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MARIJUANA USE AND MOTOR VEHICLE CRASHES

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ABSTRACT

Legalization of marijuana has been a topic of debate for decades. Advocates for legalization argue that marijuana has many medical applications and that legalization would lead to increased tax revenue, but the opposition to marijuana legalization points to the many negative effects of marijuana use, as well as the undesirable consequences of legalization. The recent legalization of marijuana for both recreational and medicinal purposes in Colorado and Washington has increased interest in this debate.

To better inform the debate over legalization of marijuana, this study was done to investigate the relationship between marijuana use and motor vehicle crash risk. Many previous studies have been done on this topic but have yielded conflicting results. This new study conducts a meta-analysis in order to use the previous studies and produce a statistically significant result. It was hypothesized that marijuana use would be positively correlated with higher motor vehicle crash risk.

The results of the meta-analysis confirm the hypothesis. The mean odds ratio using the random effects model for crash risk of drivers who tested positive for marijuana use versus drivers who tested negative was found to be 2.24 (95% CI = 1.45 to 3.47). Using the random effects model for crash culpability, a mean odds ratio of drivers who tested positive for marijuana use versus drivers who tested negative of 1.72 (95% CI = 1.19 to 2.48) was calculated. Therefore, there is a statistically significant positive association between marijuana use and motor vehicle crashes.

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ACKNOWLEDGEMENTS

This thesis is based on a research project that I worked on at the Columbia University Medical Center (CUMC) as a research intern in 2010. The methods, results, statistical analysis, and figures of this thesis are from the research completed at CUMC. While at CUMC, I worked closely with Dr. Guohua Li and other faculty members to complete a meta-analysis on the association between marijuana use and motor vehicle crashes. After that summer, we were able to publish our work in Epidemiologic Reviews, a leading public health journal, with my name listed as the first author.

I would like to thank Columbia University Medical Center and the faculty and interns there who guided and aided me in completing my original research project. In particular, I would like to thank Dr. Guohua Li for the original project idea, helping to get me started, and providing me with all the necessary tools needed.

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Chapter 1 : Introduction

Portions of this thesis are derived from my first-authored paper on the subject of the association between marijuana use and motor vehicle crashes (Li et al., 2012).

General Background

Less than a century ago, marijuana was legal within the United States. It was used both recreationally and medically. In fact, it has been used medically around the world for thousands of years. However, marijuana has become an illegal substance in the United States through the passage of the Marijuana Tax Act of 1937, removal from the US Pharmacopoeia and National Formulary, and classification as a Schedule I drug by the Controlled Substances Act of 1970.

For the past half century, however, there has been much debate over the legal status of marijuana (Joffe et al., 2004). Supporters of the ban cite all the negative effects of the drug, including loss of perception and distortion of time, whereas advocates for legalization point to effective medical uses and overall safety (Barnes, 2000). There have been many cases where patients, particularly cancer patients, claim that marijuana was instrumental for helping them deal with the symptoms (*Clearing the Smoke*, 2011). On November 6, 2012, the states of Colorado and Washington passed bills legalizing the use of marijuana (Dobuzinskis, 2012). This major event has fueled the debate over the legalization of marijuana.

To better inform the debate over legalization of marijuana, this paper provides general background information on the drug and specifically explores the relationship between marijuana use and driving. Driving safety is one of many serious concerns for determining whether marijuana use should be legalized, so this study aims to find the correlation or lack of correlation

between marijuana use and motor vehicle crashes.

Historical Background

Marijuana has been used as a medicine for thousands of years and over a century in the United States (*Clearing the Smoke*, 2011). In fact, there is evidence that marijuana was used medicinally five thousand years ago in China. Since then, marijuana has become a common medicine with many documented and successful treatments of disease such as skin inflammation, venereal disease, epilepsy, and tetanus. Even within the United States, many medical societies have found beneficial uses for marijuana in medicine (Grinspoon, 2005).

Just as there are many claimed medicinal uses of marijuana, there are also many negative effects. In 1936, the propaganda film *Reefer Madness* was financed by a church group and released to highlight the negative effects and discourage marijuana use (Grinspoon, 2005). *Reefer Madness* included skits that demonstrated supposed consequences of marijuana use such as violent crimes, addiction, psychosis, and mental deterioration (Barnes, 2000). In reality, however, though marijuana can cause hallucinations when taken in large doses, there is no evidence showing that marijuana use has the other supposed consequences (*How Drugs Work: Cannabis*, 2011). Overall, this film was successful in swaying public opinion on the dangers of marijuana use (Grinspoon, 2005).

The following year, the Marihuana Tax Act of 1937 banned the possession and transfer of marijuana except in the case of medical or industrial use, for which a large tax of up to $100 per ounce ($100 in 1937 is equivalent $1,600 today after being adjusted for inflation) was levied ("The Marihuana Tax Act of 1937", 2013; “CPI Inflation Calculator”, 2013). The American Medical Association (AMA) opposed this act because it imposed the tax on physicians prescribing cannabis, pharmacists selling cannabis, and medical cannabis providers (Galliher &

Walker, 1977). Despite the AMA's objections, the Marihuana Tax Act was passed and few people could afford to purchase cannabis anymore. Consequently, the amount of medical cannabis sold legally decreased dramatically (Galliher & Walker, 1977).

In 1941, medical products derived from marijuana were removed from the U.S. Pharmacopoeia and National Formulary (Grinspoon, 2005). This text is a national standard for accepted drug substances, excipients, medical devices, and dietary supplements ("USP-NF Overview", 2013). Consequently, physicians were no longer allowed to prescribe marijuana for medical use.

The Controlled Substances Act of 1970 classified marijuana as a Schedule I drug. The United States Drug Enforcement Administration (DEA) ranks drugs based on potential for abuse with Schedule I having the highest potential for abuse and Schedule V having the lowest potential for abuse. Schedule I drugs are defined by the DEA as "drugs with no currently accepted medical use and a high potential for abuse" and includes drugs such as heroin, lysergic acid diethylamide (LSD), and 3,4-methylenedioxymethamphetamine (ecstasy). For comparison, Schedule III drugs have moderate potential for abuse and includes testosterone, anabolic steroids, and combination drugs with less than 15mg of Vicodin per dosage unit ("Drug Scheduling", 2013). Classification as a Schedule I drug effectively banned marijuana (Grinspoon, 2005).

Methods for Testing for Marijuana Use

There are numerous methods used to test for marijuana use, the most common of which are urine testing, blood testing, hair testing, and saliva testing. It is important to note that frequency of drug use, dosage of drug use, and variation among unique individuals are strong factors in determining the effectiveness and accuracy of each testing method. If two people each smoked marijuana only once and were tested a week later, for example, one may escape detection

in all four of the main testing methods while the other may test positive for marijuana use in urine, blood, and hair tests. Table 1-2 below shows the approximate effective detection time frame for each of the four main testing methods of marijuana.

Table 1-1: Drug Detection Times for Various Marijuana Testing Methods

	Urine	Blood	Hair	Saliva
Single Use	1-7 days	12-24 hours	-	0-24 hours
Regular Use	7-30 days	2-7 days	Months	0-24 hours

Urine testing detects metabolites of marijuana, some of which can remain in the body up to about a month ("Marijuana Drug Test Detection Times", 2012). False positive tests for marijuana use are possible due to common, similar molecules derived from other drugs or substances, so positive results are often followed up with a blood test (Cary, 2006). Due to its reliability, low cost, and relatively long detection period, urine testing is the most common test method for job applicants and employees undergoing drug screening (Niedbala et al., 2001).

Blood testing is a more reliable method of screening for marijuana use and can measure the amount of THC (tetrahydrocannabinol) present in a subject's blood. Since THC is the main psychoactive substance in marijuana, this information can be used to determine the level of impairment of a subject (Huestis et al., 1992). Consequently, blood testing is often used in investigations to determine if a subject was under the influence (Cary, 2006).

Hair testing is another common method of screening for marijuana use in job applicants. It takes about 7-10 days before residues from marijuana reach the hair and become detectable ("Marijuana Drug Test Detection Times", 2012). However, once there, these residues can be detected for months after marijuana use (Mieczkowski et al., 1998).

Saliva testing is the newest and quickest of the main four testing methods. Because of the convenience of quick results and not requiring lab equipment, saliva testing is often used by

police officers in some countries to screen if a driver may have been under the influence ("Marijuana Drug Test Detection Times", 2012). This method of testing has a sensitivity to marijuana use that may be as low as only 5%, however, and therefore is often followed up by a blood test (Yacoubian et al., 2001).

Observational studies that investigate the association between marijuana use and events such as traffic crashes are limited by the effectiveness of method utilized to detect marijuana use. In particular, detection of marijuana only indicates prior use within an interval of time (see Table 1-1). Using blood tests on subjects in traffic crashes, for example, a positive result for marijuana use would only indicate that the subject had used marijuana within the past week but not necessarily that the subject was driving under the influence of marijuana.

Arguments for Legalization

The most popular arguments for marijuana legalization are that marijuana has effective medical uses, marijuana is improperly classified as a Schedule I drug, and legalization of marijuana would result in financial benefits for the government such as additional tax revenue and decreased law enforcement costs.

Marijuana has numerous demonstrated clinical uses including reducing muscle spasms, increasing appetite, and pain relief (Grinspoon, 2005). Because of its ability to increase appetite, reduce nausea, and relieve pain, many cancer patients argue that no other drug available can match the effectiveness of marijuana, and therefore it should be legalized (*Clearing the Smoke*, 2011). In fact, the National Cancer Institute recognizes marijuana as having benefits in treating cancer symptoms and side effects of cancer therapies. So far, seventeen states have already legalized medical marijuana use for patients suffering from certain conditions (“Cannabis and Cannabinoids”, 2013).

Though the DEA defines Schedule I drugs as having high potential for abuse and no accepted medical treatment, marijuana fits neither criteria and therefore is incorrectly classified as a Schedule I drug ("Marijuana: A Chronic History", 2010). The National Cancer Institute already acknowledges that medical marijuana can be beneficial for cancer patients and marijuana has been found to be less addictive than cigarettes ("Cannabis and Cannabinoids", 2013; "Marijuana", 2012; DiFranza, 2008). Consequently, it is argued that marijuana should be considered for legalization for medical use or at least stripped of its Schedule I drug classification status.

Legalizing marijuana and then taxing it for government revenue has been a common argument for legalization of marijuana, but the financial benefits for the government may not be limited to increased tax revenue (Venkataraman, 2006). In an analysis signed by over 500 leading economists, including Nobel laureate Milton Friedman, Harvard visiting professor Jeffrey Miron discusses the financial costs and benefits of marijuana legalization for the government. With an estimated $35.8 billion annual marijuana production within the United States, a tax on marijuana could generate $6.2 billion each year (Gettman, 2006; Miron 2002). Additionally, the government would save $7.7 billion annually in law enforcement costs due in large part to eliminating the current cost of investigating, convicting, and imprisoning individuals for producing, possessing, or distributing marijuana (Miron, 2002).

Arguments Against Legalization

Opponents to the legalization of marijuana argue that marijuana has many harmful effects, that legalization would lead to higher usage, and that tax revenue would not overcome the negative effects to society.

There are many potentially harmful effects of marijuana use, including distortion of time,

loss of perception and coordination, and short-term memory loss (“Marijuana”, 2012). Additionally, chronic marijuana use is linked to increased rates of anxiety, depression, suicidal thoughts, and schizophrenia (*How Drugs Work: Cannabis*, 2011). Smoking marijuana also has many of the same negative effects as smoking, such as increased risk for lung cancer (Earleywine, 2007).

According to a study performed by the RAND Corporation, a global policy think tank, and endorsed by the White House legalization of marijuana would lead to lower prices and therefore higher usage of the drug (“Marijuana Legalization”, 2010). To show this, the RAND Corporation built a model based on the consumption of marijuana, current and future prices, and other factors. Their model predicts that legalization would lead to increased production of marijuana and competition for sales within the United States. The result would be decreased prices, increased access for consumers, and therefore increased usage by consumers (Kilmer et al., 2010).

Though marijuana would be taxed, the damage would outweigh the increased government revenue. Evidence of this can be seen by the damage caused by cigarettes and alcohol. The government currently collects about $25 billion a year from tobacco taxes and $14.5 billion a year from alcohol taxes, whereas social costs are about $200 billion a year for tobacco and $185 billion a year for alcohol (“Marijuana Legalization”, 2010).

Chapter 2 : Choosing a Research Method

Previous Studies

Hundreds of previous studies have been done to study the effects of marijuana on driving. Investigation into the literature yielded two major types of studies. The first type analyzed statistical databases of motor vehicle infractions and crashes. The second type involved subjects smoking marijuana and then using driving simulators subjects while under the influence of marijuana in order to study the effects of marijuana on a host of factors including reaction time (Ramaekers, 2000; Richer, 2009).

Though there have been numerous studies, the results are not consistent. Some studies demonstrate that marijuana use impairs driving ability or is positively correlated with traffic crashes. Other studies show no statistically significant effect of marijuana. Finally, some other studies conclude that marijuana use is actually negatively correlated with traffic crashes. Because of conflicting results from these studies, further analysis must be conducted to understand the results from these studies.

Meta-Analysis

A meta-analysis can be an effective tool for interpreting and clarifying these conflicting results. It works by systematically collecting data from similarly conducted previous studies and then combining the individual results to produce a more statistically significant result. Ideally, each of the original studies used in the meta-analysis would have been performed in a near identical manner and results measured with the same statistic. In this thesis on the association

between marijuana use and motor vehicle crashes, each of the previous studies presented its results as on odds ratio.

Odds Ratio

An odds ratio is an effect size that measures the correlation between two binary variables. Using the generalized values from Table 2-1, an odds ratio is calculated to be $(p_{11}p_{00})/(p_{10}p_{01})$. An odds ratio of one means no correlation, an odds ratio larger than one indicates a positive correlation, and an odds ratio smaller than one indicates a negative correlation. Because probabilities can never be negative, an odds ratio can never be negative.

Table 2-1: Joint distribution of random variables X and Y

	Y = 1	Y = 0
X = 1	p_{11}	p_{10}
X = 0	p_{01}	p_{00}

Data Collection for a Meta-Analysis

As with any scientific study, each step should be well documented so that others can duplicate the results. In order to maintain a high quality and duplicability of systemic reviews such as meta-analyses, a group of clinical epidemiologists, clinicians, statisticians, editors, and researchers, conferenced together to write the PRISMA statement, a set of guidelines for conducting systemic reviews (Moher et al., 2009). A set of guidelines more specific to meta-analyses of observational studies in epidemiology, the MOOSE guidelines, provides further guidelines as to how meta-analyses should be conducted and reported (Stroup et al., 2000).

After determining a topic of study, data collection for a meta-analysis requires the next three major steps as described by the PRISMA statement and MOOSE guidelines. First,

eligibility criteria need to be determined to decide what studies should be included within a meta-analysis. Eligibility criteria should be strict enough that it is logical to combine each qualifying study (i.e. do not include both observational and experimental studies because each type of study has a unique set of extraneous variables that may affect the results). At the same time, they need to be lenient enough such that there are at least a few studies that do meet the criteria. Also, practical issues may be taken into account when defining eligibility criteria. For example, it is not uncommon for researchers to only include studies in a certain language (e.g. an American researcher only including studies published in English).

The second step is searching in the literature. To do this, information sources need to be chosen (e.g. PubMed). A variety of search terms should be used on numerous databases for an encompassing search. The goal is to find all studies that meet the eligibility criteria. According to the PRISMA statement, search terms and databases used should be recorded so others can duplicate the results.

The next step according to the PRISMA statement is to select which studies found while searching in the literature meet the eligibility criteria and should be included within the meta-analysis. This step is the most time-consuming portion of conducting a meta-analysis because it involves individually reviewing each of the studies found in the literature search. Based on the topic of the meta-analysis, there could be tens to thousands of previous studies found that should be reviewed. After reviewing each study, the details are coded. This means the eligibility criteria are recorded (i.e. if it fits each criterion such as language) as well as the statistical results from each study. If a study is chosen not be included in the meta-analysis, the reasoning as to why not should be recorded. Based on the results from the coding process, the eligibility criteria may be revised to produce a more complete meta-analysis.

Data Analysis for a Meta-Analysis

After the studies for inclusion have been chosen and data extracted from those studies, data analysis can be done. Since not all included studies are identical in sample size or variance, each included study is weighted differently for its impact on the final odds ratio. Two of the main models used for meta-analyses, which use different methods for weighting including studies, are the fixed effects model and the random effects model.

The fixed effects model weights each study based on the inverse of the variance of its odds ratio. This model is the simpler of the two but has the drawback that a single large study with low variance can dominate the final result whereas the smaller studies with larger variances may be virtually ignored. The following equations for calculating a meta-analysis are based on the variance method as presented in *Practical Meta-Analysis*, a comprehensive guidebook to completing an analysis (Lipsey & Wilson, 2001).

$$w_i = \frac{1}{SE_i^2} \tag{2.1}$$

$$\overline{OR} = exp\left(\frac{\sum_1^n [w_i * ln(OR_i)]}{\sum_1^n w_i}\right) \tag{2.2}$$

$$\overline{SE} = \sqrt{\frac{1}{\sum_1^n w_i}} \tag{2.3}$$

$$^{95\%}CI = (\overline{OR} - 1.96 * \overline{SE}, \overline{OR} + 1.96 * \overline{SE}) \tag{2.4}$$

To calculate the mean odds ratio of a meta-analysis, first the weight of each individual study included, w_i, is determined by the inverse of its variance (2.1). Then the mean odds ratio of the meta-analysis, $\overline{OR}$, is calculated as shown in (2.2). The standard error of the meta-analysis, $\overline{SE}$, is then calculated as shown in (2.3) where *n* is the number of studies. This standard error can then be used to determine the 95% confidence interval of $\overline{OR}$ (2.4). If a mean odds ratio of 1 does

not fall within the 95% confidence interval, then the meta-analysis yields a significant result.

The random effects model addresses the possibility that a single large study could dominate the final result by adding a random effects variance component. This model is based upon the idea that the studies included within the meta-analysis are a random sample of all possible studies that could have been included (Hedges et al., 1985). There are several methods for specifying a random effects model including the restricted maximum likelihood approach and the most commonly used DerSimonian-Laird method (Hardy & Thompson, 2006; DerSimonian & Kacker, 2007). The DerSimonian-Laird method, as described by the authors themselves, is explained below (DerSimonian & Laird, 1986).

$$Q = \sum_{1}^{n}[w_i * ln(OR_i)^2] - \frac{\sum_1^n[w_i * ln(OR_i)]}{\sum_1^n w_i} \tag{2.5}$$

$$\widehat{v}_\theta = \frac{Q - n - 1}{\sum_1^n w_i - \left(\frac{\sum_1^n w_i^2}{\sum_1^n w_i}\right)} \tag{2.6}$$

$$w_i^* = \frac{1}{SE_i^2 + \widehat{v}_\theta} \tag{2.7}$$

$$ln(\overline{OR}) = \frac{\sum_1^n[w_i^* * ln(OR_i)]}{\sum_1^n w_i^*} \tag{2.8}$$

$$\overline{SE^*} = \sqrt{\frac{1}{\sum_1^n SE_i^2 + \widehat{v}_\theta}} \tag{2.9}$$

$$^{95\%}CI = \left(exp(ln(\overline{OR}) - \overline{SE}), exp(ln(\overline{OR}) + \overline{SE})\right) \tag{2.10}$$

where w_i = weight of study as calculated in (2.1)
Q = homogeneity statistic
n = number of studies included
$\widehat{v}_\theta$ = additional variance component based on Q
w_i^* = weight of study for random effects model
$\overline{SE^*}$ = standard error of mean odds ratio

To calculate the mean odds ratio for the random effects model, first calculate the weight of each study for the fixed effects model (2.1). Then use this weight to find Q, the homogeneity statistic, as shown in (2.5). Using Q, the additional variance component of the random effects model can be calculated (2.6). Then w_i^*, the weight of each study for the random effects model, can be found using $\widehat{v}_\theta$ (2.7). Finally the log of the mean odds ratio (2.8), standard error (2.9), and 95% confidence interval (2.10) can be determined.

In addition to calculating an odds ratio and confidence interval for the meta-analysis using one of the models, it is common to conduct further data analysis in order to adjust for confounding variables or address potential limitations. Publication bias, for example, can be analyzed using funnel plots and Rosenthal's fail-safe *n* as explained in the research method section of this thesis.

Limitations of Meta-Analyses

Though a meta-analysis can be a powerful statistical tool, there is only a limited amount of control when conducting a meta-analysis since the data comes from previous studies. As a result, the meta-analyses include many inherent limitations that stem from the quality of included studies, similarity of methods of studies included, and publication bias.

A meta-analysis can only be as accurate as the studies entered. This is one of the most apparent limitations of a meta-analysis, since all the data comes from the previous studies included. Any limitations or errors from those previous studies would therefore also be present in the meta-analysis.

Another significant limitation of meta-analyses is the lack of similarity of methods of studies included. This is because two studies on the same topic can have significantly different results depending on the method or details of the study. If studying the crash risk of drivers under

the influence of alcohol, for example, an observational study conducted by analyzing databases containing information on crashes and prevalence of driving under the influence of alcohol may have significantly different results from an experimental study conducted by having subjects consume alcohol and driving in a virtual simulation. The difference in results could be attributed to extraneous factors, such as drivers in the experimental study driving more aggressively since their lives are not at risk (Banks et al., 2004). Therefore, the methods of these two studies are different in such a way that they should not both be included within the same analysis. Having strict eligibility criteria is important to minimize the impact of this limitation for meta-analyses.

One common bias of meta-analyses is publication bias, also know as the file-drawer problem (Scargle, 2000). Published studies tend to have more significant results because studies without significant results may be rejected for publication or may not be submitted for publication in the first place (Rotton et al., 1995). Consequently unpublished studies are metaphorically tucked away in a file-drawer, inaccessible to other researchers. Therefore, though an ideal meta-analysis would include all studies that fit the eligibility criteria, published or unpublished, it may be impossible to acquire all the unpublished studies.

Chapter 3 : Research Method

The following methods used to conduct this meta-analysis were based on the guidelines set forth by the PRISMA statement and MOOSE guidelines (Moher et al., 2009; Stroup et al., 2000).

Eligibility Criteria

This meta-analysis focused on two different groups of studies: crash risk and crash culpability under the influence of cannabis. Only observational studies that measured the association between marijuana use alone with at least one of these groups were included. Other eligibility criteria included being published in English and being published after 1990.

Studies that were excluded included those in which drivers were pulled over for being suspected of driving under the influence of drugs, studies published in any language other than English, or any study that did not match the criteria of measuring crash risk of cannabis users or crash culpability of cannabis users. Experimental studies in which subjects consumed cannabis were also excluded because of extraneous variables, such as increased aggressiveness in driving behavior by subjects because they were only driving in a virtual simulator and were not at risk of injury in the event of a crash (Banks et al., 204).

Searching and Coding

To search for relevant papers, several databases were used: PubMED, MedlinePlus, and the Cochrane Library. Search terms included “marijuana” and “systematic”, “marijuana” and

"motor vehicle", "marijuana" and "crash", "marijuana" and "driving", "THC" and "crash", and "drugged driving" single and in combination. Also, the related citations feature was used extensively in PubMED to find related articles to seemingly relevant studies. Some references found within certain papers were also examined.

All the articles were then transferred to EndNote X3 for further investigation. Duplicate articles were removed. Titles and abstracts were then read to remove irrelevant studies. Then full-text PDF files were obtained for each of the remaining articles. These remaining articles were then sorted based on eligibility criteria into three different groups: those comparing culpability versus non-culpability of crashes, those comparing event of crashes versus no crashes, and those articles that did not fit in either group.

Data were extracted from the remaining relevant studies and entered into Excel. The data entered included odds ratios, confidence intervals, and the effect measures used to calculate those statistics.

Data Analysis

After sorting the two main groups of articles, the random effects model was used to determine a mean odds ratio because of its advantage in weighting studies over the fixed effects model. Comprehensive Meta-Analysis (CMA) was used to calculate the mean odds ratios using the DerSimonian-Laird method. CMA is a statistical software tool developed by Biostat, a company funded by the National Institutes of Health (NIH) and dedicated to producing statistical software (Bax et al., 2007). In addition to calculating a mean odds ratio, CMA was used to generate funnel plots and calculate Rosenthal's fail-safe *n*, two tools of which can be used to assess publication bias.

A funnel plot is useful for visual assessment for publication bias by comparing the mean odds ratio and standard error for all the studies included within a meta-analysis. Each funnel plot created by CMA consists of a scatterplot with points of standard error against log odds ratio for each included study. On this scatterplot, CMA also creates a triangle, or inverted funnel, that contains the 95% confidence interval for the log of the mean odds ratio. According to Dr. Egger, a professor of clinical epidemiology and expert with funnel plots, indicators of publication bias on a funnel plot would include the presence of many points outside the funnel or significant asymmetry of points on each side of the funnel. These indicators are not absolute signs of publication bias, but they do graphically show the likelihood or degree of publication bias being present (Egger et al., 1997).

In contrast to the funnel plot, Rosenthal's fail-safe *n* is a numerical tool used to analyze if the publication bias is significant. Under the assumption that unpublished studies would average a null effect in a meta-analysis, Rosenthal's fail-safe *n* is the number of studies with insignificant results that would be needed to increase the *p*-value of the meta-analysis to above 0.05 (Orwin, 1983).

$$\overline{Z} = \frac{\sum Z}{\sqrt{N_0}} \tag{3.1}$$

$$N_{fs} = (N_0/Z_c^2)(N_0\overline{Z}^2 - Z_c^2) \tag{3.2}$$

where Z = Z score of an individual meta-analysis
$\overline{Z}$ = overall Z score of meta-analysis
Z_c = critical value of Z
N_0 = number of studies included
N_{fs} = Rosenthal's fail-safe *n*

Equations (3.1) and (3.2) demonstrate how to calculate Rosenthal's fail-safe *n*, N_{fs}, by using the Z scores of studies included (Rosenthal, 1979). Rosenthal suggests as a benchmark that if $N_{fs} > 5N_0 + 10$, then publication bias is a concern. The value $5N_0 + 10$ is commonly referred to as the threshold.

Chapter 4 : Results

Studies Included

Using the search terms specified in the methods section, 2,960 articles were found within the databases. Following the abstract and title review, 90 articles were found to correlate cannabis use with driving and were entered into the EndNote X3 database. Their full-text articles were then located and downloaded for further review. Of those 90 articles, only 17 were found to meet the eligibility criteria. Of these 17 studies, 9 of the studies contained data pertinent to crash risk and 9 of the studies were on crash culpability. One of the studies contained data for both. These studies are listed below along with their odds ratio, standard error, and detection methods.

Table 4-1: Studies included for crash risk, along with odds ratios, standard errors, and sources of exposure data.

	First Author, Year	Odds Ratio	Standard Error	Source of Exposure Data
Crash Risk				
	Asbridge, 2005	4.128	1.121	Self-report
	Blows, 2005	7.163	1.624	Self-report
	Dussault, 2002	3.374	1.155	Urine and/or blood test
	Chipman, 2003	1.299	2.355	Self-report
	Gerberich, 2003	1.178	1.179	Self-report
	Mann, 2010	3.284	1.202	Self-report
	Movig, 2004	2.822	1.401	Urine and/or blood test
	Mura, 2003	2.300	1.179	Blood test
	Woratanarat, 2009	0.845	1.739	Urine test

Table 4-2: Studies included for crash culpability with odds ratios, standard errors, and sources of exposure data.

	First Author, Year	Odds Ratio	Standard Error	Source of Exposure Data
Crash Culpability				
	Laumon, 2005	3.319	1.125	Urine and/or blood test
	Drummer, 2004	3.159	1.603	Blood test
	Williams, 1985	0.465	1.686	Blood test
	Biecheler, 2008	1.952	1.124	Blood test
	Lowenstein, 2001	1.105	1.443	Urine test
	Lenguerrand, 2008	3.174	1.116	Urine and/or blood test
	Fergusson, 2001	1.294	1.496	Self-report
	Chipman, 2003	1.201	3.243	Self-report
	Longo, 2000	0.817	1.357	Blood test

Crash Risk

Of the 17 studies used in this meta-analysis, nine were found to contain relevant data for crash risk and compared the crash risk of a user of exclusively cannabis against a drug free control group. These are shown graphically in a forest plot (Figure 4-1). All the figures in this results section were produced using CMA (Borenstein et al., 2005).

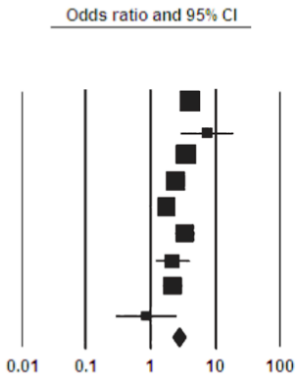

Figure 4-1: Forest plot of odds ratios for crash risk and marijuana use. The nine squares represent the odds ratios of the included studies, listed in the same order as in Table 4-1. The diamond near the bottom represents the mean odds ratio. The horizontal line through each shape shows the corresponding 95% confidence. If the 95% confidence interval line is small enough to fit within its corresponding shape, then it may not be visible.

As can be seen on the forest plot (Figure 4-1), five of the studies showed a significant increase in crash risk among cannabis users. The remaining four studies had a 95% confidence interval that included the odds ratio of 1, one of which showed a protective effect from cannabis use. The combined mean odds ratio of 2.24 (95% CI = 1.45 to 3.47) indicates a statistically significant positive association between crash risk and marijuana use.

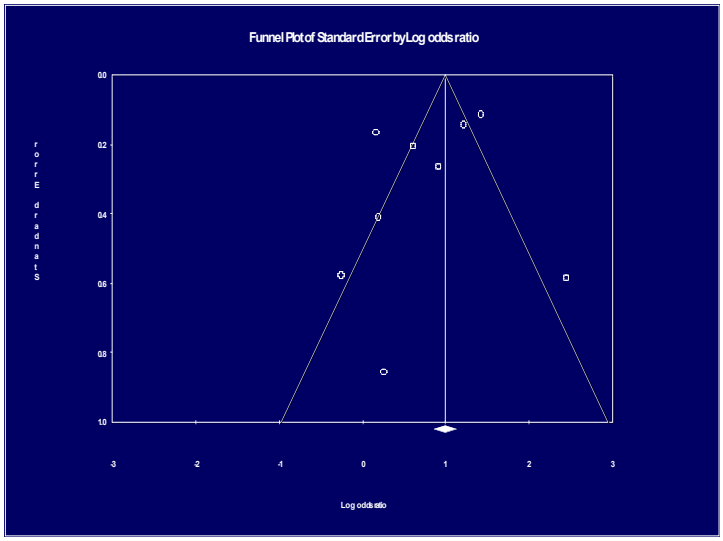

Figure 4-2: Funnel plot of crash risk creating using CMA

Publication bias was assessed graphically using a funnel plot (Figure 4-2) and numerically with Rosenthal's fail-safe *n*. On the funnel plot, the points show little asymmetry,

with the majority of points falling within the funnel, implying minimal publication bias. Since Rosenthal's fail-safe *n* was found to be 273 studies, well above the threshold of 55 studies, the result of a significant mean odds ratio is unlikely to due to publication bias.

Crash Culpability

Because one of the studies (Chipman, 2003) contained data for both crash risk and crash culpability, nine of the 17 studies were found to contain relevant statistics on crash culpability, comparing a user of exclusively cannabis against a drug free control group. These are shown visually on a forest plot (Figure 4-3).

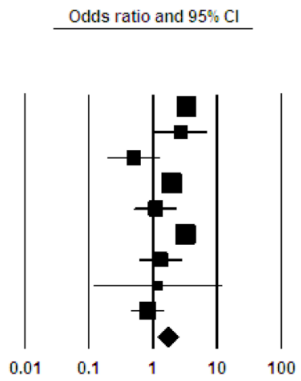

Figure 4-3: Forest plot of odds ratios for crash culpability with marijuana use. The squares represent the odds ratios of the included studies, listed in the same order as in Table 4-2 and the diamond represents the mean odds ratio. Horizontal lines through each shape represent the corresponding 95% confidence intervals, and these lines may not be visible if the 95% confidence interval fits within the shape.

As can be seen on the forest plot (Figure 4-3), only 3 of the studies showed a significant increase of crash culpability from cannabis use. The rest of the studies had 95% confidence intervals that included an odds ratio of 1, two of which actually had an odds ratio showing a protective effect associated with cannabis use. The combined mean odds ratio of 1.72 (95% CI = 1.19 to 2.48) indicates that cannabis use is significantly positively associated with crash culpability.

In order to judge for publication bias, a funnel plot was created (Figure 4-4) and Rosenthal's fail-safe *n* was calculated. Since there are only 9 studies here, it is difficult to visually judge the funnel plot. The funnel plot, though containing most points within the funnel, does seem asymmetrical, indicating that publication bias may be present. Checking with Rosenthal's fail-safe *n*, however, this concern was relieved. Rosenthal's fail-safe *n* was found to be 196 studies, which is well above the threshold of 55 studies. Therefore, there is no strong evidence that the result of a significant mean odds ratio is due to publication bias.

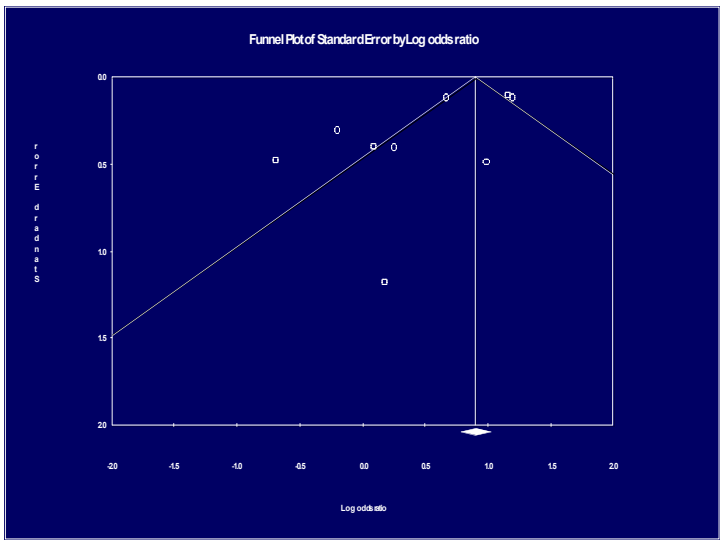

Figure 4-4: Funnel plot of crash culpability

Chapter 5 : Discussion

Conclusion

These results indicate that marijuana is indeed associated with increased crash risk and crash culpability. Association does not imply causation, however, and we cannot conclude that marijuana use causes increased crash risk. It is possible that there is one or more extraneous variables that cause both marijuana use and increased crash risk, thereby leading to the association between marijuana use and increased crash risk. Young adults, for example, are easily influenced to try new things and are more likely than older adults to smoke marijuana (Hansen et al., 1987). At the same time, young adults are less experienced and more aggressive drivers, therefore having a higher than average crash risk (Williams & Carsten, 1989). Consequently, the extraneous factor of age could be causing the positive association between marijuana use and crash risk/crash culpability. Future studies might attempt to correct for as many such extraneous factors as possible, thereby reducing the possibility of improper claims of causation.

Limitations

There are several limitations to the accuracy of this meta-analysis. Many of these limitations are inherent to meta-analyses in general, including publication bias, accuracy of studies included, and heterogeneity of studies.

There is the possibility of publication bias. In addition to researchers being less likely to publish insignificant results, marijuana being an illicit substance may also reduce the chance of

publication. However, this was analyzed though funnel plots and by Rosenthal's fail-safe *n*, and publication bias does not seem to be the cause of the significant results.

The accuracy of a meta-analysis is limited by the accuracy of the studies used. (Lipsey & Wilson, 2001) Any underlying biases that are present within the studies used will also be in the meta-analysis. One of these biases was the means of determining cannabis use. As summarized in Table 1-1, the different methods of checking for cannabis use included surveys, urine tests, and blood tests, all of which have different accuracies (Grotenhermen, 2007). The surveys, for example, could easily be inaccurate because of participants hiding their cannabis use. Also, most of these screenings could only determine if cannabis was used within the past few weeks, whereas marijuana's acute impairment on driving skills only lasts 3-4 hours (Grotenhermen, 2007). Most of the included studies determined marijuana use through self-reporting of smoking before driving on surveys; however, most of the data would suggest marijuana's acute effects were present when driving.

Another issue with meta-analyses is the presence of heterogeneity. Within the scientific community, studies are done by different people with different backgrounds, at different places, using varying methods, and interpreting with varying definitions. In this study specifically, there were a few areas of inconsistencies. The average age, gender, and personal background of the subjects used within the studies varied. The inherent issue of heterogeneity could not be avoided, but was limited due to strict eligibility criteria when selecting the studies that would be included in the meta-analysis calculations and by use of the random effects model.

Future Studies

Though this meta-analysis study revealed that cannabis use is positively associated with motor vehicle crashes, there are many factors that this study did not examine. An example of this

is dose response of cannabis use. Medical marijuana, for example, may sometimes be administered in small amounts, which may not lead to a significant negative effect on driving (Fergusson, 2001). Furthermore, marijuana can be consumed through various methods such as smoking, eating, or vaporizing. Due to a strong advisory against smoking medical cannabis from the FDA, medical cannabis is often consumed in the form of a pill or using a vaporizer (Earleywine, 2007). Perhaps the different forms of consumption may have a different effect on driving ability. As recreational marijuana use has been recently legalized in Washington and Colorado, further experimental and observational studies could be performed to further analyze these relationships (Dobuzinskis, 2012). In addition, future studies might attempt to correct for potential confounding covariates that are related to both marijuana use and driving outcomes, as stated earlier.

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