.4%, 56.1% and 52.6%, respectively whilst among US adults aged 26 years and above, lifetime prevalence were 88.3%, 67.5% and 46.1%, respectively [12]. With a likely increase in marijuana use arising from legalization of marijuana, it is important to assess the relationship with determinants of cardiovascular disease.

Method

Data and variables

This is a cross-sectional study of adults aged 20 years and above who participated in the National Health and Nutrition Examination Survey (NHANES) 2011-2012. Only participants who responded to the question, "Have you ever even once used marijuana or hashish?" were enrolled.

Dependent variable: Our main dependent variable was MetS. We used the four most widely accepted definitions of MetS. In accordance with 2005 modification of ATP III criteria for Mets, we classified participants as having MetS if they had a co-occurrence of three or more of the following: Hypertension-an average blood pressure >130/85 mm Hg or use of medication for hypertension; Hyperglycemia-defined as fasting plasma glucose (FBG) ≥ 100 mg/dl or use of medication for diabetes; Abdominal obesity or high waist circumference-defined as females with waist circumference >88.0 cm and males with waist circumference >102.0 cm; Low HDL cholesterolemia-defined as plasma HDL-C levels <50 mg/dl for females and <40 mg/dl for males or use of medications for hypercholesterolemia; and Hypertriglyceridemia-defined as plasma triglycerides ≥ 150 mg/dl or use of medication for hypercholesterolemia. Details of laboratory and clinical procedures are described in the NHANES manual.

By WHO criteria, participants who said they had been diagnosed with diabetes by a doctor or were using medications for diabetes, or had a two hour oral glucose tolerance test (OGTT) result 140 mg/dl, or fasting insulin levels >25.2 μIU/ml and had any two or more of the following: average blood pressure 140/90 mmHg; body mass index >30 kg/m^2; plasma triglycerides 150 mg/dl; plasma HDL-C levels <39 mg/dl (for females) or <35 mg/dl (for males); and albumin creatinine ratio 30.

By EGIR criteria, participants whose fasting insulin level fell above 75th percentile of this study group and had two or more of the following: average blood pressure ≥ 140/90 mm Hg or use of medications for hypertension; waist circumference ≥ 94 cm if male or ≥ 80 cm if female; plasma triglyceride ≥ 150 mg/dl; HDL-C ≥ 39 mg/dl.

By IDF criteria, ethnicity-specific waist circumference being ≥ 94 cm (for black males) or ≥ 80 cm (for black females); ≥ 102 cm (for white males) or ≥ 88 cm (for white female), and ≥ 94 cm or ≥ 80 cm for males and females respectively who were Asians/Mexican American/ Multiracial and had any two or more of the following: average blood pressure>130/85 mmHg or on medication for hypertension; plasma triglyceride ≥ 150 mg/dl or on anti-cholesterol medications; plasma HDL-C ≤ 50 mg/dl (for females) or ≤ 40 mg/dl (for males); and fasting plasma glucose ≥ 100 mg/dl diagnosis of diabetes by a doctor.

Main independent variable: According to the questions in NHANES, participants who had never used marijuana/hashish were categorized as never marijuana users. Those who said they had used marijuana/hashish but not up to once a month for more than a year were classified as non-regular marijuana users and those who had used marijuana or hashish at least once a month for more than a year were classified as regular marijuana users.

We estimated years of marijuana use by subtracting each participant's age at regular marijuana use from their current age. For participants who were non-regular users of marijuana, we assigned zero years of marijuana use. Our multivariate logistic analysis included only marijuana users (regular users or non-regular-users) to enable us assess the effect among those who had ever used marijuana and avoid placing non-regular marijuana users and never marijuana users on the same level.

Variable	Diagnostic Criteria			
	WHO	EGIR	ATP III	IDF
Metabolic Syndrome				
Overall	9.21	8.55	23.17	23.37
BY SUBSTANCE USE (Yes)				
Regular marijuana	8.40	8.40	20.93	21.3
Current cigarette smoker	9.41	9.14	24.83	24.69
BY RACE (Yes)				
NHW	9.43	9.97	24.71	22.01
NHB	9.21	8.07	25.73	25.98
MA	14.89	10.33	24.62	28.27
OHISP	7.83	5.69	21.71	25.27
ASIANS	5.39	6.79	15.46	18.03
ORACE	8.33	6.48	18.52	19.44
Hypertension				
Overall	10.56	23.89	31.69	31.69
Hyperglycemia				
Overall	19.04	8.19	21.86	23.43
Hyperinsulinemia				
Overall	3.61	61.42	-	-
High OGTT Level				
Overall	5.97	5.97	-	-
Hypertriglyceridemia				
Overall	11.67	11.67	18.49	18.49
Low HDL-C				
Overall	10.49	15.34	34.81	34.81
High WC				
Overall	-	69.59	49.80	64.15
NHW	-	-	-	50.07
NHB	-	-	-	69.59
ASIANS/MA/OHISP/OR	-	-	-	74.57
BMI >30 kg/m^2				
Overall	35.59	-	-	-
High Albumin/Creatinine Ratio				
Overall	13.27	-	-	-

Table 1b: Prevalence in Percentages of Metabolic Syndrome Diagnosis and its Components by the Different Criteria.
NHW: Non-Hispanic Whites; NHB: Non-Hispanic Blacks; MA: Mexican Americans; OHISP: Other Hispanics; ORACE: Other Race or Multiracial; OGTT: Oral Glucose Tolerance Test; HDL-C: High Density Lipoprotein Cholesterol; WC: Waist Circumference; BMI: Body Mass Index.

Other independent variables: We included cigarette smoking. We classified participants who reported they have smoked at least 100 cigarettes their entire life and still smoke every day or some days as current cigarette smokers. Those who have smoked at least 100 cigarettes but do not currently smoke at all were past smokers. Those who had never smoked cigarettes were non-smokers. Non-smokers or past smokers were

assigned zero years of smoking cigarettes. Years of smoking for current smokers was estimated by subtracting reported initial age at regular smoking from their current age.

In the multivariate model, we controlled for age of participant, gender, race, education, marital status, poverty to income ratio (PIR), participation in at least moderate physical activity, days of alcohol use in a week, other recreational substance use (methamphetamine, heroin or cocaine) and participation in rehabilitation. Details of the measurement of these control variables are described in NHANES manual.

Statistical analysis

We used Stata/IC 14.0 software package for analysis. We estimated the proportions of demographic and clinical variables by race to have an appreciation of the differences. Disparities in socioeconomic factors as well as race/ethnicity have been described as important factors for metabolic abnormalities as well as recreational substance use [13,14]. Using logistic regression analysis, we estimated unadjusted and adjusted odds ratios for MetS among regular and non-regular marijuana users. In all analyses we applied the appropriate weights for the NHANES multi-stage survey design and used a two-tailed significance level of α=0.05 (http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/NCHS/MANUALS/WGT_EXEC.PDF).

Results

Demographic and metabolic syndrome characteristics of study participants

Characteristics for the basic demographics and MetS with its components are shown in Tables 1a and 1b, respectively. Overall, 26.2% of participants were regular marijuana users and 24.0% were current cigarette smokers (Table 1a). Among the different racial/ethnic groups, people of other race/Multi-racials had the highest prevalence for marijuana use (40.7%) with Asians having the least (7.6%). Among all participants, the prevalence of other illicit drug use (cocaine, heroin or methamphetamine) was 17.7% whilst multiracial had the highest prevalence (28.7%). A higher proportion of Non-Hispanic Blacks (7.8%) have had rehabilitation compared to Multiracial (7.4%).

Of the four criteria, ATP III and IDF classify more people as having MetS (23.2% and 23.4%, respectively) and WHO criteria classify the least (9.2%) and EGIR (8.6%) (Table 1b). This pattern is also seen for MetS prevalence among marijuana users and cigarette smokers: the proportion of MetS among marijuana users was 21.3% (IDF) and 20.9% (ATP III) whilst the proportion of MetS among cigarette smokers was 26.0% (IDF) and 25.7% (ATP III). By race/ethnicity, ATP III classifies the 25.7% of non-Hispanic Blacks as having MetS. All other criteria predominantly classify Mexican Americans (MA) as having MetS (28.3%-IDF, 14.9%-WHO and 10.3%-EGIR).

Hypertension, hypertriglyceridemia, and Low HDL-C are more prevalent (31.7%, 18.5%, 34.8%, respectively) using ATP III and IDF criteria. The prevalence of hyperglycemia is 21.9% using ATP III and 23.4% using IDF. Disparities in prevalence for other components are shown in Table 1b.

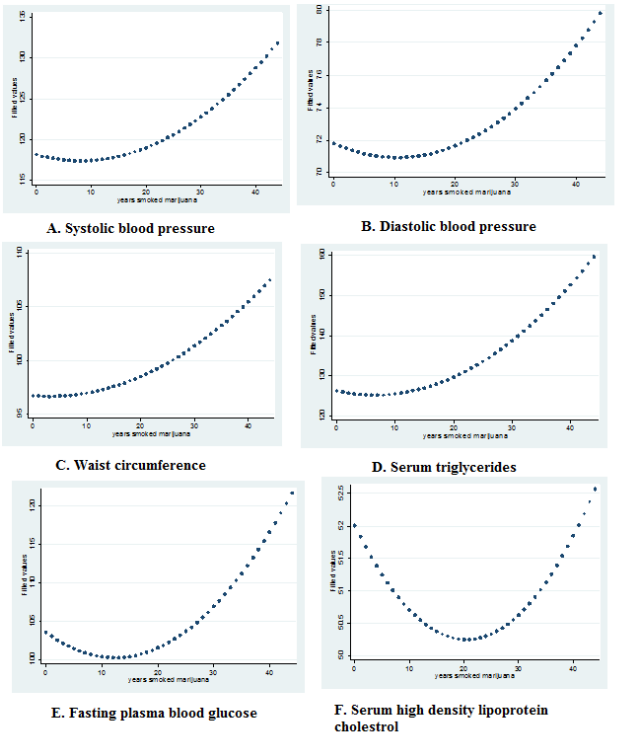

Figure 1: Graphs showing the relationship between components of metabolic syndrome and increasing years of marijuana use (Y-axis shows the respective fitted values of components of MetS).

Components of metabolic syndrome with years of marijuana use

The relationship between components of MetS and years of marijuana use are shown in Figure 1. Curvilinear relationships between years of marijuana use and components of MetS are apparent. The relationship of systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference (WC), plasma triglycerides (TG)

and fasting blood glucose (FBG) with years of marijuana used tend to be J-Shaped. This shows an initial decrease in values but eventual increase. The relationship between plasma high density lipoprotein cholesterol HDL-C and years of marijuana used was U-shaped. This shows an initial decrease and eventual increase.

Bivariate analysis of metabolic syndrome and its components with years of marijuana use and cigarette smoking

By all the criteria, unadjusted analysis showed a universal increase in odds of having MetS with every year of marijuana use. With every year increase in marijuana use, the odds ratios (OR) for having MetS are 1.06 (95% CI: 1.03, 1.08) for ATP III, 1.06 (95% CI: 1.04, 1.08) for WHO, 1.05 (95% CI: 1.02, 1.08) for EGIR and 1.05 (95% CI: 1.03, 1.07) for IDF (Table 2a). By all applicable criteria, for each year of marijuana use, a significant increase in odds is observed for hypertension, hyperglycemia, high oral glucose tolerance test levels, hypertriglyceridemia, abdominal obesity and obesity.

The relationship with cigarette use shows increases in odds for MetS which is only significant by ATP III. For hypertension, hyperglycemia and high OGTT levels a significant increase in odds is demonstrated by all the criteria (Table 2b).

Multivariate analysis

For every year of marijuana use, adjusted odds ratio (AOR) for having MetS (controlling for years of smoking, gender, age, marriage, education, country of birth, PIR, having health insurance, participating in at least moderate physical activity, weekly alcohol intake, other illicit drug use and undergoing rehabilitation) by ATP III and IDF criteria was 1.05 (95% CI: 1.02, 1.08). By WHO, AOR was 1.08 (95% CI: 1.04, 1.13) and by EGIR criteria, AOR was 1.06 (95% CI: 1.01, 1.11) (Table 3a).

Each year of marijuana use showed AORs for hypertension as: 1.07 (95% CI: 1.03, 1.12) by ATP III and IDF, 1.05 (95% CI: 1.01, 1.09) by WHO and 1.08 (95% CI: 1.03, 1.12) by EGIR All the applicable criteria show increased odds for abdominal obesity: 1.06 (95% CI: 1.00, 1.11) by ATP III, 1.09 (95% CI: 1.05, 1.14) by EGIR and 1.07 (95% CI: 1.01, 1.13) by IDF. For obesity the AOR was 1.03 (95% CI: 1.01, 1.06) according to WHO. The AOR for having a high oral glucose tolerance test level was 1.12 (95% CI: 1.07, 1.18) by WHO and EGIR.

Every year increase in smoking cigarette by this model, was associated with AOR of 1.05 (95% CI: 1.01, 1.09) for hypertension by WHO criteria. For abdominal obesity, the AOR was 0.97 (95% CI: 0.95, 0.99) by EGIR criteria (Table 3b).

Discussion

Duration of marijuana use seems to be a significant factor associated with MetS. Its effect is small, but of the same order of magnitude or possibly greater than the effect of years of cigarette smoking. It must be noted that conventionally, cigarette smoking status has been used in analysis, but we attempted assessing the effect of years of smoking cigarette on MetS. Although current studies on marijuana use and MetS show a protective effect of marijuana on glycemic factors, this may be the result of not considering the years of using marijuana in cross sectional analysis. All criteria, demonstrate that every year increase in marijuana use is associated with at least 5% increase in odds of having MetS. In relation to components of MetS, a general increase in odds is observed with progress in years of using marijuana, however they vary by significance.

Variable	Diagnostic Criteria			
	ATP III	WHO	EGIR	IDF
Metabolic Syndrome				
Marijuana use[1]	**1.06 (1.03-1.08)**	**1.06 (1.04-1.08)**	**1.05 (1.02-1.08)**	**1.05 (1.03-1.07)**
Hypertension				
Marijuana use[1]	**1.06 (1.03-1.09)**	**1.09 (1.04-1.15)**	**1.08 (1.04-1.11)**	**1.06 (1.03-1.10)**
Hyperglycemia				
Marijuana use[1]	**1.04 (1.00-1.08)**	**1.04 (1.00-1.09)**	**1.04 (1.00-1.08)**	**1.04 (1.00-1.08)**
Hyperinsulinemia	-			-
Marijuana use[1]		1.03 (0.98-1.08)	**1.04 (1.00-1.07)**	
High OGTT	-			-
Marijuana use[1]		**1.07 (1.05-1.10)**	**1.07 (1.07-1.10)**	
Hypertriglyceridemia				
Marijuana use[1]	**1.05 (1.03-1.07)**	**1.03 (1.01-1.06)**	**1.03 (1.01-1.08)**	**1.05 (1.03-1.07)**
Low HDL-C				
Marijuana use[1]	**1.03 (1.00-1.06)**	1.00 (0.97-1.03)	**1.03 (1.00-1.05)**	**1.03 (1.00-1.06)**
Abdominal Obesity		-		

Marijuana use[1]	**1.03 (1.00-1.07)**		**1.07 (1.05-1.10)**	**1.03 (1.00-1.06)**
Obesity	-		-	-
Marijuana use[1]		**1.03 (1.01-1.05)**		
High Albumin/Creatinine Ratio	-		-	-
Marijuana use[1]		0.99 (0.96-1.02)		

Table 2a: Unadjusted analysis of having metabolic syndrome and risky levels of components by the different criteria for each year of marijuana use, bold values indicate significance at $\alpha<0.05$, Marijuana use[1] - each year of marijuana use among regular or non-regular marijuana users.

We observed different strengths in AORs for MetS with each year of marijuana use based on the different criteria for Mets, but the same direction of associations. Even though literature has discussed the possibility of a common definition for MetS [15-17], this suggests that the different criteria for metabolic syndrome may be comprehensive and can produce unified relationships with respect to marijuana use. This is irrespective of the fact that WHO and EGIR set predefined risk factors on glucose or insulin impairment. However, WHO and EGIR criteria, showed marked reductions in prevalence. This is primarily due to the prequalifying criteria for glucose/insulin impairment.

Variable	Diagnostic Criteria			
	ATP III	**WHO**	**EGIR**	**IDF**
Metabolic Syndrome	**1.02 (1.01-1.05)**	1.02 (0.98-1.05)	1.01 (0.99-1.04)	1.01 (0.99-1.03)
Cig smoking[1]				
Hypertension	**1.03 (1.00-1.06)**	**1.07 (1.03-1.12)**	**1.08 (1.04-1.11)**	**1.03 (1.00-1.06)**
Cig smoking[1]				
Hyperglycemia	**1.02 (1.00-1.03)**	**1.02 (1.00-1.04)**	**1.04 (1.00-1.08)**	**1.02 (1.00-1.03)**
Cig smoking[1]				
Hyperinsulinemia	-	1.03 (0.99-1.07)	**1.04 (1.00-1.07)**	-
Cig smoking[1]				
High OGTT	-	**1.02 (1.00-1.05)**	**1.07 (1.05-1.10)**	-
Cig smoking[1]				
Hypertriglyceridemia	**1.02 (1.01-1.04)**	**1.03 (1.00-1.05)**	**1.03 (1.01-1.06)**	**1.02 (1.01-1.04)**
Cig smoking[1]				
Low HDL-C	1.01 (0.99-1.02)	0.97 (0.94-1.01)	**1.02 (1.00-1.05)**	1.01 (0.99-1.02)
Cig smoking[1]				
Abdominal Obesity	1.00 (0.98-1.02)	-	**1.07 (1.05-1.10)**	1.00 (0.98-1.02)
Cig smoking[1]				
Obesity	-	1.00 (0.98-1.02)	-	-
Cig smoking[1]				
High Albumin/Creatinine Ratio	-	1.01 (0.99-1.03)	-	-
Cig smoking[1]				

Table 2b: Unadjusted analysis of having metabolic syndrome and risky levels of components by the different criteria for every year of cigarette smoking, bold values indicate significance at $\alpha<0.05$, Cig smoking[1]-each year of cigarette use among regular or non-regular marijuana users.

Metabolic syndrome is a powerful tool for identifying people at risk for CVD and diabetes [15]. It is important that research on marijuana relationship with MetS and it components. These findings could provide a behavioral path to

preventive and therapeutic interventions for CVD and diabetes [15] in relation to marijuana use.

Criteria of MetS is not settled, neither is the definition of marijuana use. Metabolic syndrome is a complex condition and there may be more factors intrinsic and extrinsic to MetS and marijuana use that need attention. This study finds that prolonged use of marijuana is a likely associated factor for MetS, glucose intolerance and hypertension. Increased years of marijuana use are also associated with hypertriglyceridemia but are significant using ATP III and IDF criteria. Even though all the criteria use a plasma triglyceride cut off ≥ 150 mg/dl, WHO and EGIR do not account for the use of cholesterol lowering medications and this could be a factor in the difference in significance. The recreational use of marijuana may ultimately threaten public health gains in the area of cardiovascular disease prevention. A longitudinal study of the relationship between recreational marijuana use and MetS concerning clinical factors and biological markers for all the four core attributes of MetS: insulin resistance, visceral obesity, atherogenic dyslipidemia and endothelial dysfunction [15] are exigent.

The active constituent of marijuana, delta-9-tetrahydrocanabinol (D-THC), acts on the endocannabinoid system (ECS), primarily CB1 receptors and CB2 receptors. The ECS plays a role in regulation of appetite and metabolism [18]. Modulation of the ECS affects the four core attributes of MetS [19]. These effects are being studied for management of obesity [20,21], dyslipidemia [21], atherosclerosis [22] and insulin resistance [20,23]. Cannabinoids or cannabis extracts may have therapeutic indications but, because absorption is erratic, the pharmacodynamics is still under active investigation for therapeutic purposes [24]. Arguments for recreational use of marijuana based on research for therapeutic use may need re-evaluation.

In Figure 1, initial reductions in blood pressure and glucose values change to increases after about five years of use. This shows a probable eventual deleterious effect on blood pressure and glycemic levels. However, after about twenty years of using marijuana, low levels of HDL-C tend to increase, which may allude an ultimate beneficial effect on HDL-C. This further stresses the complex relationship between cannabinoids and metabolic processes. All the applicable criteria show that increased years of marijuana use is associated with abdominal obesity. Active investigation of marijuana in long term metabolic derangements is important. Criteria by IDF show higher odds for abdominal obesity than ATP III. This is because IDF uses racial-ethnic specific waist circumference.

Variable	ATP III	WHO	EGIR	IDF
Marijuana use[1]	**1.05 (1.02, 1.08)**	**1.08 (1.04, 1.13)**	**1.06 (1.01, 1.11)**	**1.05 (1.02, 1.08)**
Cigarette smoking[1]	1.01 (0.98, 1.04)	0.99 (0.95, 1.04)	1.00 (0.96, 1.04)	1.00 (0.97, 1.03)
Age 25+	2.70 (0.66,11.10)	0.67 (0.12, 3.78)	0.92 (0.19, 4.45)	1.01 (0.37, 2.78)
Males	0.78 (0.29, 2.09)	2.54 (0.98, 6.63)	1.29 (0.45, 3.64)	0.71 (0.27, 1.90)
Asians	1.37 (0.18,10.19)	1.72 (0.27,10.82)	0.98 (0.19, 5.14)	1.41 (0.24, 8.19)
Blacks	0.74 (0.33,1.66)	0.63 (0.13, 2.96)	0.59 (0.20, 5.08)	0.81 (0.36, 1.83)
M Americans[2]	0.63 (0.22, 1.80)	1.54 (0.55, 4.27)	2.02 (0.96, 4.23)	1.16 (0.31, 4.28)
Other Hispanics	0.22 (0.02, 2.55)	1.44 (0.33, 6.22)	1.01 (0.20, 5.08)	2.39 (0.40,14.24)
Other Race	0.99 (0.22, 4.48)	0.89 (0.18, 4.46)	0.69 (0.20, 2.40)	1.45 (0.39, 5.47)
Born in USA	3.87 (0.44,34.28)	3.04 (0.60,15.29)	4.08 (0.84,19.75)	**5.53 (1.39,22.08)**
Education	0.97 (0.59, 1.59)	1.26 (0.94, 1.71)	1.39 (0.80, 2.40)	0.98 (0.61, 1.58)
PIR[3]	0.93 (0.78, 1.10)	1.01 (0.65, 1.57)	0.91 (0.76, 1.09)	0.99 (0.81, 1.21)
Insured	1.25 (0.68, 2.27)	0.52 (0.25, 1.04)	0.66 (0.38, 1.15)	1.00 (0.52, 1.93)
Married	1.17 (0.53, 2.58)	0.83 (0.30, 2.33)	1.75 (0.63, 4.83)	1.78 (0.54, 2.58)
Moderate PA[4]	1.17 (0.54, 2.51)	0.74 (0.31, 1.76)	0.85 (0.40, 1.79)	1.16 (0.53, 2.53)
Alcohol Intake[5]	**1.84 (1.10, 3.08)**	0.74 (0.28, 1.99)	0.95 (0.52, 1.74)	**1.69 (1.04, 2.74)**
Other drug use	0.92 (0.45, 1.89)	0.49 (0.21, 1.18)	**0.39 (0.23, 0.64)**	0.99 (0.46, 2.14)
Rehabilitation	1.01 (0.44, 2.33)	1.33 (0.50, 3.57)	1.66 (0.58, 4.77)	1.23 (0.55, 2.72)

Table 3a: Multivariate analysis of metabolic syndrome with years of marijuana use by different criteria controlling for cigarette smoking and other variables, 1-Each year increase in marijuana use or cigarette smoking; 2-Mexican American; 3-Family Income-to-Poverty Ratio; 4-At least moderate physical activity (recreational); 5-Weekly, bold values indicates significant at $\alpha<0.05$; ATP III-National Cholesterol Examination Panel, Adult Treatment Panel III; EGIR: European Group for the Study of Insulin Resistance; IDF: International Diabetes Federation; WHO: World Health Organization.

In this study, non-significant varying relationships are observed with each year of cigarette smoking and the different criteria for MetS. This relationship could be explained by the combination of non- smokers and past smokers. For marijuana use, all participants had at least used marijuana before. The association of cigarette smoking status with hypertension is established knowledge [25,26]. Increased years of cigarette smoking was also associated with increased odds for high OGTT levels (WHO and EGIR). Research has shown that diabetic patients who continue to smoke have uncontrolled glucose levels even with treatment [27]. Studies have long shown that nicotine from cigarette smoking impairs glucose metabolism [28-30] and reflects as high proportions of glycated hemoglobin, high OGTT and high fasting insulin [31,32].

Strengths and limitations

Demographic, lifestyle, clinical, laboratory parameters and a large nationally representative sample was obtained from NHANES data, however this cross-sectional study estimates associations not risks. Marijuana use was self-reported and the study may have a reporting bias especially with information on illicit substance use as marijuana. We initially controlled for the quantity of marijuana used but this did not significantly affect the results and was excluded from the model.

	ATP III	WHO	EGIR	IDF
Hypertension				
Marijuana use[1]	**1.07 (1.03, 1.12)**	**1.05 (1.01, 1.09)**	**1.08 (1.03, 1.12)**	**1.07 (1.03, 1.12)**
Cigarette smoking[1]	1.02 (0.98, 1.05)	**1.05 (1.02, 1.09)**	1.02 (0.99, 1.05)	1.02 (0.98, 1.05)
Hyperglycemia				
Marijuana use[1]	1.02 (0.98, 1.07)	1.02 (0.98, 1.07)	1.02 (0.98, 1.07)	1.02 (0.98, 1.07)
Cigarette smoking[1]	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)
Hyperinsulinemia				
Marijuana use[1]	-	1.01 (0.92, 1.11)	1.04 (0.99, 1.11)	-
Cigarette smoking[1]	-	1.00 (0.97, 1.03)	1.00 (0.96, 1.04)	-
High Oral Glucose Tolerance Test level				
Marijuana use[1]	-	**1.12 (1.07, 1.18)**	**1.12 (1.07, 1.18)**	-
Cigarette smoking[1]	-	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)	-
Hypertriglyceridemia				
Marijuana use[1]	**1.04 (1.00, 1.07)**	1.02 (0.98, 1.05)	1.02 (0.98, 1.05)	**1.04 (1.00, 1.07)**
Cigarette smoking[1]	1.01 (0.99, 1.03)	1.01 (0.98, 1.05)	1.01 (0.98, 1.05)	1.01 (0.99, 1.03)
Low HDL-C				
Marijuana use[1]	1.03 (0.99, 1.07)	1.02 (0.98, 1.07)	1.04 (0.99, 1.08)	1.03 (0.99, 1.07)
Cigarette smoking[1]	0.99 (0.97, 1.02)	0.97 (0.92, 1.02)	0.98 (0.93, 1.03)	0.99 (0.97, 1.02)
Abdominal obesity				
Marijuana use[1]	**1.06 (1.00, 1.11)**	-	**1.09 (1.05, 1.14)**	**1.07 (1.01, 1.13)**
Cigarette smoking[1]	0.99 (0.97, 1.02)	-	**0.97 (0.95, 0.99)**	0.95 (0.95, 1.01)
Obesity by (BMI)				
Marijuana use[1]	-	**1.03 (1.01, 1.06)**	-	-
Cigarette smoking[1]	-	0.99 (0.97, 1.01)	-	-
High Albumin/ Creatinine ratio				
Marijuana use[1]	-	0.96 (0.91, 1.01)	-	-
Cigarette smoking[1]	-	1.01 (0.97, 1.05)	-	-

Table 3b: Multivariate analysis of components of metabolic syndrome with each year of marijuana use and cigarette smoking by different criteria

We did not control for diet, an important factor for MetS, however, we controlled for factors important in dietary and health decisions as income to poverty ratio (PIR), alcohol use, physical activity, health insurance and education. For ethnic-specific waist circumference by IDF, we classified NHBs as Europids based on ancestral genesis [33] that the ancestry of Blacks or African-American are predominantly Niger-Kordofanian (~71%), European (~13%) or other African (~8%) populations [34]. All NHWs were classified using values for Americans since distinctions based on the ethnic classification were unavailable. We however controlled for place of birth to possibly account for these differences.

Conclusion

Irrespective of the criteria for metabolic syndrome, each year of marijuana use showed increased odds of having metabolic syndrome, hypertension or high oral glucose tolerance test levels. Extended duration of marijuana use could possibly increase the risk for the development of metabolic syndrome. Longitudinal studies can show this risk. Irrespective of the criteria for MetS, we estimated increased odds of MetS with each year marijuana use. This may constitute an important pathway between marijuana use and cardiovascular disease in later life. The impact of duration of marijuana use should be considered in assessing the relationships with MetS.

Longitudinal research is required to define the true relationship between marijuana use and metabolic syndrome. If a cardiovascular risk is established, a good understanding of the pathogenesis of metabolic syndrome and metabolic pathways of marijuana metabolites should be laid out. This will help address any risk factors which may initiate and facilitate CVD progression among marijuana users.

Conflict of Interest

We declare no conflict of interest in processes associated with this study. All authors contributed equally in the research. Grants or Financial Support: The authors received no financial support for the study.

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CHAPTER 4.

Effect of marijuana use on cardiovascular and cerebrovascular mortality: a study using the NHANES linked mortality file

Abstract

Background: Reports associate marijuana use with cardiovascular emergencies. Studies relating marijuana use to cardiovascular mortality are scarce. Recent advance towards marijuana use legalization emphasizes the importance of understanding relationships between marijuana use and cardiovascular deaths; the primary ranked mortality. Recreational marijuana is primarily smoked; we hypothesize that like cigarette smoking, marijuana use will be associated with increased cardiovascular mortalities.

Design: Mortality follow-up.

Method: Data from 2011 public-use linked mortality file of National Center for Health Statistics, Centers for Disease Control and Prevention was used. Participants were aged 20 years and above, and responded to questions on marijuana use during the 2005 National Health and Nutrition Examination Survey. Only participants eligible for mortality follow-up were included. We conducted cox proportional hazards regression analyses to estimate hazard ratios for hypertension, heart disease and cerebrovascular mortality due to marijuana use. We controlled for cigarette smoking and other relevant variables.

Results: Seventy-two and five-tenths percent of the 1213 eligible participants were presumed to be alive. The total follow-up time was 19,569 person-years. Adjusted hazard ratios for death from hypertension among marijuana users compared to non-marijuana users was 3.42 (95% CI: 1.20, 9.79) and for each year of marijuana use was 1.04 (95% CI: 1.00, 1.07).

Conclusion: From our results, marijuana use increases the risk for hypertension mortality. Increased duration of marijuana use is associated with increased risk of death from hypertension. Recreational marijuana use potentially has cardiovascular adverse effects which needs further investigation.

Key words

THC, marijuana, cannabis, hypertension, cardiovascular mortality

Introduction

Cardiovascular diseases (CVDs) rank first as cause of mortality worldwide and most are preventable [1]. Cardiovascular mortality encompasses death from diseases, emergencies or conditions associated with heart and blood vessels [2]. In 2013, one out of every four deaths in United States (US) was due to heart disease (HD), stroke or other CVDs [3]. Cardiovascular death rates have been declining in US since year 2000 [4] due to clinical and public health interventions including smoking cessation. Irrespective of this decline [5], CVDs retain their lead as cause of mortality globally. Lifestyle modification including smoking cessation, physical activity, healthy diet, maintaining normal body mass index, and avoidance of harmful alcohol use reduce cardiovascular morbidity and mortality [6-8].

Reports associate marijuana use with cardiovascular emergencies. Marijuana like cigarette is primarily smoked but contrary to marijuana, mortalities from CVDs due to cigarette smoking has been studied extensively [9-11]. Recent advance towards legalization of marijuana in US, necessitates the determination of its association with cardiovascular mortality. The active constituent of marijuana, Delta-9-tetrahydrocannabinol (THC), accounts for some cardiovascular effects of marijuana [12, 13]. Marijuana smoking increases heart rate from 20-100% for about two to three hours [14], causes postural hypotension, fainting, ischemic stroke and disruption of cardiac functions [12, 15, 16]. We hypothesize that similar to cigarette smoking, recreational marijuana will be associated with increased cardiovascular mortalities.

Methods

We merged results of interviews in 2005 National Health and Nutrition Examination Survey (NHANES) with 2011 public-use linked mortality file of the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC) [17], since NHANES participants were interviewed on marijuana use starting 2005. The NHANES assesses the health and nutritional status of civilian noninstitutionalized US population. About 5000 nationally representative participants are selected through complex, multistage probability sampling yearly. Interviews are conducted by physicians and other healthcare professionals in participant's homes and examinations conducted in a mobile center. Mortality information on participants in NCHS public-use linked mortality file is obtained from death

certificates or probabilistic matching from the National death index (NDI). Causes of death occurring in US before 1999 were based on the 9th revision of International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-9) guidelines and subsequently recoded into comparable ICD-10 rubrics, as cause of deaths occurring from 1999 are coded on the 10th (ICD-10) revision. Deaths are classified as due to diseases of the heart (001), malignant neoplasms (002), chronic lower respiratory disease (003), accidents-unintentional injuries (004), cerebrovascular diseases (005), Alzheimer's diseases (006), diabetes mellitus (007), influenza and pneumonia (008), nephritis, nephrotic syndrome and nephrosis (009) and all other causes (010) with another coding for hypertension and diabetes deaths. Those assumed alive, ineligible for follow up, or with cause of death unavailable are left un-coded.

We selected participants eligible for mortality follow up, aged 20 years and above who answered "yes" or "no" to the question, "Have you ever used marijuana or hashish?" Participants who answered yes were classified marijuana users and those who answered no, as non-marijuana users. Duration of marijuana use was estimated by subtracting participant's age at marijuana use initiation from the age at 2005 screen. Follow-up period for eligible participants was 1991-2011. This study collectively refers to marijuana use, cigarette smoking and alcohol use as substance use. Participants who reported having smoked at least 100 cigarettes in their lifetime and still smoke were classified current smokers, with those who have ceased smoking as past-smokers. Those who never smoke nor smoked 100 cigarettes in lifetime were classified non-smokers. High-risk drinking is defined in dietary guidelines for Americans 2015-2020 as consumption of four or more drinks any day or eight or more drinks weekly for women (five or more drinks any day or 15 or more drinks weekly for men). Participants who confirmed ever having five or more drinks almost every day at a point in life were classified as alcohol users. Participants reported their age, gender, educational status and race/ethnicity and prior diagnosis of hypertension, angina, congestive heart failure, heart attack or stroke by a doctor or other health professional.

Statistical Analysis

We estimated mortality rates and hazard ratio (HR) with 95% confidence intervals from Cox proportional hazards regression, for hypertension, heart disease and cerebrovascular deaths among

marijuana users and current cigarette smokers. Our main independent variables were marijuana use status and years of marijuana use. We controlled for cigarette smoking (non-smokers as reference), gender (female as reference), age (25 years and below as reference), race/ethnicity (Non-Hispanic Whites as reference), having health insurance (not having health insurance as reference), alcohol use (not having had five drinks or more on some days in life as reference), diagnosis of hypertension (no diagnosis of hypertension as reference) or CVD: angina, heart attack, congestive heart failure or coronary heart disease (no diagnosis of CVD as reference), education and body mass index (BMI), were controlled using continuous increasing level. Age was dichotomized as 25 years and below, or above 25 years. Research shows the age cut off point associated with illicit substance use, smoking and heavy alcohol consumption is 25 years [18]. Interaction factor between smoking status and marijuana use status was not significant in the survival model, so the interaction factor was excluded. We estimated cumulative hazard for hypertension, heart and cerebrovascular disease mortality by marijuana use or cigarette smoking status over the 20 year period of follow up. Nelson-Aalen curves estimate cumulative hazard functions of censored data [19]. The follow-up was right censored at the end of 2011.

Results

Demographic characteristics, marijuana use and cigarette smoking

Total eligible participants were 1213 with one observation ending on or before entry and 72.5% presumed alive. Person-years follow up was 19,569. Average age at entry of participants was 37.7±11.2. Average BMI for all participants was 29.0±7.0, for marijuana users, 28.6±7.1 and for cigarette smokers, 27.7±6.9. Demographic distribution is shown in Table 1. Among all 1213 participants, 34.3% neither use marijuana nor smoke cigarettes, 20.9% use only marijuana, 20.0% use marijuana & smoke cigarettes, 15.6% use marijuana & are past-smokers, 4.8% are past-smokers and 4.4% smoke only cigarettes. Average duration of marijuana use was 11.5±12.8 years and 10.1±13.8 years for cigarette smoking.

Diagnosis of hypertension or other cardiovascular diseases

Twenty and a third percent of marijuana users compared to 20.6% of non-marijuana users had prior diagnosis of hypertension. Among current smokers, 21.8% had prior diagnosis of hypertension

compared to 23.4% of past-smokers and 18.7% of never smokers. Prevalence for prior diagnosis of any other CVDs was 3.8% among marijuana users and 3.6% for non-marijuana users, 6.1% for current smokers, 5.7% past-smokers and 1.9% for never smokers. Distribution of hypertension, heart and cerebrovascular mortality is shown in Table 1.

Mortality incidence rates and ratios

For all-cause mortality among marijuana users, incidence rate ratio was 1.29 (95% CI: 1.03, 1.61) and among current smokers 1.16 (95% CI: 0.90, 1.48). Mortality incidence rates by marijuana use and cigarette smoking stratified by cause of death are shown in Table 2.

Unadjusted and adjusted hazard ratios

Unadjusted hazard ratio for hypertension mortality among marijuana users compared to non-marijuana users was 1.86 (95% CI: 0.95, 3.66). Unadjusted HRs are shown in Table 3. For HD mortality, unadjusted HR was 1.21 (95% CI: 0.76, 1.92) among marijuana users compared to non-marijuana users and 1.01 (95% CI: 0.99, 1.03) for each year of marijuana use. For cerebrovascular disease mortality, all unadjusted HRs were non-significant for marijuana use and cigarette smoking (not shown in Table).

Adjusted HRs for hypertension mortality among marijuana users compared to non-marijuana users was 3.42 (95% CI: 1.20, 9.79), and for each year of marijuana use was 1.04 (95% CI: 1.00, 1.07) (Table 3). All adjusted HRs for HD and cerebrovascular mortality showed non-significant estimates in this model for marijuana use and cigarette smoking in this model most likely due to sample size. Adjusted HR for HD mortality was: a) 1.09 (95% CI: 0.63, 1.88) for marijuana users compared to non-marijuana users and b) 1.00 (95% CI: 0.98, 1.02) for each year of marijuana use (Not shown in Table).

Cumulative Hazard Curves

Nelson-Aalen cumulative hazard estimates show that marijuana users have a higher risk for hypertension mortality than non-marijuana users (Figure 1A). For hypertension mortality, there are more flattened areas for smokers; non-smokers seem to have a higher risk. Cumulative hazard for all-cause mortality is higher among marijuana users and cigarette smokers than their counterparts (Figure 1B).

Discussion

Marijuana users had an increased risk of hypertension mortality even after controlling for prior diagnosis of hypertension. Opiates have more deleterious consequences on the cardiovascular system than marijuana [20], but hypertensive crisis following marijuana use has been described [21], also cases of cardiac infarction and stroke following marijuana use among normotensives and people lacking history of cardiovascular diseases have however been described [21-23]. Increase in risk for hypertension, HD or cerebrovascular disease mortality associated with cigarette use was not significant, largely due to the small sample size ($n < 30$) of mortalities among cigarette smokers under investigation. The hazardous effect of cigarette smoking on cardiovascular system has however been largely demonstrated in studies [9] and is established knowledge. Also, our study focuses on marijuana use, and initial selection criteria was based on responses to marijuana use among adults. Our assumption that marijuana use or cigarette smoking continues throughout the period of follow up, may not be so. Taking into consideration the availability of smoking cessation programs, these behaviors may change with time, from participation in an intervention. Specific marijuana use cessation interventions are yet to be documented. Also use of cocaine/heroin/methamphetamine or participation in rehabilitation was not statistically relevant in our model and was excluded. We however controlled for relevant demographic factors. The observed large confidence intervals for marijuana use estimates can also be attributed to sample size.

Within our limitations, our results however support a possible increased risk of mortality from CVDs related to marijuana use. Taking into consideration results of study by Aronow, W.S. and J. Cassidy [24], it is possible that the cardiovascular risk associated with marijuana use and prolonged years of marijuana use is even greater than the risk already described for cigarette use in studies.

Delta-9-Tetrahydrocannabinol (THC) acts primarily on the endocannabinoid system which regulates behavior, metabolism and cardiovascular function. The endocannabinoid system consists of neuro-modulatory lipids (primarily the endogenous cannabinoid anandamide and 2-arachidonylglycerol), their metabolites and cannabinoid receptors CB1 and CB2. Cannabinoid receptors are distributed in the central nervous system, cardiovascular system and peripheral tissues. Cannabinoids including the

phytocannabinoid THC, exert sympathetic stimulation. Delineated cardiovascular effects of THC are increased heart rate, increased supine blood pressure, orthostatic hypotension [14], increased cardiac output, reductions in left ventricular ejection time[16] and increases in venous carboxyhemoglobin levels[24] which cause unhealthy cardiovascular and cerebrovascular outcomes.

The 2020 goal of American heart association is to improve cardiovascular health of all Americans by 20%, and reduce mortality from CVDs and stroke by 20%. Public health and clinical interventions have helped to promote the life's simple seven indicators of good cardiovascular health: blood pressure control, increased physical activity, healthy diet, total cholesterol control, healthy weight, blood glucose control and smoking cessation which contributes to plummeting age standardized death rates from CVDs since 2009 [25]. Smoking is still the leading cause of preventable disease and death, and since recreational marijuana is primarily smoked, its use may contribute to increases in morbidities and mortalities. Factors of interest include effects of marijuana use on cardiovascular mortality among the youth and people with existing chronic conditions. The youth, especially those aged 18-25 years are more liable to substance use [26] and adults are more likely to live with chronic conditions. This expands the demographic coverage of poor health consequences of marijuana use. In the interest of individual health, population health and lowering costs associated with healthcare, education on the adverse effects of recreational marijuana use should be a priority as recommendations and advancements are made towards its legalization.

Conclusion

Marijuana use increases the risk of hypertension mortality. Longer years of marijuana use increases risk of death from hypertension. This cardiovascular risk associated with marijuana use, may be greater than the cardiovascular risk already established for cigarette smoking. We are not disputing the possible medicinal benefits of standardized cannabis formulations; however, recreational use of marijuana should be approached with caution. It is possible that discouraging recreational marijuana use may ultimately impact reductions in mortality from cardiovascular causes. A purposeful longitudinal study modeled with inclusion of listed relevant limitations is recommended.

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Table 1: Sociodemographic characteristics of participants, showing overall prevalence (%) and mortality rates (%) from hypertension, heart diseases and cerebrovascular disease.

Variables	Participants		Total Mortality	HBP	HD	CBV
	Sample	**%**	**Sample**	**%**	**%**	**%**
Age ≤ 25years	226	18.6	63	9.5	22.2	11.1
Age >25years	987	81.4	269	12.6	23.0	6.3
Total	**1213**	**100.0**	**332**	**12.1**	**22.9**	**7.2**
Male	550	45.3	168	8.3	23.2	4.8
Female	663	54.7	164	15.9	22.6	9.8
Total	**1213**	**100.0**	**332**	**12.1**	**22.9**	**7.2**
Non-Hispanic Whites	579	47.7	162	14.8	26.5	7.4
Non-Hispanic Blacks	286	23.6	76	7.9	19.7	10.5
Mexican Americans	246	20.3	63	7.9	22.2	3.2
Other Hispanics	45	3.7	11	27.3	18.2	0
Other Race	57	4.7	20	10.0	10.0	10.0
Total	**1213**	**100.0**	**332**	**12.1**	**22.9**	**7.2**
< 9th grade	89	7.3	20	15.0	30.0	5.0
9th - 11th grade	166	13.7	43	7.0	20.9	9.3
High school graduate	277	22.9	76	7.9	21.1	7.9
Some College/Associate degree	394	32.5	112	15.2	19.6	8.0
≥ College graduate	286	23.6	81	13.6	28.4	4.9
Total	**1212**	**100.0**	**332**	**12.1**	**22.9**	**7.2**
Marijuana users	686	56.5	204	13.7	22.5	7.4
Non-marijuana users	527	43.5	138	9.4	23.4	7.0
Total	**1213**	**100.0**	**332**	**12.1**	**22.9**	**7.2**
Current cigarette smokers	296	24.4	89	10.1	15.7	9.0
Past-cigarette smokers	248	20·4	74	14.9	27.0	9.5
Non-cigarette smokers	669	55.2	169	11.8	24.8	5.3
Total	**1213**	**100.0**	**332**	**12.1**	**22.9**	**7.2**
Alcohol use	190	17.7	55	10.9	29.1	7.3
No Alcohol use	882	82.3	243	11.1	22.6	6.2
Total	**1072**	**100.0**	**298**	**11.1**	**23.8**	**6.4**

HBP, Hypertension **HD,** Heart Disease **CBV,** Cerebrovascular disease

Note: Mortality rates shown are row percentages based on total mortality but do not add up to 100% because mortality rates of other diseases are not shown.

Table 2: Incidence estimates for mortality from hypertension, heart disease and cerebrovascular disease by substance use among study participants

Cause of mortality	Marijuana
Hypertension	
Incidence rate in exposed/1000	2.57
Incidence rate in unexposed/1000	1.39
Incidence rate in population/1000	2.04
Incidence rate ratio	1.85 (0.92, 4.00)
Attributable fraction in exposed	46.0%
Attributable fraction in population	32.1%
Heart disease	
Incidence rate in exposed/1000	4.22
Incidence rate in unexposed/1000	3.47
Incidence rate in population/1000	3.88
Incidence rate ratio	1.22 (0.75, 2.00)
Attributable fraction in exposed	17.8%
Attributable fraction in population	10.8%
Cerebrovascular Disease	
Incidence rate in exposed/1000	1.37
Incidence rate in unexposed/1000	1.04
Incidence rate in population/1000	1.23
Incidence rate ratio	1.32 (0.54, 3.43)
Attributable fraction in exposed	24.4%
Attributable fraction in population	15.2%

Table 3: Unadjusted and adjusted analysis showing hazard ratios for hypertension mortality among (a) marijuana users and (b) each year of marijuana use

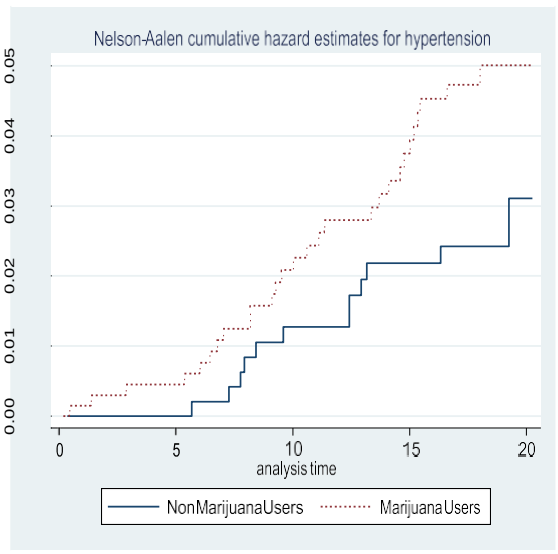
Substance use and demographic factors	Unadjusted hazards ratio (95% Confidence interval)	Adjusted hazards ratio (95% Confidence interval)
A)		
Marijuana user	1.86 (0.95, 3.66)	3.42 (1.20, 9.79)*
Current smoker	1.06 (0.48, 2.33)	1.06 (0.40, 2.77)
Former smoker	1.56 (0.75, 3.25)	1.33 (0.57, 3.10)
Alcohol user	1.03 (0.43, 2.50)	0.95 (0.37, 2.45)
Body mass index	1.03 (1.00, 1.08)*	1.05 (1.01, 1.10)*
Age >25years	1.29 (0.54, 3.08)	1.25 (0.42, 3.67)
Education	1.19 (0.90, 1.57)	1.00 (0.70, 1.43)
Male	0.67 (0.35, 1.29)	0.72 (0.35, 1.49)
Blacks	0.51 (0.21, 1.24)	0.42 (0.14, 1.27)
Mexican Americans	0.49 (0.19, 1.28)	0.91 (0.28, 2.94)
Other Hispanics	1.58 (0.48, 5.25)	2.51 (0.54, 11.63)
Other Race	0.92 (0.22, 3.89)	1.23 (0.29, 5.35)
Have health insurance	2.66 (1.04, 6.79)*	2.24 (0.75, 6.72)
Diagnosed with hypertension	0.86 (0.38, 1.93)	0.81 (0.32, 2.06)
Diagnosed with a CVD	2.18 (0.67, 7.06)	1.94 (0.42, 8.97)
B)		
Each year of marijuana use	1.03 (1.00, 1.05)*	1.04 (1.00, 1.07)*
Current smoker	1.06 (0.48, 2.33)	1.14 (0.43, 3.01)
Former smoker	1.56 (0.75, 3.25)	1.35 (0.57, 3.20)

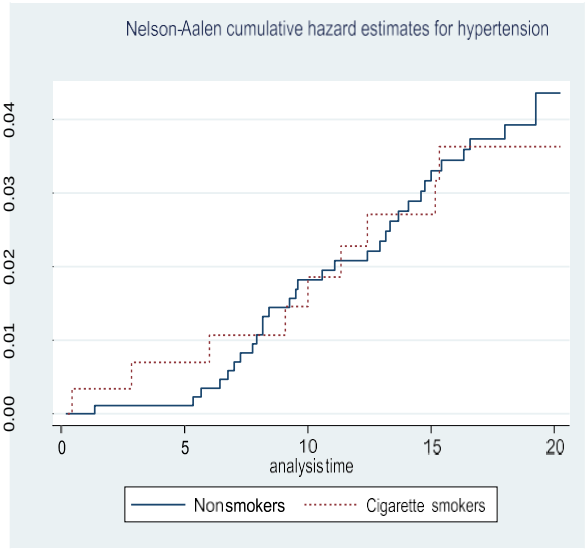
CVD, Cardiovascular disease (angina, heart attack, congestive heart failure or coronary heart disease)

Note: In Model A, hazard ratios are estimated based on substance use status, In Model B based on each year of marijuana use controlling for the same variables in Model A

*P<0.05

A





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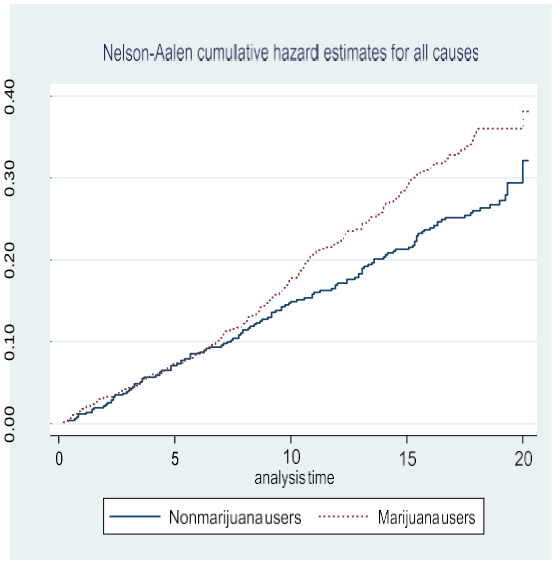

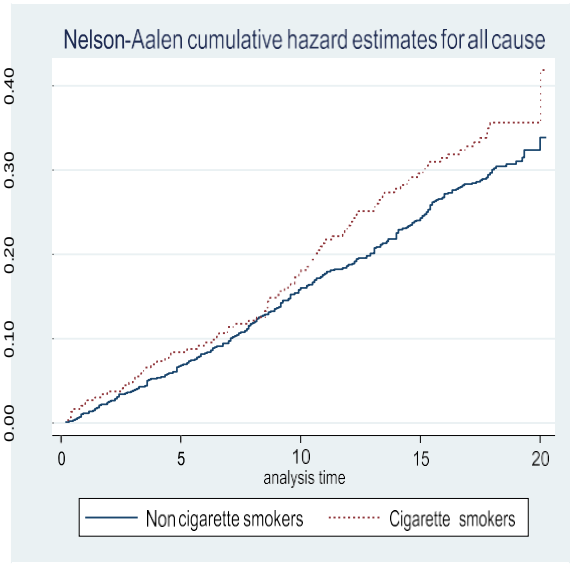

Figure 1: Nelson-Aalen cumulative hazard estimate of mortality from (A) hypertension and (B) all-causes associated with marijuana use and cigarette smoking. Y-axis shows cumulative hazard rate and X-axis shows follow-up time.

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CHAPTER 5.

Summary of three studies

Smoking seems to find a way of sustaining its popular social practice despite evidence of its detrimental effects on health. After several years of use, the deleterious effect of tobacco on health and economic growth cannot be overstated and the impact of public health measures towards smoking cessation and successes cannot be understated. The current inclination towards legalization of marijuana questions the possibility of a replay of the journey with tobacco.

The use of marijuana in adults is also increasing especially among adults aged 25 years and above. Schedule I substances under the Federal Controlled Substances Act (CSA) are considered as having a high potential for abuse and not having any currently accepted medical use in treatment, consequently its use is reserved for very limited circumstances. The current move towards reclassification of marijuana as a legal substance places an urgent call to investigate the relationship of marijuana with cardiovascular diseases; the number one cause of morbidities and mortalities.

In our first study, we assessed the relationship between marijuana use, cigarette smoking and metabolic syndrome (as well as components of metabolic syndrome) among adults in the United States, with emphasis on marijuana use. Our hypothesis was that in the United States, adults who use marijuana or/and tobacco are more likely to have unhealthy levels of the factors of metabolic syndrome and ultimately metabolic syndrome. We conducted multiple logistic regression analyses using data from the 2011–2012 United States National Health and Nutrition Examination Survey (NHANES). We classified metabolic syndrome using the definition by National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III) 2004 modification, which adapts the International Diabetes Federation (IDF) definition for hypertension and diabetes. The ATP III criteria is commonly used because of its clinical applicability. We estimated odds ratios for metabolic syndrome and its

components among participants who reported that they have smoked marijuana regularly for at least a year and still use marijuana. We also estimated odds ratios for metabolic syndrome and its components among current smokers. In the multivariate model, we included years of marijuana use and years of cigarette smoking and adjusted for factors endogenous and exogenous to marijuana use and relevant to metabolic syndrome: age, gender, race/ethnicity, education, income to poverty ratio, having health insurance, marriage, physical activity, alcohol use, use of other substances of abuse, participation in rehabilitation, joints of marijuana used and cigarette packs smoked. We estimated increased odds ratios for metabolic syndrome (OR 1.05; 95% CI: 1.01, 1.09), and hypertension (OR 1.04; 95% CI: 1.01, 1.07) with each year of marijuana use. We also estimated increased odds ratios for hypertension (OR 1.03; 95% CI: 1.00, 1.06) and hyperglycemia (OR 1.03; 95% CI: 1.01, 1.05) with each year of cigarette smoking. Consistent with research, those who reported using marijuana showed a decrease odd ratio for metabolic syndrome (OR 0.23; 95% CI: 0.06, 0.90) compared to those who do not use marijuana. The finding that years of marijuana use is increases the odds for metabolic syndrome and hypertension stresses a possible factor that has been missed in assessing the marijuana use with metabolic syndrome. In separate analysis among those who smoke cigarette and those who use marijuana compared to their counterparts, this increase in odds ratios was still evident, and there was also an increased odds ratio for hypertriglyceridemia with each year of marijuana use (OR 1.03; 95% CI: 1.01, 1.06) and each year of cigarette use (OR 1.04 (1.02, 1.06).

Because metabolic syndrome has different criteria, in our second study, we assessed the relationship between metabolic syndrome and marijuana use based on the four common criteria by National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III), World Health Organization (WHO), European Group for the study of Insulin Resistance (EGIR), and International

Diabetes Federation (IDF). The different criteria used could also impact the results of the relationship between metabolic syndrome and marijuana use. Our hypothesis was that the definition used for metabolic syndrome may change the estimates of the associations between marijuana use and metabolic syndrome. We estimated the prevalence of marijuana use and cigarette smoking by race and conducted multiple logistic regression to estimate odds ratios. In the multivariate model, we controlled for age, gender, race, education, marital status, income to poverty ratio (PIR), participation in at least moderate physical activity, days of alcohol use per week, other recreational substance use (methamphetamine, heroin or cocaine) and participation in rehabilitation. Each year increase in marijuana use showed increased odds ratios for metabolic syndrome by all the four criteria: 1.05 (95% CI: 1.02, 1.08) using National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria, 1.08 (95% CI: 1.04, 1.13) using International Diabetes Federation (IDF) and 1.05 (95% CI: 1.04, 1.13) using World Health Organization (WHO) or European Group for the study of Insulin Resistance (EGIR) criteria. Each year of marijuana use, showed increased odds ratio for hypertension for all the criteria: 1.7 (95% CI: 1.03, 1.12) using ATP III or IDF criteria, 1.05 (95% CI: 1.01, 1.09) using WHO criteria, and 1.8 (95% CI: 1.03, 1.12) using EGIR criteria. The ATP III, EGIR and IDF criteria for metabolic syndrome include increased waist circumference (abdominal obesity) in defining metabolic syndrome. All the criteria showed increased odds ratios for abdominal obesity: 1.06 (95% CI: 1.00, 1.11) for ATP III, 1.09 (95% CI: 1.05, 1.14) for EGIR and 1.07 (95% CI: 1.01, 1.13) for IDF. The World Health organization and European Group for the study of Insulin Resistance have oral glucose tolerance test as part of the components for metabolic syndrome. Each year of marijuana use was associated with increased oral glucose tolerance test levels; OR 1.12 (95% CI: 1.07, 1.18). We also fitted residuals of each component of metabolic syndrome (systolic blood pressure, diastolic blood pressure, waist circumference, plasma

glucose, serum triglycerides and serum high density lipoprotein cholesterol) with years of marijuana use. This graphs showed an initial decrease in values but eventual increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference (WC), plasma triglycerides (TG) and fasting blood glucose (FBG) with progress in years of marijuana use. However, the relationship between plasma high density lipoprotein cholesterol (HDL-C) and years of marijuana used showed an initial decrease and eventual increase.

Metabolic syndrome is associated with increased risk for cardiovascular morbidities and mortalities. With our estimates of increased odds of metabolic syndrome relative to duration marijuana use, we assessed the relationship of marijuana use with cardiovascular mortality. We used data from 2011 public-use linked mortality file of National Center for Health Statistics, Centers for Disease Control and Prevention and linked them to participants aged 20 years and above who responded to questions on marijuana use during the 2005 National Health and Nutrition Examination Survey and were eligible for mortality follow-up. Because recreational marijuana is primarily smoked; our hypothesis was that: like cigarette smoking, marijuana use will be associated with increased cardiovascular mortalities. We conducted cox proportional hazards regression analyses to estimate hazard ratios for hypertension, heart disease and cerebrovascular mortality due to marijuana use. We controlled for cigarette smoking, alcohol use, age, education, gender, race, having health insurance, diagnosis of a cardiovascular disease (angina, congestive heart failure, heart attack or stroke) or hypertension. Marijuana use increased the risk for hypertension mortality. Adjusted hazard ratios for death from hypertension among marijuana users compared to non-marijuana users was 3.42 (95% CI: 1.20, 9.79) and for each year of marijuana use was 1.04 (95% CI: 1.00, 1.07).

Results of our study consistently show that marijuana use is associated with metabolic syndrome and detrimental cardiovascular health. Increased years of marijuana use was associated with increased odds of hypertension, increased values of systolic and diastolic blood pressures as well as increased risk for hypertension mortality. Contrary to research that marijuana use may be safe, our research shows that prolonged use of marijuana is associated with detrimental cardiovascular health. The endocannabinoid system plays an important role in metabolic regulation and current studies should explore the pathways associated with cardio-metabolic function and health.

Our research is primarily cross sectional and exploratory, but the results point to the urgency and importance of investigating the relationship between marijuana use and cardio-metabolic health for the benefit of the public who believe that recreational marijuana use is probably not harmful to health, especially during an era where marijuana legalization is gaining support.

Public health significance of study

Metabolic syndrome is an emerging public health problem which may reach global epidemic levels because of changing lifestyles towards a more westernized lifestyle. Smoking is a major lifestyle associated with cardiovascular problems and hence metabolic syndrome. It is projected that metabolic syndrome may overtake smoking as a known risk factor for cardiovascular problems especially heart diseases. With the increasing support for legalizing marijuana use, it is important to demonstrate the relationship of marijuana with metabolic syndrome. If marijuana is found to be a risk factor for components of metabolic syndrome and cardiovascular disease at the same magnitude as cigarette smoking or even more, public health gains in cardiovascular disease prevention stand threatened. This is especially dependent on the likelihood of increased marijuana use with its legalization.

Metabolic syndrome can be controlled with healthy lifestyle. Even though the focus has been on healthy diet and participation in physical activity, smoking cessation should be an integral part of metabolic syndrome management. If marijuana use is found to have detrimental effect on metabolic activity and cardiovascular health, it will be important to develop intervention plans to reduce recreational marijuana use. The management and control of metabolic syndrome requires the effort of individuals at risk, families, communities, health care providers and health care systems.

The goal of healthy people 2020 on substance use is to reduce substance abuse to protect the health, safety, and quality of life for all, especially children (Health et al., 2000). Substance use has a major impact on the quality of life, on families, on communities, on nations and on health systems. Substance use especially marijuana use is on the ascendancy among adults. Increasing age is already an independent factor for several chronic diseases and coupling this with the detrimental effects of substance use can pose a significant health burden. Substance use carries economic, social, mental and public health problems. In 2005, about 22 million Americans had a drug use or alcohol problem with 95% of them unaware of their drug use or alcohol problem. About 24.8% of those who know their problem and seek treatment are not successful at obtaining treatment.

Heart disease, stroke and other cardiovascular disease, are highly prevalent in the United States and pose significant economic and health burden. The goal of healthy people 2020 for cardiovascular health is to improve cardiovascular health and quality of life through prevention, detection, and treatment of risk factors for heart attack and stroke. This includes early identification and prompt treatment of heart attacks and strokes, interventions to prevent repetition of cardiovascular events and ultimately reduction in cardiovascular mortalities. Risk factors listed as

modifiable for cardiovascular disease are high blood pressure, high cholesterol, diabetes, unhealthy diet, physical inactivity, overweight and obesity and cigarette smoking.

Evidence suggests that, rates of cardiovascular morbidity and mortality among the US population would decline significantly with major interventions on, and improvements in lifestyle concerning diet, physical activity, control of high blood pressure and cholesterol, appropriate aspirin use and smoking cessation with emphasis on bridging disparities (Barr, 2016) .

Healthy people 2020 aims increase overall cardiovascular health in the US population, reduce coronary heart disease and stroke mortalities, reduce the proportion of persons in the population with hypertension, reduce the proportion of adults with high total blood cholesterol levels and mean levels of total blood cholesterol among the population, increase the proportion of adults who are advised by health care providers on cholesterol lowering management, healthy lifestyles as well as use of aspirin where indicated for people with elevated low density lipoprotein cholesterol. Healthy People 2020 aims to reduce the disease burden of diabetes mellitus and improve the quality of life for all persons who have, or are at risk for diabetes mellitus. Some objectives towards this goal relevant to our study include reducing the annual number of new cases of diagnosed diabetes in the population and reducing the rates of cardiovascular deaths among people diagnosed with diabetes. The association of marijuana use with hyperglycemia in our study makes marijuana use an important indicator of the rates of incident diabetes which needs further investigation. If this relationship is established, education on the harms of marijuana to glycemic factors and subsequent interventions to reduce incidence of diabetes through reductions in rates of marijuana use will be relevant.

Our research seeks to raise awareness of the health impact on the co-occurrence of these factors among populations and the detrimental effects it can cause on health, and to document the

urgency of investigating the relationship of recreational marijuana use among populations with cardiovascular morbidity and mortality. The finding that increasing years of marijuana use is associated with increased odds for metabolic syndrome and mortality from hypertension is an observation that calls for urgent investigation to delineate the mechanisms underlying marijuana use and cardiovascular health, especially among a nation with increasing support for legalization of marijuana use. About one in every three adults in the US has hypertension and only about 50% of them have their blood pressure under control (S. S. Yoon, Carroll, & Fryar, 2015).

Primary prevention methods for sustaining cardiovascular health are highly effective. Stressing on lifestyle changes to improve and preserve cardiovascular health is a major activity of public health. Prevention efforts on substance use which carry cardiovascular risk are thus very important. Some of the Healthy People 2020 objectives towards reducing substance use include: increasing the proportion of adolescents aged 12 to 17 years who perceive great risk with substance abuse, increasing the proportion of adolescents who disapprove of trying marijuana or hashish once or twice by ten percent, increase the proportion of persons who received specialty treatment for abuse or dependence in the past year from 16% as 2008 to 17·6% by 2020 among those who need alcohol and/or illicit drug treatment, and to reduce illness, disability, and death related to tobacco use and secondhand smoke exposure.

The objectives on substance use prevention are strongly related to the constructs of social cognitive theory; the theoretical basis for explaining substance use. It is important that the populace build a solid cognitive disposition on substance use based on the information available on its effects on health especially during the early years of life. This can help improve self-efficacy and ultimately prevent the use of substances that can be detrimental to health. With increase in the prevalence of substance use

among adults, it is important the education on substance use is targeted toward adults as well, especially those who already have existing chronic diseases.

Demonstrating the true effects of recreational substance use (especially those that are easily accessible and seem harmless) on health will help prevent substance use and protect the health of the public. The framework for ending tobacco use epidemic outlined by Healthy People 2020 can be applied to marijuana use prevention if research establishes marijuana use as detrimental to health. Policies as outlined for tobacco prevention may include comprehensive marijuana-free policies, abstinence and cessation programs on marijuana use and access to these programs, hard-hitting anti marijuana media campaigns, funding for marijuana control programs and research, measures of controlling access to marijuana based on its eventual decriminalization, and limiting advertising and promotion aimed at adolescents.

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Appendices

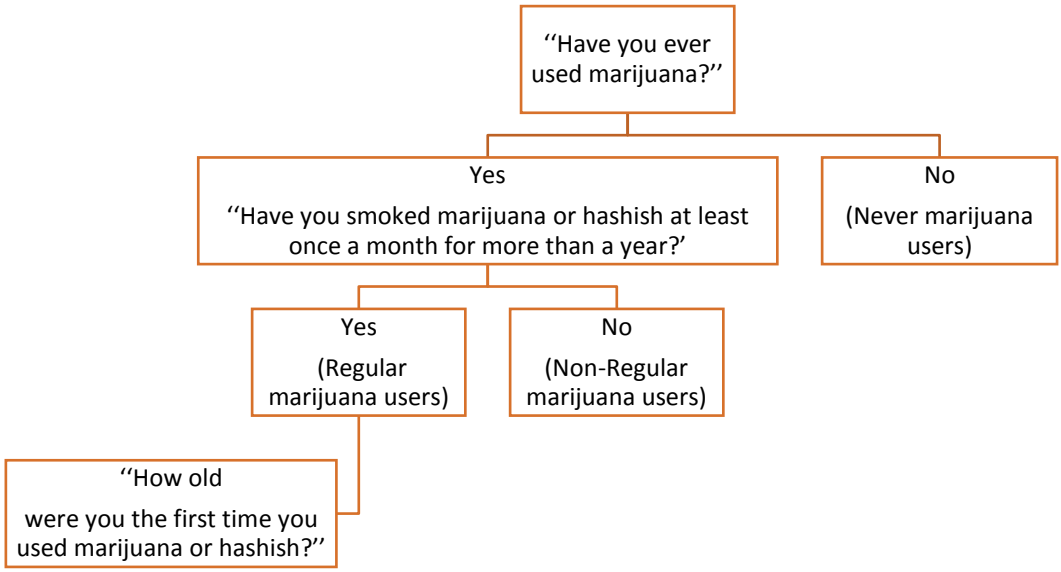

Figure 1.1 Measurement of independent variable (marijuana use)

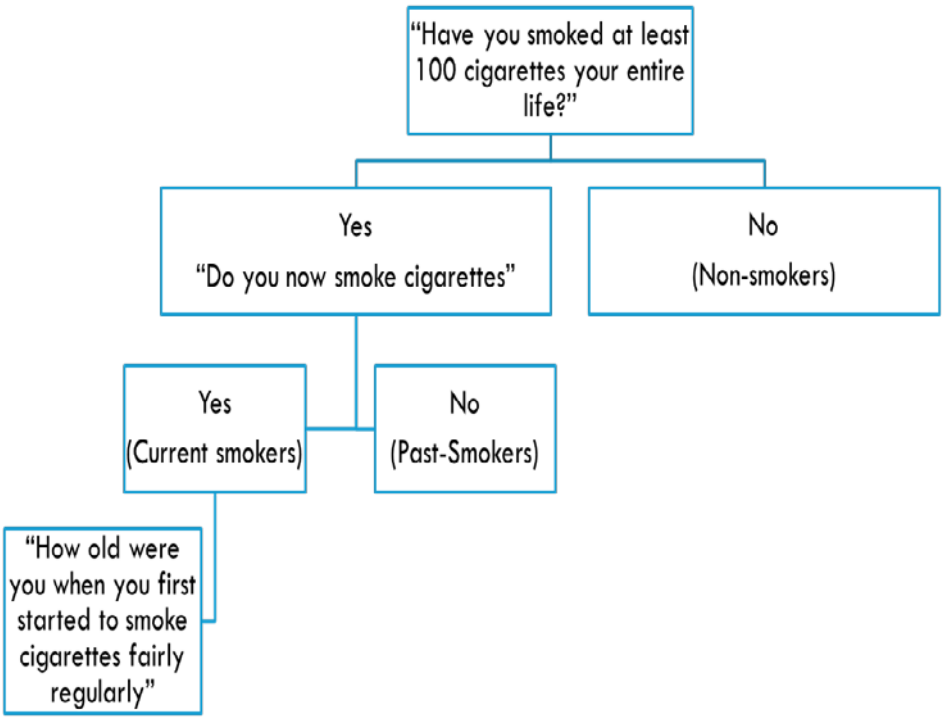

Figure 1.2 Measurement of independent variable (cigarette smoking)

Alternate Criteria for Metabolic Syndrome

Component	WHO	EGIR	ATP (III)	IDF
Insulin resistance	IFG, IGT, T2DM, LIS, FPI >25.2 µIU/ml + any 2	Plasma Insulin > 75th percentile + any 2	No insulin resistance requirement; any 3 below	No insulin resistance requirement
Body weight	Waist/Hip, >0.90 (men), >0.85 (women), BMI >30 kg/m^2	Waist circumference, ≥ 94 cm (men), ≥ 80 cm (women)	Waist circumference, ≥102 cm (men), ≥ 88cm (women)	Increased population specific waist circumference + any 2
Lipid	TG ≥150 mg/dl and/or HDL-C <35mg/dl (men), < 39mg/dl (women)	TG ≥150 mg/dl and/or HDL-C < 39mg/dl	TG ≥150 mg/dl HDL-C < 40mg/dl (men) < 50 mg/dl (women) or Medication for cholesterol	TG ≥150 mg/dl HDL-C < 40 mg/dl (men) < 50 mg/dl (women) or Medication for cholesterol
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or Medication for hypertension	>130/85 mm Hg or Medication for hypertension	>130/85 mm Hg or Medication for hypertension
Plasma glucose	IFG, IGT, T2DM OGTT ≥140 mg/dl	IGT, IFG	≥ 100 mg/dl Medication for Diabetes	≥ 100 mg/dl Medication for Diabetes
Other	ALB/CR ≥30			

Figure 2.1 Definition of metabolic syndrome by four common criteria

Chart adapted from Scott M. Grundy, James I. Cleeman, et al., AHA/NHLBI Scientific Statement: Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement *Circulation. 2005;112:17 2735-2752*

ALB/CR – Albumin creatinine ratio
ATP (III) – National Cholesterol Education Program Adult Treatment Panel III
BMI – Body mass index
EGIR – European Group for the Study of Insulin Resistance
FPI – Fasting plasma Insulin
HDL-C – High density lipoprotein cholesterol
IDF – International Diabetes Federation
IFG – Impaired fasting glucose
IGT – Impaired glucose tolerance
LIS – Low insulin sensitivity
T2DM – Type 2 diabetes mellitus
TG – Triglycerides
OGTT – Oral glucose tolerance test
WHO – World Health Organization

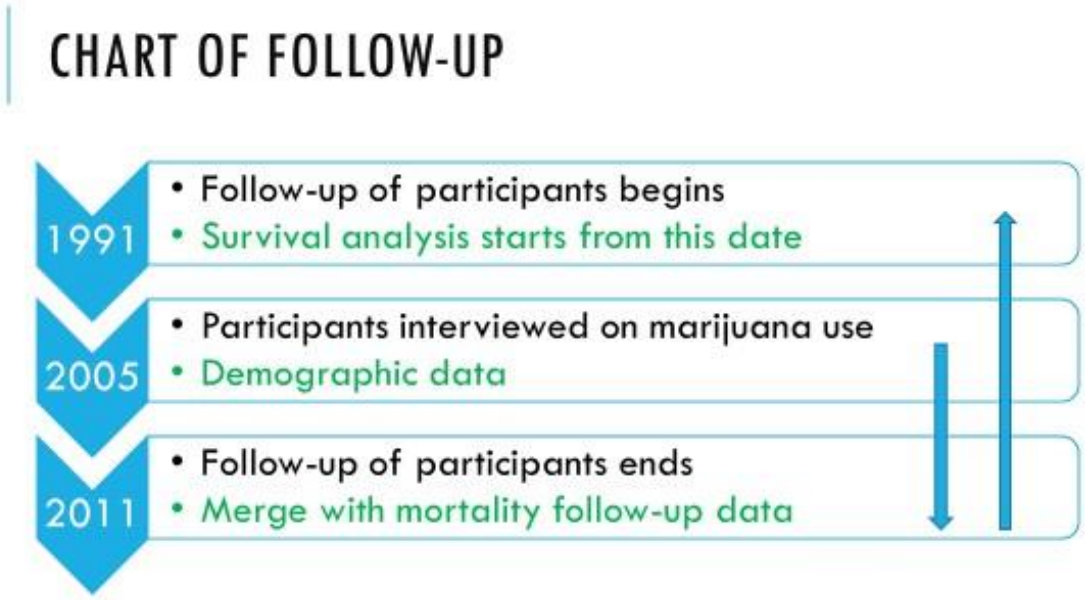

Figure 3.1 Chart showing selection of participants for merging and mortality follow-up

Substance use	Percentage
Neither used marijuana nor smoked cigarettes	34.3
Marijuana only users	20.9
Marijuana users & current cigarettes smokers	20.0
Marijuana users & past smokers	15.6
Past cigarette smokers	4.8
Smoke only cigarettes	4.4
Total	100.0

Figure 3.2 Distribution of participants by substance use