Cannabis Use Is Associated with a Substantial Reduction in Premature Deaths in the United States

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Abstract

Background: Adverse effects of moderate *Cannabis* use on physical health are subtle and rarely fatal, while *Cannabis* use is associated with decreased rates of obesity, diabetes mellitus, mortality from traumatic brain injury, use of alcohol and prescription drugs, driving fatalities, and opioid overdose deaths. These data suggest that *Cannabis* use may decrease premature deaths. To date, no studies have attempted to estimate impacts of Cannabis use on premature death that include both adverse and beneficial effects on physical health.

Methods: A systematic review, meta-analysis, and narrative summary of effects of *Cannabis* use on mortality are performed. Studies addressing the impact of *Cannabis* use on physiological systems and metabolism, and fatality rates following brain injury, are used with reported numbers of deaths from these causes and the proportion of the population using *Cannabis* to obtain an initial estimate of the effects of *Cannabis* use on premature death. Changes in death rates and alcohol consumption following legalization of medical marijuana are used with census data from states with legal access to estimate the impact of legalization of medical marijuana.

Results: Marijuana use is estimated to reduce premature deaths from diabetes mellitus, cancer, and traumatic brain injury by 989 to 2,511 deaths for each 1% of the population using *Cannabis*. Using a monthly user rate of 12.2% in the analysis, this results in an estimated 12,100 to 30,600 deaths from these causes prevented annually due to marijuana consumption. Including MMJ, *Cannabis* use appears to prevent approximately 17,400 to 38,500 premature deaths annually under current policiesh. The analysis predicts an estimated 23,500 to 47,500 deaths prevented annually if medical marijuana were legal nationwide. A number of other potential causes of reduced mortality due to *Cannabis* use were revealed, but were excluded from the analysis because quantitative data were lacking. These estimates thus substantially underestimate the actual impact of *Cannabis* use on premature death. Including states with legal access as of 2015, prohibition is responsible for an estimated minimum of 6,100 to 9,000 deaths annually due to lack of access to medical marijuana, in addition to the increased deaths from cancer, diabetes mellitus, and TBI arising from a decrease in the numbers of people using marijuana. Overall, prohibition is estimated to lead to similar numbers of premature deaths as drunk driving, homicide, or fatal opioid overdose.

Conclusions: *Cannabis* use prevents thousands of premature deaths each year, and *Cannabis* prohibition is revealed as a major cause of premature death in the U.S.

Introduction:

There is growing acknowledgement of the medical and therapeutic benefits of the unique pharmacologically active compounds produced by *Cannabis* (marijuana). These compounds, known collectively as cannabinoids, include Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) that act on the endocannabinoid system of vertebrates and other animals [1]. Millions of people find relief from a variety of medical conditions including chronic and neuropathic pain, neurodegenerative and neuroinflammatory diseases, inflammation, and nausea and emesis using *Cannabis* [2-9]. In recent surveys of medical marijuana patients, eighty percent of patients report reduced use of prescription drugs upon initiation of medical marijuana, citing more effective relief of symptoms, less withdrawal, and fewer adverse side effects as reasons for the switch [10,11]. Prescriptions for drugs used to treat pain, anxiety, nausea, psychoses, seizures, sleep disorders, depression, and spasticity decrease following legalization of medical marijuana [12]. Decreases are also reported in use of illicit drugs and alcohol by medical marijuana (MMJ) patients [10,11,13].

Recent reviews have addressed the adverse effects of *Cannabis* [14-17], and several have attempted to estimate the impact of *Cannabis* on the global burden of disease or the number of deaths caused by *Cannabis* use [18-21]. It is clear that heavy use of *Cannabis* has deleterious effects on health. However, these recent analyses only include deleterious effects of *Cannabis* use. Recent studies documenting potentially beneficial effects of *Cannabis* use on health are ignored. It is the net effect on health and mortality, including both adverse and beneficial effects, that is most important for public health - if only deleterious effects were considered, then water, food, and exercise would all be considered harmful. Furthermore, it should be obvious that non-fatal detrimental effects such as *Cannabis* use disorder are less important than effects on premature death. While use disorders can have significant negative impacts on quality of life, one can recover from use disorders. Premature death, on the other hand, is final.

Evidence for harmful effects leading to a net increase in mortality due to *Cannabis* use is weak. A number of recent studies have found no increase in the mortality rate of *Cannabis* users. One study followed a cohort of users from age 18 to 38, and found that the only negative health outcome in the end of this period arising from *Cannabis* consumption was periodontal disease, while some health outcomes (HDL, cholesterol, triglyceride, and glycated Hb levels) were improved in users [22]. The failure to detect an association between *Cannabis* use and poor physical health in midlife was not due to better initial health, or healthier lifestyles in *Cannabis* users counteracting harmful effects of *Cannabis* use, but rather arose from an absence of any significant effect of *Cannabis* use (Meier et al. 2016) [22]. A study following adolescent users into their mid-thirties did not find any association of even heavy marijuana use with health problems [23]. Another longitudinal study found

no increase in mortality over fifteen years, after adjustment for social background variables, in a group of over 45,000 Swedish military conscripts [24]. Fuster et al. [25] found that daily *Cannabis* use was not associated with increased emergency hospital visits (aOR 0.67, 95% CI 0.36 – 1.24), or rates of healthcare utilization, among patients reporting use [25]. Sidney et al. found that, after accounting for increased rates of *Cannabis* use in AIDS patients, marijuana use was not associated with increased mortality [26]. One study from Switzerland even detected a dose dependent and significant decrease in the risk of injury with *Cannabis* use (OR = 0.33, 95% CI .12 - .92) [27]. There is thus little or no support for the hypothesis that moderate marijuana use leads to significant health problems, or increased mortality rates, even following years of use.

While evidence is not consistent with moderate *Cannabis* use leading to fatal outcomes, even after years of use, there is emerging evidence suggesting that moderate *Cannabis* use may lead to significant positive health outcomes. A number of recent studies have shown lower rates of obesity, or healthier BMI, in current *Cannabis* users, effects that remain after full adjustment of the data for confounding factors [22,28-30]. The United States is in the midst of an obesity epidemic, and obesity is positively correlated with increased rates of a number of significant health issues, including cancer, cardiovascular disease, chronic kidney disease, diabetes mellitus, and Alzheimer's disease [31,32]. These obesity-related diseases have a huge impact on public health. Given that extensive research has shown that deleterious effects on physical health are subtle, and generally are not fatal, this leads to the prediction that inclusion of beneficial effects in estimates of the public health impact of *Cannabis* use will reveal that *Cannabis* use decreases the premature death rate. The present systematic review and meta-analysis attempts to provide an initial, rough estimate of the overall effects of *Cannabis* use on the mortality rate that includes evidence for both beneficial and deleterious effects.

Rationale: Recent studies have attempted to estimate the harm caused by *Cannabis* use from its effects on mortality and burden of disease. These studies are biased as they only consider deleterious effects and ignore substantial evidence for beneficial effects of moderate *Cannabis* use through effects on obesity rates and oxidative damage. The data available at this time thus suggest that the net impact of *Cannabis* use on public health, at least in terms of premature death, may be beneficial. Analyses considering both harmful and beneficial effects of *Cannabis* use in estimates of the net impact on public health are needed.

Objectives: The current study has four main objectives. These are:

1. Identify in the literature quantitative data on causes of death influenced by *Cannabis* use.
2. Determine whether available evidence on the impact of *Cannabis* use on physical health is consistent with a net beneficial or harmful impact on public health.
3. Provide an initial, rough estimate the magnitude of the effects of *Cannabis* use on the rate of premature deaths in the U.S.
4. Provide a supporting framework to assist interpretation of the results.

Methods:

Systematic review of the literature on the influence of *Cannabis* use on mortality:

This research did not involve human subjects as it is a systematic review analyzing published data. The study was performed as a systematic review with meta-analysis and narrative synthesis following PRISMA protocols [33].

Review protocol: The effects of *Cannabis* use on mortality from effects on organ systems and disease states considered most likely to be influenced by *Cannabis* were investigated. These were cancer, appetite and metabolism, cardiovascular disease, liver disease, lung disease, and brain injury. Then, data on changes in mortality rates or harmful behaviors following legalization of medical marijuana were sought and analyzed. The search engines Google Scholar and PubMed were used to identify relevant papers on these topics. The initial screen of the articles emerging from these searches selected papers reporting odds ratios or equivalent measures comparing rates of disease states in users and non-users, survival rates of users and non-users, or changes in fatalities following changes in legal status. Additional articles were sought in the reference sections of primary and review papers identified in this initial search. These studies were subjected to further analysis and supplemented with qualitative evidence allowing context. A second round of targeted searches was then performed for articles that illuminated issues arising in the initial search. The screen was performed twice, most recently in August 2016.

Eligibility criteria: Studies published since 2000, that addressed the impact of marijuana on potentially fatal diseases, survival of accidents and accident rates, or the effects of legalization of medical marijuana on mortality, were sought. Relevant studies were in English. Studies included in the quantitative analysis must report quantitative data comparing the incidence of diseases, such as rates

of cancer, diabetes mellitus, cardiovascular disease, liver disease, or lung disease, in *Cannabis* users and non-users. To be included into the meta- analysis, studies must adjust for tobacco use and other confounding factors, and provide data for usage typical of the US population.

Information sources: Google Scholar, PUBMED, and reference sections of identified research and review articles were screened for relevant papers.

Search: The initial search for articles on the correlation between cancer rates and *Cannabis* use was performed using search terms "*Cannabis* and cancer" and 'marijuana and cancer'. Search terms used for diabetes mellitus were "*Cannabis* and diabetes mellitus" and 'marijuana and diabetes mellitus". Search terms for traumatic brain injuries were "*Cannabis* and brain injury" and 'marijuana and brain injury'. Search terms for cardiovascular disease were "*Cannabis* and cardiovascular disease" and "marijuana and cardiovascular disease". Search terms for lung disease were "*Cannabis* and lung disease" and "marijuana and lung disease". Search terms for liver disease were "*Cannabis* and liver disease" and "marijuana and liver disease". For medical marijuana (MMJ), an initial search was performed using the phrases "Medical marijuana and mortality", indicating possible effects on suicides, opioid use and overdose deaths, driving fatalities, and alcohol use. This initial search was followed by searches for "*Cannabis* and suicide" and "marijuana and suicide", "*Cannabis* and opioid or opiate overdose" and "marijuana and opioid or opiate overdose", "*Cannabis* and driving fatalities" and "marijuana and driving fatalities", and "*Cannabis* and alcohol use" and "marijuana and alcohol use", respectively.

Data collection process: Citations appearing in database searches were copied into word and endnote files by search topic: i.e. *Cannabis* and cancer, *Cannabis* and DM, etc., and were initially screened for relevance by reading the title. Those articles selected in the initial screen were then considered in more detail by reading the abstract, and those providing data relevant to the study were then read in detail. Additional sources identified in reference sections of primary and secondary literature, and results of further searches to illuminate and clarify questions arising during the analysis of mortality data, were included in the analysis.

Data items: Quantitative data for effects of *Cannabis* use on causes of death hypothesized to be influenced by *Cannabis* use were identified. Causes of death investigated included obesity-related diseases such as cancer, diabetes mellitus, cardiovascular disease, and Alzheimer's disease, and diseases associated with exposure to toxins including liver disease and lung disease. Due to the well

known neuroprotective effects of cannabinoids, impact of Cannabis use on mortality from traumatic head injury was also investigated. The impact of legalization of medical marijuana on death rates was also investigated.

Potential effects on other causes of death revealed during the search, but for which quantitative data are not available, were included in the qualitative analysis.

Summary measures: The principal summary measure is changes in the rates of diagnoses and premature deaths due to *Cannabis* use, as estimated from published odds ratios or hazard ratios for disease states and TBI, and percentage changes in reported deaths following legalization of medical marijuana.

Calculations to estimate the impact of *Cannabis* use on the mortality rate from impact on physical health:

The search revealed data for cancer, diabetes mellitus, and traumatic brain injury that could be used to estimate the impact of *Cannabis* use on deaths. For cancer and diabetes mellitus, reported odds ratios, relative risk, or hazard ratios comparing users and non-users are used to estimate the effect of *Cannabis* use on the numbers of diagnoses and deaths from cancer and diabetes mellitus. While these are not identical measures, they are similar, represent the best data available, and can be used to provide a preliminary estimate of impact on premature death, revealing at minimum whether the impact is positive or negative and providing a rough estimate of the relative impact. For traumatic brain injury, the odds ratio for mortality of similarly injured patients testing positive and negative for *Cannabis* use are used. Estimates of the effects of *Cannabis* use on the number of fatalities from cancer, diabetes mellitus, and traumatic brain injury are calculated using Formula 1:

Formula 1: $E = DUR$

In formula 1, E = the change in diagnoses or deaths from a cause due to *Cannabis* use, D = reported annual number of diagnoses or deaths from that cause, R = (1 - the published odds ratio, hazard ratio, or relative risk), and U = the estimated *Cannabis* user rate as a percent of the population. Calculations are made the estimate of 12.2% the proportion of people age 12 and over using *Cannabis* in the previous month, from the National Health and Nutrition Examination Survey, 2007-2010 [34], giving U = 0.122. A positive value for E is the estimated reduction in numbers of diagnoses or deaths from that cause due to use of *Cannabis*, whereas a negative value for E is the estimated increase in diagnoses or deaths as a result of *Cannabis* use.

Statistical methods for analysis of cancer data:

When publications report relative rates of cancer for a variety of different usage patterns, the odds ratio for ever users versus never users (reflecting average or typical use), or for current users vs. non-users, from the fully adjusted model, was used as available. If these were not presented, the mean of the relative rates of cancer across user groups was used (see supplemental excel file). Numbers in 2013 of diagnoses for each cancer type were obtained from the American Cancer Society, and the numbers of deaths are the mean of numbers reported for 2013 by the American Cancer Society and the Centers for Disease Control, which differed slightly [35,36]. The number of deaths from HNSCC, pharyngeal cancer, or oral cancer were not reported in either the CDC or American Cancer Society databases [35,36]. Therefore, the estimate the impact of *Cannabis* use on cancers of the head and neck used the mean OR across undistributed HNSCC, nasal, oral, oropharyngeal, pharyngeal, and laryngeal cancers (mean = 0.83, 95% CI 0.64 – 1.02) with the sum of the numbers of diagnoses and deaths reported for these cancers (55,640 diagnoses and 13,005 deaths) (Table 1, see also supplemental excel file).

Screening of cancer studies:

Studies that presented data on the impact of *Cannabis* use on cancer rates were selected and screened for data quality. Thirty one such articles were identified through database searches and through other sources (most of these were published prior to the cutoff date of 2000 used in the initial search) [37-68]. Only studies that provided odds ratios or hazard ratios that could be used to estimate the impact of *Cannabis* use on rates of cancer, that were adjusted for known confounding factors including tobacco or alcohol use, or demonstrated no effect of these factors on the cancer in question, were included in the analysis (Supplemental excel file). The studies meeting the selection criteria provided 38 data points (some studies provided odds ratios for multiple cancer types or sites) (Supplemental excel file). An additional 15 studies presented quantitative data but did not meet selection criteria and were removed during screening, as follows: the study by Zhang et al. [38] on lung cancer did not report data for ever vs. never users, or odds ratios that could be averaged across user groups. The study by Zhang et al. [39] reported an odds ratio of 2.6 for HNSCC, well outside the range of the data from other studies of head and neck cancers and HNSCC (mean = 0.83, 95% CI 0.63 – 1.02, N = 17). This was found to be a statistical outlier using the Grubbs test [69] ($P < 0.01$, $G = 2.91 > G_{crit} = 2.821$, $N = 18$, $\bar{Y} = 0.93$, and $s = 0.57$) and was eliminated from the analysis. Efird et al. [41] reported an odds ratio for *Cannabis* use and gliomas, but the study was designed to detect

effects of cigarette smoking, and included a large proportion of subjects who declined to state whether they used *Cannabis*. Furthermore, multiple laboratory studies have consistently shown that THC and cannabinoids eliminate gliomas in rats and destroy glioma cells *in vitro* with no cytotoxicity for surrounding cells [70,71]. A pilot clinical study in patients with recurrent, treatment resistant glioblastoma showed that THC decreased proliferation of the tumor cells [72], The reported odds ratio for gliomas [40] was therefore excluded from the analysis. Reports on effects of *Cannabis* consumption on cancer rates from studies performed in North Africa were excluded because *Cannabis* is consumed as hashish or kiff with tobacco in North Africa [41-46] and does not represent typical ingestion methods used in the US [47]. These studies consistently show higher rates of lung cancer than studies performed in the US or Europe. Other reports were excluded as follows. One study was rejected because no adjustment was made for tobacco and only the highest usage group was included (average 48 joint years) [45]. Five studies were rejected because no adjustment was made for tobacco use [46,48,51,63,65]. Three were rejected because the study did not report odds ratios nor present data that could be extrapolated to give an estimate of OR [49-51], and one was rejected because data for effects of *Cannabis* use were only reported for HIV positive patients who might be expected to have compromised immune systems [52].

Results:

The systematic search results are presented as a PRISMA diagram (Figure 1). The primary database searches yielded 3605 articles. An additional 345 articles were identified through other sources. Removal of duplicates yielded a net of 1401 articles that were subjected to further screening. Of these, 898 were excluded and 503 were assessed further. A total of 222 articles were included in the qualitative analysis, and 23 were identified that provided data comparing relative rates of diseases of deaths in users and non-users, that could be used to estimate the impact of *Cannabis* use on the premature death rate. These were as follows: cancer (16), DM (2), TBI (1), driving fatalities (2), OD (1), and alcohol (1).

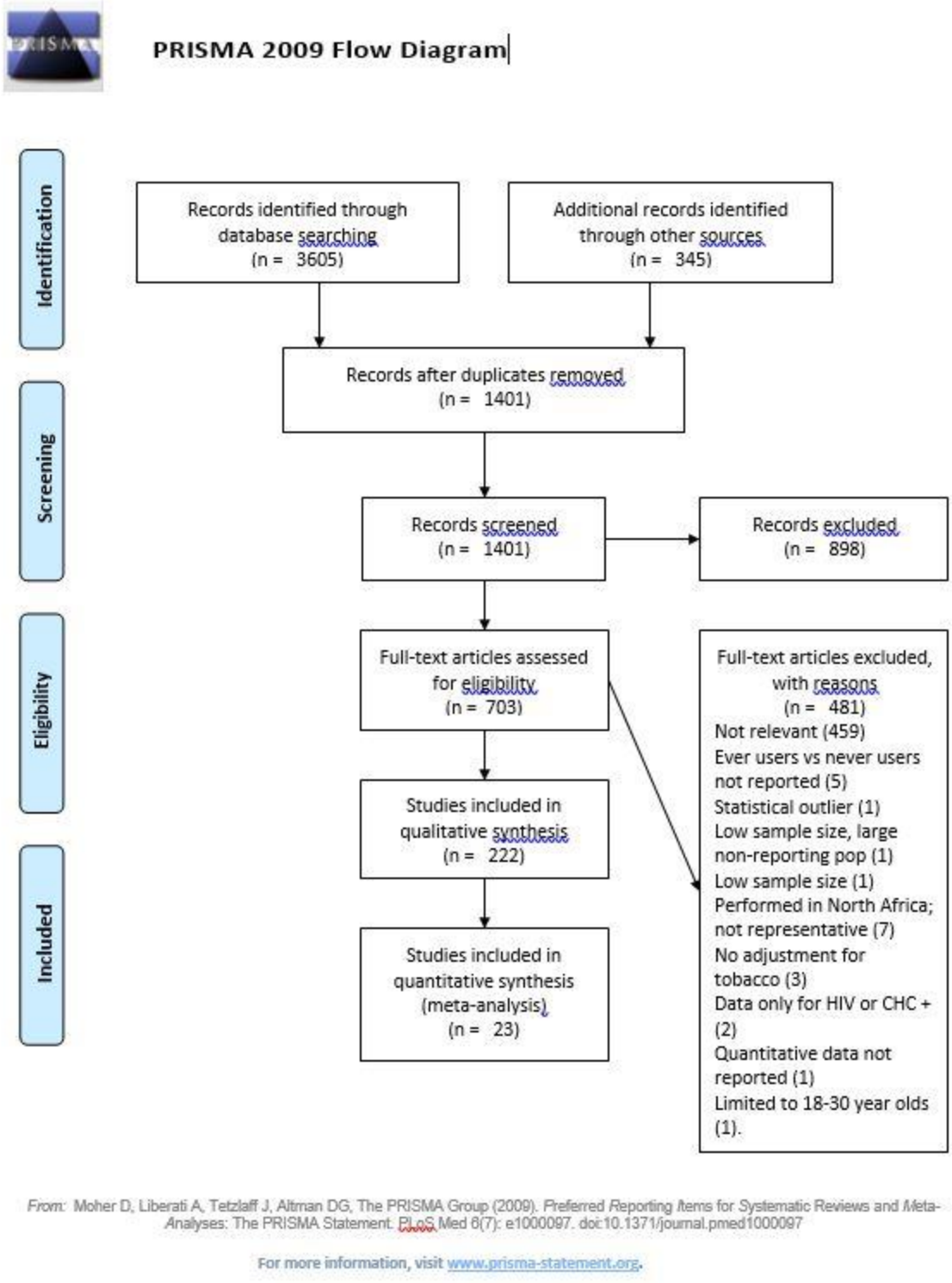

Figure 1: Prisma flow diagram of systematic search.

Effects on BMI and obesity.

Emerging evidence demonstrates critical roles for the endocannabinoid system in appetite, food intake, energy balance, and metabolism [73]. The United States, and much of the developed world, is currently in the midst of an obesity crisis, and obesity is causally associated with a number of significant health problems including diabetes mellitus [31]. Diabetes mellitus (DM) is a leading cause of death worldwide, accounting for an estimated 3.96 million premature deaths (15.7% of all deaths), in the year 2010 [74]. The economic cost in 2007 of DM, in the US alone, was estimated at 174 billion dollars [75].

Evidence strongly supports reduced obesity and diabetes mellitus in people who use *Cannabis*. The most common finding of studies to date have shown lower BMI, waist circumference, or rates of obesity in *Cannabis* users [22,28-30,76]. Le Strat and Le Foll [30] presented data from two epidemiological surveys, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and the National Comorbidity Survey – Replication survey (NCS-R). These data sets included 41,654 and 9,106 respondents, respectively. The prevalence of obesity was lower in marijuana users, and the proportion of obese individuals decreased with frequency of marijuana use, in both surveys. These effects remained after adjustment for confounding factors [30]. Rajavashisth et al. [76] reported that marijuana use was associated with a dosage-dependent decrease in the obesity rate, with the most frequent usage (≥ 5 times/month) showing one half the obesity rate of non-users, and the effects on obesity were dose-dependent and remained after adjustment for confounding factors. Ngueta et al. [29] investigated the relative rates of obesity among Inuits, and found a significant decrease in BMI in current *Cannabis* users ($P < 0.001$), who showed 56% the obesity rate of non-users. Meier et al. [22] showed decreased BMI in cannabis users. Because of these observations, Le Foll et al. [77] have proposed therapeutic use of *Cannabis* or THC for weight loss.

Effects on Cancer.

The relationship between *Cannabis* and cancer is complex. Cancer is positively correlated with obesity [31], and obesity decreases in a dose-dependent fashion with *Cannabis* use [28-30], whereas *Cannabis* smoke contains carcinogens. On the other hand, a casual examination of the literature reveals numerous laboratory studies demonstrating that cannabinoids have potent anti-tumoral properties *in vitro* and in mouse models. Cancers inhibited by cannabinoids include gliomas, thyroid epithelioma, lymphoma, neuroblastoma, and carcinomas of the oral region, lung, skin, uterus, breast, prostate, pancreas, and colon [70-72,79-87]. Thus, *Cannabis* may reduce the risk of getting cancer by reducing obesity rates and by direct inhibition of tumor formation or growth. In addition to these anti-tumor and anti-obesity properties, there is growing interest in the use of *Cannabis* and cannabinoids

in palliative cancer care due to their abilities to reduce opioid use and counteract a number of negative effects of chemotherapy [88-90]. Potential palliative effects include suppression of nausea and emesis, bone loss, nephrotoxicity, and cardiotoxicity, as well as improving mood and outlook and providing relief from insomnia [88-90].

Which effect predominates, the carcinogenic properties of the smoke, or the anti-tumor and anti-obesity properties of the cannabinoids? A recent review by Huang et al. [91] noted that some studies investigating the link between *Cannabis* use and cancer report decreased cancer rates in *Cannabis* users, while others report increased rates. Overall, however, they found no significant association between cancer rates and marijuana use. The current systematic review includes a number of data points not included in the study by Huang et al. [91], and screens the reports more aggressively. Furthermore, Huang et al. [91] made no attempt to relate the data for the effects of *Cannabis* use on risk of individual cancer types to the overall impact of *Cannabis* use on premature deaths from cancer. The current study attempts to do so using estimates of the proportion of the population using *Cannabis*, the odds ratios for cancer in users and non-users, and the number of deaths from cancer annually, for each cancer type. Thus, impacts of *Cannabis* use on cancers are weighted to take into account the numbers of diagnoses and deaths from each cancer type as well as the impact of *Cannabis* use, to determine the overall impacts on cancer deaths.

The conclusions reached in the present study for cancers of the head and neck differ from those of the recent meta-analysis of de Carvalho et al. [92], who found no effect of *Cannabis* use on head and neck cancers (grand mean OR 1.02). The current analysis screened the data more carefully (see above). After screening of the data, the current analysis, using reported fully adjusted values from relative rates of cancer types comprising 1,159,120 (70% of total) cancer diagnoses and 355,855 (61% of total) cancer deaths, yields a mean of 0.86, (95% CI = 0.77 - 0.96, N = 34) across all reported values meeting the selection criteria. The grand mean of values for each cancer site yielded a value of 0.89 (95% CI 0.75 – 0.98, N = 15). This estimate is lower than other studies due to a more complete search of the literature and more aggressive screening of the data, as described above. Many studies showed decreases in multiple user groups. The results of this analysis suggest that moderate *Cannabis* may reduce cancer rates in U.S. users. This effect would be expected to increase if consumers shifted to delivery methods other than smoking, such as edibles or vaping, thus avoiding the carcinogens produced during combustion.

Meta-analysis:

A total of 38 data points representing 15 cancer sites were found to meet the screening requirements and were accepted into the final analysis. Summary of these data points support decreased rates of cancer in *Cannabis* users. Of these 38 data points, 22 (58%) showed a relative

rate below 1.0, and only 12 (32%) showed a relative rate of cancer > 1.0 (Fig. 2).

There is clear evidence justifying assumptions of causality for decreased cancer in users, in the abundant laboratory studies showing anti-tumor properties of cannabinoids [70-72,79-87] and in the dosage dependent decrease in BMI or obesity rates of *Cannabis* users [22,28-30,76]. The studies and data included in the cancer meta-analysis are presented in supplemental excel file and Table 1, and in Figure 2.

When numbers of diagnoses and deaths from each cancer type with reported OR are entered into Formula 1 together with the reported OR for that cancer type, and using a user rate of 12.2% in the analysis, the analysis yields a decrease of 5,231 cancer diagnoses and 2,717 deaths each year (Table 1). These numbers for cancers with reported relative rates in users and non-users are used as lower estimates of the impact of *Cannabis* on cancer (Table 1). Odds ratios for *Cannabis* use on rates of a number of cancer types, including pancreatic, kidney, and uterine corpus cancers, are not available, but rates of these cancers are strongly correlated with obesity [93]. Pancreatic, kidney, and uterine cancers cause an additional 162,970 deaths/year (CDC) [35]. Because *Cannabis* users have significantly reduced rates of obesity relative to non-users [22,28-30,76], *Cannabis* is likely to reduce the risk of these cancer types even if it is found to have no direct anti-tumor activity on these cancers. This does not appear to be the case, however, as cannabinoids inhibit *in vitro* cell growth of uterine and pancreatic carcinomas, as well as thyroid epithelioma and neuroblastoma, other cancer types for which odds ratios are not reported [70-72,79-87]. The cannabinoids, with their potent anti-tumor properties, would be distributed throughout the body and thus expected to act on many distinct cancer types, whereas the carcinogens from *Cannabis* smoking would be at highest concentrations in certain organs (oral region, airways, lungs, esophagus) that have been the main targets of investigations of the effects of *Cannabis* on cancer rates. The overall effects of *Cannabis* use on cancer diagnoses and deaths is therefore likely to be greater than the effects estimated using data on cancers with reported OR. The overall effects of *Cannabis* use on all cancers were therefore extrapolated from cancers with reported OR using the mean reported relative incidences across cancer sites (mean OR = 0.89) and the total numbers of diagnoses and deaths from all cancer types (1,665,540 diagnoses and 585,720 deaths, [35,36]). This extrapolation results in an estimated overall decrease of 22,351 diagnoses and 7,860 deaths at an estimated user rate of 12.2%.

Some of the cancer studies presented data that could be assigned to at least one of the following groups: low use (0-1 joint-year), medium use (1-10 joint-years), and high use (10+ joint-years) (Supplemental excel files). In this subset of the data, the low and medium usage groups show significantly reduced rates of cancer relative to non-users (low usage: OR = 0.76, 95% CI 0.62 – 0.94; N = 22, medium usage: OR = 0.77, 95% CI = 0.63 – 0.92, N = 15). This decrease was not observed in

the high usage group (OR = 1.34, 95% CI = 0.83 – 1.85, N = 22) (supplemental excel file; Figure 3). The relationship between *Cannabis* and cancer therefore does not appear to be dose dependent. Note that no usage group showed a significant increase in rates of cancer from *Cannabis* use in this data set.

CANCER TYPE	Total Diagnoses	Total Deaths	Odds ratio (N)	Decrease diagnoses	Decrease deaths
H&N	55,640	13,005	0.83 (17)	1154	270
Esophageal	17,990	14,950	0.61 (1)	856	711
Lung	228,190	157,866	1.02 (5)	-557	-385
Prostate	238,590	28,701	1.3 (1)	-8,732	-1,050
Cervical	12,340	4,024	1.1 (1)	-150	-49
Colorectal	136,830	50,310	0.75 (2)	4,173	1,534
Melanoma	76,100	9,710	1.15 (2)	-1,393	-177
Testicular	7,920	370	1.0 (5)	0	0
Bladder	72,570	15,484	0.55 (1)	3,984	850
Anal	7,060	880	0.8 (1)	172	21
Penile	1,570	310	1.0 (1)	0	0
Breast	234,580	40,678	0.8 (1)	5,724	993
Lower Est.	**1,159,120**	**355,855**	**0.86 (38)**	**5,231**	**2,717**
Upper Est.	**1,665,540**	**585,720**	**0.89 (15)**	**22,352**	**7,860**

Table 1: Summary of effects of *Cannabis* use on cancer diagnoses and deaths, by cancer type. Effects of *Cannabis* use on mortality rates were calculated using Formula 1 with data in the Supplemental excel files, using an estimated user rate of 12.2%. The numbers of diagnoses and deaths reported for each cancer type in the year 2013 were obtained from the American Cancer Society and the Centers for Disease Control [35,36]. H&N refers to cancers of the head and neck include HNSCC, oral, oropharyngeal, pharyngeal, and laryngeal cancers. NHL refers to non-Hodgkin's lymphoma. Positive values in the columns for reduction in diagnoses or deaths show a decrease, while negative values show increased diagnoses or deaths. **"*Lower Est.*"** shows the result across cancers with reported OR (70% of total cancer diagnoses and 61% of deaths) using the grand mean of the relative rates of cancer in users and non-users across studies, and is used as the lower estimate for effects of *Cannabis* use on cancer rates. **"*Upper Est.*"** is the estimate generated extrapolating the mean of reported relative incidence values by cancer site to all cancers, and is used as the upper estimate of effects of *Cannabis* use on cancer. The references and data used to create this table are presented in the Supplemental excel file.

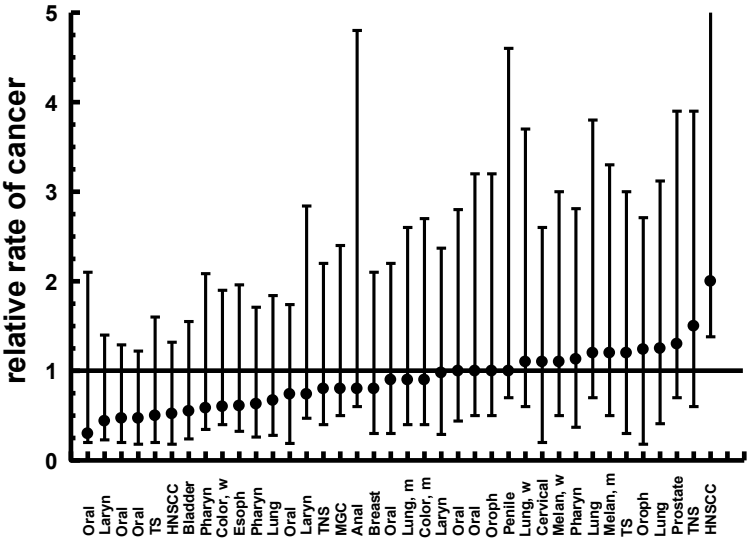

Figure 2: Forest plot of adjusted cancer data. Data are represented as mean ± 95% CI of data reported in the Supplemental excel file. Relative frequency refers to raw data in the form of odds ratios, hazard ratios, and relative risk. HNSCC = head and neck squamous cell carcinoma, Pharyn = pharyngeal, larynx = laryngeal, esoph = esophageal, color = colorectal, melan = melanoma, TS = testicular seminoma, TNS = testicular nonseminoma, N-HL = non-Hodgkins lymphoma, m = men, w = women. Note that only one data set shows significantly higher rates of cancer in *Cannabis* users, and that nearly twice as many data sets show relative rates < 1 (N = 22) than > 1 (N = 12). The references and data used to create this figure are presented in the Supplemental excel file.

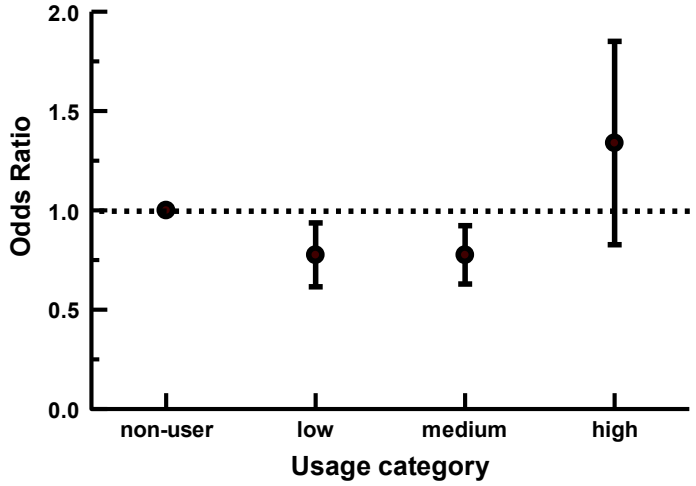

Figure 3: Effects of usage patterns on cancer risk. Some studies (identified in Table 1 with (UR) reported OR for low, medium, and heavy use. Values that could be categorized into low usage (0 – 1 joint-years; N = 22), medium usage (1-10 joint years; N = 15), and high (10+ joint years; N = 22) usage rates were pooled. The references and data used to create this figure are presented in the Supplemental excel file.
Data are presented as mean ± 95% CI.

Effects on diabetes mellitus (DM)

Diabetes mellitus (DM) is strongly correlated with BMI and obesity [31], and is also associated with inflammation [94]. Because *Cannabis* use reduces obesity rates, and cannabinoids have potent anti-inflammatory properties, *Cannabis* may decrease rates of DM. Two studies to date in the U.S. have compared rates of DM in *Cannabis* users and non-users, and both detected significantly decreased rates of DM in *Cannabis* users that hold up after adjustment for confounding variables [76,78]. Rajavashisth et al. [76] performed a multivariate model based on the Centers for Disease Control's National Health and Nutrition Examination Survey (NHANES III), using data sets from 1988 to 1994. This study included 10,896 adults, and robust multivariate analysis adjusting for sociodemographic variables, laboratory values, inflammatory marker, and comorbidity showed that *Cannabis* users had a large and significant reduction in rates of DM (fully adjusted OR 0.36, 95% CI 0.24 – 0.55, $P < 0.0001$). This effect was driven primarily by differences in the 41- 59 year old age group. Users also showed reduced LDL and elevated HDL, and reduced serum glucose relative to non-users. Alshaarawy and Anthony [78] then replicated these results, analyzed yearly surveys from the NHANES and the National Surveys on Drug Use and Health over the years 2005 to 2012, yielding a meta-analytic summary-adjusted OR of 0.7 for DM (95% CI 0.6-0.8) [78]. This analysis also showed that past and present *Cannabis* users had lower serum insulin and measures of insulin resistance than non-users [78]. Ngueta et al. [29] and Penner et al. [95] did not compare relative rates of DM in users and non-users, but both reported reduced fasting insulin and insulin resistance among *Cannabis* users. HIV-HCV patients using *Cannabis* were found to have significantly lower rates of insulin resistance than non-users (OR 0.4) [96]. On the other hand, two smaller and more limited studies [97,98] failed to detect differences in plasma glucose levels between users and non-users. The study by Muniyappa et al. [97] consisted of only 30 users and 30 non-users, and the data were adjusted for BMI. The analysis by Rodondi et al. [98] was limited to young adults aged 18 – 30 years old, a group which did not show decreased rates of DM in the study by Rajavashiseth et al. (OR 0.93) [76].

The correlations between *Cannabis* use, DM, and improved blood lipid and glucose metabolism are supported by laboratory studies in mice. The incidence of DM in non-obese diabetes-prone (NOD) mice was reduced from 86% to 30% with CBD treatment [99,100], and glucose uptake by insulin-resistant adipocytes is increased by exposure to THC *in vitro* [101]. There is thus strong evidence that *Cannabis* use significantly reduces the incidence of DM. Furthermore, cannabidiol is reported to be beneficial in diabetic cardiomyopathy [102], to reduce the endothelial inflammation and retinal damage caused by high blood glucose [103], and *Cannabis sativa* extracts protect against nerve damage in animal models of DM [104]. Thus, in addition to reducing the incidence of DM,

Cannabis appears to improve outcomes in people who develop DM, as well as improving quality of life by alleviating neuropathic pain [3,105].

Meta-analysis:

Two large studies were identified that presented relative rates of DM in users and non-users, and both show significant decreases in DM in fully adjusted models [76,78]. There is clear evidence justifying the assumption of causality in the relationship between *Cannabis* use and DM, in the form of replicated observational studies showing dose-dependent effects of marijuana use on BMI and obesity, and improved blood glucose and lipid levels and decreased insulin resistance of users [22,28-30,76,78,95,96]. Causation is further supported by studies of experimental models of the disease (i.e. NOD mice and adipocytes, [99-104]. The adjusted odds ratios provided by Rajavashisth et al. [76] and Alshaarawy and Anthony [78] were used in the analysis. In the US, there are approximately 1,700,000 diagnoses of DM each year [106]. DM was reported as the cause of 75,578 deaths [35], and as a contributing factor in 234,051 deaths in the U.S. [106]. These numbers are similar to the estimate of Roglic et al. [74], of 313,208 deaths from DM in North America in 2010. Deaths from DM are almost certainly underreported [107]. For example, the cardiovascular damage caused by DM is a major cause of death from DM, yet only 39% of diabetes patients dying of cardiovascular disease had DM listed on the death certificate [108].

In the current analysis, assuming that 12.2% of the adult population used *Cannabis* in the last month, *Cannabis* use is estimated to prevent 97,500 DM diagnoses annually. Upper and lower estimates of the impact on mortality suggest that *Cannabis* use prevents 4,300 to 17,800 premature deaths from DM annually (Table 2). The smaller value for each user rate is the estimate based on deaths for which DM was listed as the cause of death, and the larger value is based on total numbers of deaths with DM as cause or contributing factor.

Effects on cardiovascular disease:

Studies to date have failed to detect an effect of *Cannabis* use on atherosclerotic cardiovascular disease, or on cardiovascular health, or on net mortality from cardiovascular problems [28-30,109-111]. Cardiovascular disease is strongly associated with increased BMI and obesity, and both measures are reduced in *Cannabis* users [22,28-30,76]. *Cannabis* use is not correlated with cardiovascular risk factors, including hypertension, atherogenic dyslipidemia, or DM when alcohol and tobacco use are accounted for [76,95,96,111,112]. However, *Cannabis* smoking poses a risk for acute, potentially fatal cardiovascular episodes due to increased blood pressure and vasospasms

[113-124] . Many, but not all, of reported cases involve alcohol and/or other drugs [122], and deaths involving only *Cannabis* appear to be rare [114], although mortality is increased in patients who use *Cannabis* following MI [125,126]. However, tolerance to the acute cardiovascular effects develops rapidly [110,122], and over longer periods of use *Cannabis* reduces multiple risk factors for cardiovascular disease including DM and obesity [22,28-30, 76,68]. Furthermore, cannabinoid therapy reduces the progression of atherosclerosis in mice [127] and cannabinoids are potent inhibitors of inflammation [128], a hallmark of atherosclerosis thought to contribute strongly to its harmful effects [129]. Ingestion of cannabinoids (by means other than smoking) has been suggested as a way to reduce the progression of atherosclerosis [130]. CBD also protects the myocardium against ischemic reperfusion injury [131] and cannabidiol reduces the cardiovascular damage caused by elevated blood glucose levels characteristic of DM, a major cause of death associated with DM [102,103]. In addition, increased *Cannabis* use following legalization of medical marijuana is correlated with a decrease in alcohol consumption [13], and alcohol use is associated with an increased risk of stroke [132]. The neuroprotective effects of *Cannabis* are likely to reduce the risk of death and the extent of damage from strokes. Thus, the relationship between *Cannabis* use and cardiovascular disease or mortality is complex. *Cannabis* probably causes some deaths and prevents others.

Jouanjus et al. [118] reported an average of 1.8 deaths/year from acute *Cannabis*-related cardiovascular accidents in France, a country with a regular user population of 1.2 million. Mittleman et al. [120] reported increased OR for CVA in the hour immediately following ingestion, and extrapolated an increased annual risk of a MI from 1.5 to 3% due to *Cannabis* use although they did not determine overall OR of users vs non-users. Rumalla et al. [112] detected an increased rate of acute ischemic stroke in *Cannabis* users, but the effect was modest (OR 1.17, 95% CI 1.15 – 1.20) a value lower than tobacco [112] and similar to the effect of ibupropen [133]. The magnitude of the response appears to be greatest in novice or occasional users and is rapidly attenuated with repeated use [110], so that longitudinal studies fail to detect increased rates of hospitalization in regular users [22-26]. Similarly, Barber et al. [115] and Westover et al. [134] reported overall OR for *Cannabis* use but both studies were rejected from the analysis, as follows. In the study by Barber et al. [115] only one patient did not also use tobacco, so no adjustment for tobacco use could be made, while Westover et al. [134] did not adjust for either alcohol or tobacco use. Evidence shows that *Cannabis* triggers acute CV accidents, this appears to be rare, similar to the risk posed by ibupropen and lower than tobacco, the risk appears to be rapidly attenuated in regular users, and regular use reduces multiple risk factors for cardiovascular disease.

Meta-analysis:

The available data shows no net effects of *Cannabis* use on mortality rates from cardiovascular disease, stroke, or MI, as multiple studies have failed to detect such effects [22-24,109-112,130,135]. *Cannabis* lowers risk of cardiovascular disease but also triggers acute cardiovascular accidents, effects that may counteract each other. A net effect of zero is used in the summary (Table 2). More research is needed in this area to identify delivery methods with lower risk, and people with cardiovascular disease who are considering initiation of medical use of *Cannabis* should be warned of the potential risk.

Effects on lung disease:

Numerous studies address effects of *Cannabis* use on lung and respiratory system health. While many articles report respiratory problems arising from *Cannabis* smoking, especially at high usage rates, it is clearly less harmful than tobacco [137]. No consistent association has been found between *Cannabis* use and lung cancer after accounting for confounding factors [138,139]. This result was supported by the current study, in which the mean adjusted odds ratio for lung cancer across those studies that met acceptance criteria was 1.03 (N = 4; supplemental excel file). On the other hand, reports of acute injury to lungs during *Cannabis* smoking are not uncommon, and heavy, chronic *Cannabis* use is clearly associated with increased airway resistance, symptoms of bronchitis, lung hyperinflation, and inflammation of the lungs as well as cellular changes resembling those caused by tobacco smoking prior to onset of cancer [140,141]. Case studies suggest that heavy *Cannabis* use may be associated with bulla formation or histopathological changes predisposing to emphysema, lung cancer, or pneumothorax [142-144] although a systematic review concluded that a causative link with bullae is unlikely [145] or represent uncommon responses in exceptionally heavy smokers [146]. A recent longitudinal study did not detect significant lung problems following 20 years of use [22]. There is also no clear link of *Cannabis* smoking with lung fibrosis as *Cannabis* use is associated with increased measures of lung volumes or capacities, including total lung capacity, forced vital capacity, functional residual capacity, or residual volume [22,34,139,140,146]. The data are inconclusive for increased rates of lower respiratory tract infections arising from the chronic bronchitis from frequent use [139]. Contaminants of *Cannabis* such as *Aspergillis* have been reported to cause serious lung problems in medical marijuana patients, especially those who are immunocompromised [147,148]. Patients should be made aware that the harms to the lungs and airways associated with smoking can be reduced by vaping [149], or eliminated with edible delivery methods.

Meta-analysis:

While frequent or heavy *Cannabis* smoking is associated with respiratory tract problems, and it may exacerbate the respiratory problems arising from tobacco use [150], *Cannabis* use by itself does not appear to increase mortality from respiratory problems, and no quantitative data on disease incidence or mortality are available for estimates of mortality from such problems. A net effect of zero is included in the meta-analysis of effects of *Cannabis* use on premature death from lung disease (Table 2).

Effects on liver disease:

There are at this time no data showing changes in mortality from liver disease arising from *Cannabis* use. Cannabinoids both stimulate and inhibit liver fibrosis, depending on the receptor activated, and cannabinoids enhance liver steatosis [151-153] and may exacerbate effects of hepatitis C on the liver [154,155]. A cross-sectional study reported a strong correlation between daily marijuana use and moderate to severe liver fibrosis in individuals infected with HCV [155]. In another study, daily marijuana use was correlated with increased steatosis in patients with chronic hepatitis C [156]. However, a subsequent longitudinal study did not support causation of liver disease by *Cannabis* in such patients [157], finding no evidence that *Cannabis* use accelerated fibrosis (Hazard Ratio 1.02 (CI 0.93 – 1.12) or cirrhosis (HR 0.99 (0.88 – 1.12) [157]. Instead, the evidence was consistent with the correlation having arisen due to self-medication to treat the symptoms of liver disease [157]. Thus, *Cannabis* does not appear to increase mortality from liver disease in the absence of underlying disease states such as hepatitis C or toxin exposure, but may interact with other factors that cause harm to the liver.

On the other hand, legalization of medical marijuana results in a reduction in alcohol consumption [13], and reduces the use of prescription pain and other medications [12], actions that would reduce injury to the liver. For example, the popular over-the-counter pain medication acetaminophen was involved in 881 overdose deaths in 2010 [158] and is a common cause of liver toxicity. Combining acetaminophen and alcohol is especially harmful. Furthermore, nonalcoholic steatohepatitis is significantly correlated with obesity and insulin resistance, leads to cirrhosis, and is the third- most important indication for liver transplant [159,160]. The decrease in BMI and insulin resistance in *Cannabis* users [22,28-30,76,78,95,96] could therefore reduce nonalcoholic steatohepatitis in *Cannabis* users.

No published OR values for nonalcoholic steatohepatitis in *Cannabis* users, or data addressing whether mortality from liver disease is influenced by *Cannabis* use, were encountered during the

search, but it is possible that *Cannabis* use could reduce deaths from liver disease due to these indirect effects. Patients should be urged to use strains high in CBD, or avoid high THC-low CBD strains, due to potential aggravation of harmful effects of other drugs and alcohol by activation of liver CB_1 receptors.

Meta-analysis:

Both beneficial and harmful effects of *Cannabis* use are detected, but no quantitative data showing relative rates of liver disease in users and non-users were identified that could be used in the analysis. The effect of *Cannabis* use on premature death from liver disease was detected in the study, and a value of zero is included in the meta-analysis (Table 2). Further research is strongly merited especially for potential beneficial effects and for further evaluation of the potential for harmful interactions with other drugs.

Effects on deaths from traumatic brain injury (TBI):

Cannabinoids have well known neuroprotective effects, reducing damage from excitotoxicity, Ca^{++} influx, free radical formation, and neuroinflammation following traumatic brain injury (TBI), ischemia, and neurotoxins [161-167,169-171]. Two studies were identified that addressed relative mortality rates of *Cannabis* users and non-users from traumatic brain injury [167,168]. Both these studies reported reduced mortality in *Cannabis* users, but only one [167] presented quantitative data on relative survival rates of *Cannabis* users and non-users. The study by O'Phelan et al. [168] reported an odds ratio of 0.33 for all illicit drug use but did not report data for *Cannabis* specifically, and was therefore excluded from the analysis. The remaining study [167] reported an odds ratio for mortality, following comparable TBI, of 0.224 ($P < 0.05$). This neuroprotective effect of *Cannabis* use in survival of brain injuries is supported by several clinical and laboratory studies. Knoller et al. [169] reported that patients with severe closed head injuries who were administered the synthetic cannabinoid HU-211 showed highly significant decreases in the duration of elevated intracranial pressures, reduced cerebral perfusion pressures, and decreased systolic blood pressures, and showed better outcomes at three and six months, relative to patients who did not receive the drug. Similarly, application of CBD to rats resulted in long-lasting neuroprotection from hypoxia and ischemia [170], and the endogenous cannabinoid 2-AG is neuroprotective following brain injury [171].

Of course, increased rates of TBI in *Cannabis* users would offset increased survival following injury. The evidence at this time does not support significant increases in rates of head injuries due to

Cannabis use, however. Effects of *Cannabis* use on coordination are quite different from alcohol. Even at high doses, *Cannabis* has no noticeable effect on the ability of experienced users to ride a bicycle [172]. Several studies [22-27,173-174] were identified that addressed the relative rates of injury, hospitalizations, or TBI in *Cannabis* users. Bechtold et al. [23] found no difference in incidences of concussions among *Cannabis* user groups. Kolakowsky-Hayner et al. [173] found no statistical differences in *Cannabis* use prior to brain and spinal cord injury, and Tait et al. [174] found that marijuana problems did not predict subsequent serious brain injury. Meier et al. [22] found no associations between persistent cannabis use and health outcomes in early midlife after years of use, and noted that the lack of effects was not driven by better health when *Cannabis* use was initiated [22]. Fuster et al. [25] identified no correlation between rates of emergency room admissions and frequency of *Cannabis* use. Gmel et al. [27] reported a dose-dependent reduction in risk of injury in *Cannabis* users (RR: 0.33; 95% CI = 0.12 - 0.92), though the sample size for *Cannabis* users was small. Two studies finding increased rates of hospitalizations were rejected. Ilie et al. [175] failed to account for alcohol use. Gerberich et al. [176] identified increased rates of injury hospitalizations in past and present *Cannabis* users, driven by increased motor vehicle accidents, assaults (men) and self- inflicted injuries. However, a recent major study found that the correlation of *Cannabis* use with motor vehicle accidents disappeared when the data were adjusted for confounding factors [177]. Assaults correlated with *Cannabis* appear to be linked to prohibition rather than *Cannabis* use itself as assaults and homicides have decreased in Colorado following legalization of *Cannabis* [178]. Self-injury would appear to be related to underlying mental health issues correlated with *Cannabis* use, and not *Cannabis* use itself [179]. Effects of *Cannabis* consumption on driving accidents are discussed below, and also do not support increased rates of head injury from automobile accidents due to *Cannabis* use.

Any increase in accident rates would need to be substantial to offset the reported increase in survival following injury (OR for death = 0.224) [167], and effects of this magnitude would be readily apparent. Available evidence thus suggests that the increased survival of *Cannabis* users following brain injury is not offset by increased injury rates arising from *Cannabis* use.

Meta-analysis:

Nguyen et al. [167] presented the only data that could be used to estimate effects on premature deaths. Justification of assumptions of causality arise from studies demonstrating neuroprotective effects of cannabinoids [161-166,169-171]. The CDC reports 53,014 traumatic brain injury deaths in 2013 [35]. Using these numbers, an estimated additional 3,003 to 5,019 deaths (estimated with a 12.2% user rate) would have occurred from TBI had no *Cannabis* consumption

taken place in 2013. These numbers are reported in the meta-analysis (Table 4). It is not clear what fraction of the reported percentage of the population using *Cannabis* each month would test positive at the time of injury, so this analysis may overestimate the impact of *Cannabis* use on deaths from TBI by assuming all *Cannabis* users who were in accidents tested positive at the time of the accident. However, cannabinoids linger in the body for a significant period of time following ingestion [180], and many of the patients who tested positive may not have been impaired at the time of the accident.

Effects on neurodegenerative and neuroinflammatory diseases and epilepsy:

Cannabinoids reduce the symptoms and progression of a number of neurodegenerative and neuroinflammatory diseases, including Alzheimer's disease, multiple sclerosis, amylotropic lateral sclerosis, Parkinson's disease, and Huntington's chorea [2,4-8,181-186]. They are also protective against toxins [164-166]. The data on Alzheimer's disease are particularly interesting. This disease is associated with neuroinflammation, excitotoxicity, oxidative stress, and reduced mitochondrial activity in the brain, and is characterized by the formation of aggregations of amyloid β peptide and neurofibrillary tangles [5]. Inflammation associated with microglia plays a key role in progression of Alzheimer's [184], and microglia-associated inflammation at senile plaques is strongly suppressed by low doses of THC [182]. Molecules of particular interest in Alzheimer's pathology, and thus in development of treatment options or preventative therapies, include acetylcholinesterase, glycogen synthase-3 (GSK-3β), phosphorylated tau, and amyloid β. Laboratory studies suggest that cannabinoids slow or stop the progression of Alzheimer's through actions on each of these targets. Low doses of THC inhibit the actions of acetylcholinesterase on amyloid β-peptide aggregation [181], and reduce levels of GSK-3β, phosphorylated GSK-3β, and phosphorylated tau protein, while simultaneously increasing mitochondrial activity [5]. Recently, Currais et al. [186] showed that THC caused dissociation of existing amyloid β plaques, characteristic of not only Alzheimer's disease but also associated with the general mental declines characteristic of the aging brain. These data are supported by Marchalant et al. [187], who showed that cannabinoids attenuate the neuroinflammation and decline in neurogenesis associated with aging in the mouse brain. Another recent study showed rejuvenation of the aging mouse brain through changes in gene expression, resulting in improvements in learning and memory, in response to low doses of THC [188]. Thus, laboratory studies show that THC and other cannabinoid receptor agonists act via multiple pathways to reduce Alzheimer's pathology and improve function of the aging brain [2,5,6,128,181-188].

Other brain diseases also benefit from the neuroprotective and anti-inflammatory properties of cannabinoids. Parkinson's disease is caused by loss of dopaminergic neurons in the substantia

nigra. *Cannabis* ameliorates the bradykinesia, rigidity, and tremor that are symptoms of Parkinson's disease, and reduces progression of the disease [4,7]. Multiple sclerosis, ALS, and Huntington's disease also benefit from cannabinoids [2,4,6,183]. *Cannabis* and cannabinoids reduce or, in a few patients, eliminate the frequent seizures of patients with treatment-resistant epilepsy [189]. Families of some such patients have become medical refugees, moving from states with more repressive policies to Colorado for legal access to potentially life-saving cannabinoids. Alzheimer's is reported as the cause of 84,747 deaths annually [35], although a recent study suggests that deaths from Alzheimer's may be as high as 503,000 annually [190]. Parkinson's disease is responsible for 25,196 deaths annually [35], while epilepsy causes approximately a three-fold increase in mortality [191] though specific numbers were not available from the CDC [35].

Meta-analysis:

There is clear theoretical evidence that *Cannabis* should reduce mortality from neurodegenerative and neuroinflammatory diseases, and may actually reduce the incidence or slow the onset of Alzheimer's and other diseases. However, no quantitative data showing relative rates of these diseases, or survival from these diseases, were identified in the analysis. Emerging evidence also shows significant neuroprotection against toxins and improved function of the aging brain. However, no data are available at this time showing relative incidences or mortality rates of Alzheimer's or other neurodegenerative diseases in *Cannabis* users and non-users. These diseases therefore could not be included in the estimates. However, a hypothetical 5% decrease in mortality from Alzheimer's disease due to *Cannabis* use, assuming that the age group prone to Alzheimer's disease uses *Cannabis* at a 3% user rate (lower than the national average among adults), results in prevention of an estimated 127 to 745 deaths each year. If this population used *Cannabis* at rates similar to the general population (12.2%), and upper estimates of deaths from Alzheimer's disease [190] are used in the analysis, *Cannabis* use would prevent or delay approximately 3,100 deaths annually due to Alzheimer's disease. In addition, Jones et al. [158] showed that antiepileptic and antiparkinsonism drugs contributed to 1,717 overdose deaths in 2010. Presumably, as with opioids, reducing use of these drugs through increased availability and use of *Cannabis* would reduce these overdose deaths as well. However, as we do not have odds ratios for incidence of or deaths from neurodegenerative diseases in *Cannabis* users, or for effects of medical marijuana on use of these drugs, a net effect of zero is included in the final estimates (Table 2). Further research is needed in this area.

Disorder	Percent of population using *Cannabis*	
	12.2%	**Each 1% of adult population using**
Cancer diagnoses	5,231 – 22,352	429 - 1,832
Cancer deaths	2,717 – 7,860	223 - 644
DM diagnoses	97,478	7,990
DM deaths	4,334 – 17,754	355 – 1,455
CV disease	No net impact detected	No net impact detected
Lung disease	No net impact detected	No net impact detected
Liver disease	No net impact detected	No net impact detected
Traumatic Brain Injury	5,019	411
Neurodegenerative diseases and epilepsy	Beneficial, quantitative data lacking	Beneficial, quantitative data lacking
Total deaths prevented	12,070 – 30, 633	989 – 2,511

Table 2: Summary of the separate meta-analyses showing estimated decreases in diagnoses and premature deaths of *Cannabis* use due to health impacts. Estimates of effects of *Cannabis* use on diagnoses and premature deaths, at the reported population user rates of 12.2%, and for each 1% change in the proportion of the population using *Cannabis*, are reported for physical health parameters hypothesized to be influenced by *Cannabis* use. Odds ratios were only available for cancer, DM, and TBI, and these all showed a decrease in death rates with *Cannabis* use. Available data do not support net increases in mortality from cardiovascular disease, liver disease, or lung disease due to *Cannabis* use, while evidence supports prevention of deaths from neurodegenerative diseases and epilepsy but quantitative data are lacking.

Changes in the mortality rate following legalization of medical marijuana.

In order to more completely estimate the impact of *Cannabis* use on premature deaths, the effects of legalization of medical marijuana were also investigated. Driving fatalities, opioid overdose deaths, and alcohol consumption have all been found to decrease following legalization of medical marijuana. The apparent impact of medical marijuana on the mortality rate from these causes is estimated below.

Calculations to estimate the impact of legalization of medical marijuana on the mortality rate:

Legalization of MMJ has been reported to influence suicides, opioid overdose deaths, driving fatalities, and alcohol use. The impact of *Cannabis* use on each of these causes of death was explored further using Google scholar and PubMed as described above. The number of fatalities from these causes prevented or caused by medical *Cannabis* use (MMJ) in the United States each year, and the total since 1996, was estimated using formula 2, with E and D as in formula 1.

Formula 2: E = D(%change/100)

The change in numbers of deaths from each cause, per state, is estimated by assuming a random distribution of deaths across all states based on their population. Data on the total numbers of fatalities/year from each cause [35] are multiplied by the fraction of the U.S. population living in each state with legal access to MMJ (as of 2015; obtained from the U.S. census) to arrive at a rough estimate of the number of fatalities occurring per year from that cause in that state (Table 3). Formula 2 is then used with these data to estimate the impact of *Cannabis* use on fatalities from each cause of death per year in each state. This is by necessity an initial rough estimate ignoring heterogeneity among states. The results were then summed across states to determine the impact of legalization of medical marijuana nationwide. To estimate the deaths prevented if MMJ was legal nationwide, formula 2 was applied to the total annual number of deaths from each cause nationwide.

Effects of medical marijuana on fatal opioid overdoses:

Opiate prescription painkillers are widely used, high risk drugs with strong potential for abuse, addiction and fatal overdose. Opioid overdose deaths are spiking, and medical *Cannabis* use has been shown to reduce opioid dose and usage by as much as 64% in the treatment of chronic pain, reducing side effects and improving quality of life [194-197]. Data such as these lead to the proposition that medical *Cannabis* use is a safer option to reduce the harm and morbidity from opioid use for treatment of pain [196]. This proposal is supported by the demonstration that legalization of medical marijuana leads to significant drops in hospitalizations from opioid pain reliever, without impacting hospitalizations related to marijuana [197]. States legalizing MMJ have seen a reduction of 24.8% in the rate of fatal opioid overdose deaths in the first 5 years following legalization, and a 33% decrease after 5 years, relative to states without such legal access [192]. About 60% of the fatalities had resulted from a prescription obtained from a single provider, suggesting that many of these deaths were accidental overdoses during treatment of pain [192]. This decrease in OD deaths held up when suicides were eliminated from the data set, and appears to arise from substitution of *Cannabis* for opioids [10-12,194-199]. It should be noted that many overdose deaths involve prescription drugs other than opioids [158]. For example, in 2010 there were 3,889 reported overdose deaths from antidepressants, 2,239 in combination with opioids, 1,717 from antiepileptic and antiparkinsonism drugs, 1,125 in combination with opioids, 6,497 overdose deaths from benzodiazepines (used to treat anxiety, insomnia, and as a muscle relaxant), 5,017 in combination with opioids), 881 overdose deaths from acetaminophen, and 228 from NSAIDS [158]. Most medical marijuana patients (80%+) report substituting *Cannabis* for prescription drugs, citing less adverse side effects and better symptom

management [10-12,196-199].

Table 3:

State	Fraction of US population
AK	0.2%
AZ	2.1%
CA	12.2%
CO	1.7%
CT	1.1%
DE	0.3%
HI	0.4%
IL	4.0%
ME	0.4%
MD	1.9%
MA	2.1%
MI	3.1%
MN	1.7%
MT	0.3%
NV	0.9%
NH	0.4%
NJ	2.8%
NM	0.7%
NY	6.2%
OR	1.2%
RI	0.3%
VT	0.2%
WA	2.2%
DC	0.2%

Table 3: State legalization and census data used to estimate effects of medical marijuana on death rates. States legalizing medical marijuana as of 2015 are included in the analysis. For each state that has legalized medical marijuana, the state population as a percentage of the total US population is shown. Data on total U.S. and state populations were obtained from the U.S. census. These data are used to estimate changes in death rates from reported changes in opiate OD, driving fatalities, and alcohol for each state following legalization of MMJ.

Table 4.

Cause of death	Fatalities / year	Annual deaths prevented in states with legal MMJ	Annual deaths prevented if MMJ was legal nationwide
Opiate OD	16,235	2,227	4,759
Alcohol, excl. driving	77,924	1,823 to 3,865	3,859 to 8,258
Driving fatalities	35,369	1,324 to 1,820	2,829 to 3,890
Total	**129,528**	**5,400 to 7,900**	**11,500 to 16,900**

Table 4: Summary of meta-analysis of estimated reductions in premature deaths following legalization of medical *Cannabis*.

Opioid overdose fatalities: Estimates are based on 16,235 prescription opioid overdose fatalities nationwide/year for 2013 [35]. For years 1-5 following legalization, a reduction of 24.8 % was used in calculations, whereas for years 6- present post-legalization the reduction of 33% was used, as reported by Bachhuber et al. [192].

Driving fatalities: Estimates of changes in driving fatalities are based on 35,369 driving fatalities/year nationwide [35]. Data on the reduction in driving fatalities was estimated using the 8 to 11% decrease following legalization, as reported by Anderson et al. [13].

Other alcohol-related deaths: Alcohol-related deaths from causes other than driving fatalities were estimated using 88,000 alcohol related deaths/year (National Institute on Alcohol Abuse and Alcoholism [193]), from which the estimated numbers of drunk driving fatalities/year were subtracted, giving an 77,924 alcohol-related non-driving deaths nationwide. A lower estimate for the decrease in alcohol related deaths other than driving was established using the 5% decrease in overall alcohol consumption, and an upper estimate using the 10.6% decrease in numbers of drinks consumed, as reported by Anderson et al. [13]. These data were used in conjunction with data on the proportion of the U.S. population living in states with legal MMJ.

Meta-analysis:

Assumptions of causality are clearly justified by the substitution of *Cannabis* for pharmaceutical pain relievers [10-12,194-199]. Bachhuber et al. [192] presented the only data that could be used to estimate impacts on mortality rates. Using the 24.8% reduction in the first 5 years and 33% reduction thereafter, this rate of reduction in overdose deaths translates to an estimated 2,227 fewer overdose deaths/year in 2015 in states with legal medical marijuana. If MMJ were legal nationwide, this number would increase to 4,800. This number does not account for people who illicitly reduced opioid use with *Cannabis* prior to legalization or do so at present in non-MMJ states.

Recently, Bradford and Bradford [13] showed that legalization of medical marijuana was

associated with decreases in prescriptions for drugs to treat pain, nausea, psychosis, seizures, sleep disorders, depression, and spasticity, suggesting that overdose deaths from non-opioids used to treat these conditions should decrease as well. In addition, medical *Cannabis* use is associated with reduced use of alcohol [10,11,13] and mixing alcohol with prescription drugs greatly increases the risk of harm. Thus, it is likely that substitution of *Cannabis* for these other pharmaceuticals, and for alcohol, would further reduce overdose deaths. An analysis to test this hypothesis has not been performed to date and no data are available for inclusion in the meta-analysis.

Effects of medical marijuana on alcohol consumption:

Alcohol is a high risk drug [200,201]. The National Institute on Alcohol Abuse and Alcoholism reports approximately 88,000 alcohol-related deaths/year in the US [193]. The relative risks posed by drugs can be quantified using the margin of exposure (MOE), defined as the ratio between the toxicological threshold and the estimated human intake. Low MOE numbers indicate high risk. For individual users, the MOE for alcohol is less than 10, signifying high risk, whereas the MOE of THC is > 100, the lowest risk category. For the overall population, alcohol also ranks as a much higher risk, with MOE < 10 compared to *Cannabis* with MOE > 10,000 [200,201]. Thus, according to any objective analysis alcohol is far more dangerous than *Cannabis*. Alcohol causes mortality in several ways, including acute overdose, increased risk of driving fatalities and other fatal accidents, and chronic liver disease, and alcohol use is strongly correlated with violent crimes including assault, domestic violence, and homicide [202]. Alcohol ranked as the fifth leading risk factor for disease in 2010, with an average of 25,793 deaths/year in the US from direct health effects of alcohol [202]. Replacement of alcohol with *Cannabis* should therefore reduce the death rate.

The relationship between *Cannabis* use and alcohol consumption is complex [203]. *Cannabis* has been found to substitute for alcohol in MMJ patients [10,11,13,198-199], and alcohol and tobacco use by teens increases during periods of *Cannabis* abstinence and decreases again upon resumption of *Cannabis* use, though these effects were not observed in individuals who remained abstinent after one month [204]. In contrast, decriminalization appears to have little consistent impact on alcohol use [reviewed by 203], while *Cannabis* use predicted increased incidence of alcohol use disorder in a longitudinal study [205].

Effects of MMJ legalization on driving fatalities and other alcohol-related deaths are analyzed separately below, because we have data specifically addressing effects of legalization of medical, but not recreational, marijuana on driving fatalities.

Effects of medical marijuana on driving fatalities:

Effects of Cannabis intoxication on driving: The effects of *Cannabis* on driving are clearly distinct from, and less detrimental than, alcohol [206]. Effects of *Cannabis* use on mortality rates are not clear-cut. Recent reviews found that studies on effects of acute *Cannabis* intoxication on driving fatalities have inconsistent results, with some studies reporting increased risk, some no effect, and some decreased risk in users [207-209]. Following meta-analysis, Asbridge et al. [207] concluded that acute *Cannabis* intoxication approximately doubled the risk of fatal collisions (OR for collisions = 1.92, OR for fatal collisions = 2.1, OR for culpability = 1.65). Another systematic review and meta-analysis failed to detect any significant effect of *Cannabis* use on fatal (OR 1.26, 0.88 – 1.81) or injury (OR 1.10, 0.88 – 1.39) crashes when data were adjusted for publication bias and other confounding factors [208]. A significant increase in property damage remained following adjustment, however (OR 1.26, 1.10 – 1.44) [203]. Li et al. [209] obtained a summary odds ratio of 2.66 for crash risk.

Following these studies, the "Crash Risk" study was performed by the National Highway Traffic Safety Association (NHTSA). In this, the largest study on crash risk associated with drug use in the U.S. [177], 3,000 crash-involved drivers and 6,000 control drivers were analyzed for illicit drug and alcohol use. The unadjusted OR for *Cannabis* use and crash risk was 1.25 (P = 0.01), resembling the results of Elvik [208]. However, adjustment of the data for age, gender, and race/ethnicity further reduced the OR to 1.05 (P = 0.65), and additional adjustment for alcohol use reduced it further still, to a final OR of 1.00 (P = 0.98). In other words, this study, the largest of its kind, detected absolutely no impact of *Cannabis* use on crash risk [177] despite being sufficiently sensitive to show dose-dependent increases in blood alcohol levels well below the legal limit. Drivers at the legal alcohol limit showed a four-fold increase in crash risk. Similarly, a longitudinal study of a birth cohort did not show increased risk of driving fatalities among *Cannabis* users when the data were adjusted for risky behaviors correlated with *Cannabis* use [210]. Thus, the evidence that *Cannabis* use increases the mortality rate from driving fatalities is weak, and the correlation may be driven by other factors, such as sex, age, and other confounding factors. This is supported by a series of studies that fail to find increased utilization of emergency services or hospitalizations by long-term *Cannabis* users [22-27, 173-174]. Furthermore, increased risk during acute *Cannabis* intoxication does not necessarily translate into increased crashes or mortality at the population level, because users may alter behavior when using *Cannabis.* Possible compensatory changes include driving less often or shorter distances, avoiding roadways with higher speed limits, reducing alcohol consumption, or otherwise altering the overall risk of crashes.

Effect of changes in the legal status of *Cannabis* on driving fatalities:

Legalization of marijuana provides a natural experiment to determine population-level changes in marijuana use on driving fatalities. Driving fatalities have been declining overall, for decades [211], Legalization of both medical and recreational marijuana use have been correlated with decreases in driving fatalities [13,211,212]. Anderson et al. [13] showed that driving fatalities decrease by 8 to 11% in the year following legalization of medical marijuana, a decrease driven primarily by reduced alcohol-related driving deaths. Santaella-Tenorio analyzed data from states legalizing medical marijuana, and showed a immediate post-legalization decrease in traffic fatalities of 10.8% [211]. Santaella-Tenorio et al. [211] performed an extensive analysis of driving fatalities in states legalizing medical marijuana, using data from the 1985 – 2014 Fatality Analysis Reporting System. This study supported the analysis of Anderson et al. [13], showing immediate reductions in traffic fatalities among drivers aged 15-24 yo, and additional yearly decreases among those aged 25-44, though no effects on older age groups were observed. Dispensaries were also associated with decreases in fatalities among those aged 25-44 [211]. As drivers aged 24-45 are disproportionately represented in driving fatalities (47%), this suggests that medical marijuana legalization has the greatest impact on the population at greatest risk for driving fatalities [211]. There was heterogeneity among states, with a couple of states showing increased fatalities while most showed decreases. The overall effect was a reduction of 10.8% in traffic fatalities in states legalizing medical marijuana, with California and New Mexico showing the largest immediate post-MMJ decreases, of 16% and 17.5% respectively, whereas Michigan saw an increase. As California is the largest state with legal access, the immediate, large decrease in fatalities would make an especially pronounced contribution to the effect of legalization on driving fatalities. Balko [212] analyzed data from the Colorado Department of Transportation, and showed that driving fatalities decreased following legalization of recreational use. Illicit *Cannabis* use may therefore decrease driving fatalities in other states where it remains illegal, an effect that was invisible until revealed by changes in legal status, though replicated data from states legalizing recreational *Cannabis* use are not yet available.

The data presented by Anderson et al. [13] are used in the analysis because they are the only numerical values encountered during the search that can be entered into Formula 2 (Balko [212] did not give numerical data). Odds ratios for driving fatalities when acutely intoxicated cannot be used to estimate effects of *Cannabis* use on driving fatalities from the values for the proportion of the population using *Cannabis* each month, as it is not clear how many users consistently drive when acutely intoxicated.

The proportion of drivers involved in fatal accidents who test positive for *Cannabis* use has increased in Colorado [213] and Washington State [214] following legalization. However, like overall

risk during acute intoxication, this does not mean that *Cannabis* use increases population level crash risk, as these studies did not include controls who were not involved in accidents. If the proportion of drivers testing positive for *Cannabis* use who were not involved in a crash increased by the same amount as those who were, then *Cannabis* does not alter crash risk. As these data were not presented it is not possible to claim that observed increases in *Cannabis* use have caused an increase in crashes following legalization. In fact, data from the Colorado Department of Transportation show that driving fatalities decreased in Colorado following legalization of recreational use [212] despite evidence for large increases in the numbers of drivers testing positive for *Cannabis* [214]. Thus, it appears that, while driving under the acute influence of *Cannabis* may increase the risk of crash, driving fatalities paradoxically decrease following legalization of medical and recreational *Cannabis* use, possibly due to changes in driving behavior or substitution of *Cannabis* for alcohol, which clearly has far greater impact on driving safety [10-11,13,206,211-212].

Meta-analysis:

Assumptions of causation are justified by the relative impacts of *Cannabis* and alcohol use on driving [206] and on coordination [172], and the decrease in alcohol use upon legalization or initiation of medical marijuana [10-11,13]. For the current analysis, the most relevant studies for estimates of effects on mortality rates are those documenting changes in fatalities following changes in the legal status of *Cannabis*. Anderson et al. [13] reported an immediate post-MMJ decrease in traffic fatalities of 8-11%, while Santaella-Tenorio et al. [211] reported a very similar immediate decrease of 10.8%.

According to the CDC [210], there were 35,369 driving fatalities in the U.S. in 2013. Using the data presented by Anderson et al. [13], an estimated 1,300 to 1,800 fewer driving fatalities/year in states with legal medical marijuana, and 12,800 to 17,500 fewer driving fatalities total since legal access began (Table 4). Had medical marijuana been legalized nationwide in 1996, an estimated 53,750 to 73,900 fewer driving fatalities would have occurred during this time. These numbers are likely underestimates of the impact of *Cannabis* use, as the rate of drunk driving fatalities has decreased during this period and illicit *Cannabis* users may well have already shown reduced risk prior to legalization.

Effects of medical marijuana on other alcohol-related fatalities:

Evidence for changes in alcohol use due to decriminalization or legalization of recreational marijuana are mixed [203]. A recent review supports both substitution and complementarity of

Cannabis and alcohol under different conditions, finding that more liberal *Cannabis* laws are associated with reduced alcohol consumption [215]. The overall impact of recreational *Cannabis* use on alcohol use is therefore unclear. There is strong evidence, however, that legalization or use of medical marijuana reduces use of alcohol and prescription drugs [10-13,194-199]. If medical marijuana reduces alcohol use, it is expected to reduce non-driving alcohol-related fatalities.

Meta-analysis:

While the relationship between recreational Cannabis use and alcohol use is not yet clear, available data suggest that medical marijuana is associated with a decrease in alcohol consumption [10,11,13,198-199]. To obtain an estimate of non-driving alcohol-related fatalities, reported numbers of drunk driving fatalities (10,076/year; [216]) were subtracted from total estimates of alcohol-related deaths (88,000/year; [193,202]) to give 77,924 alcohol related fatalities/year from remaining causes. Assuming a linear relationship between consumption and risk, the reported 5% decrease in alcohol consumption in states following legalization of MMJ [13] gives an estimated decrease in non-driving alcohol-related deaths of 1,800 deaths/year (Table 4). Had the observed 10.6% reduction in number of drinks consumed during a drinking episode [13] been used in the analysis instead, this estimate would increase to 3,900 non-driving alcohol-related deaths prevented each year. These numbers are used as lower and upper estimates of the impact of medical *Cannabis* use on the alcohol-related mortality rate (Table 4). If MMJ were legal nationwide, these numbers would increase to 3,900 to 8,300 deaths prevented each year.

Effects of medical marijuana on suicide:

Anderson et al. [217] analyzed state level suicide data from the National Vital Statistics Systems Mortality Detail files from 1990 to 2007, and found that suicide rates decreased 9.2 to 10.8% in young men aged 20-29, and 9.4 to 13.7% in men aged 30-39, in states legalizing MMJ relative to states with no legal access. No change was observed in suicide rates among young women [217]. However, subsequent studies that adjusted for additional confounding factors failed to detect a change in suicide rates following legalization of MMJ [218,219]. The estimate used in the current analysis is therefore a net change of zero in annual suicides in response to legalization of medical marijuana. Note that none of the studies found an increase in suicide rates.

Summary of effects of *Cannabis* on the mortality rate:

Published data show clear evidence for reduced deaths from cancer, diabetes mellitus, traumatic brain injury, in *Cannabis* users, and reduced deaths from opioid overdose, alcohol consumption, and driving fatalities. The greatest impacts of *Cannabis* use on the death rate are from effects of *Cannabis* use on rates of diabetes mellitus and cancer. These decreases are primarily associated with "recreational" use rather than medical use. The number of deaths from cancer, DM, and TBI decreases by an estimated 989 to 2,511 deaths for each 1% of the population using *Cannabis*. In addition, legalization of MMJ prevents an estimated 5,400 to 7,900 deaths each year in states with legal access, from reduced opioid overdose deaths, driving fatalities, and alcohol use. Under the regulatory policies in place in 2015, the effects of *Cannabis* use on mortality rates from all causes of death is estimated to be the prevention of between 17,400 to 38,500 deaths prevented/year assuming that 12.2% of the population uses *Cannabis*. If MMJ was currently legal in all states, the total reduction in premature deaths would increase to 23,500 to 47,500 at a 12.2% user rate (Table 5, Figure 4).

These numbers are likely underestimates for several reasons. Laboratory studies suggest that *Cannabis* use reduces the incidence or progression of neurodegenerative and neuroinflammatory diseases, epilepsy, and harm from exposure to neurotoxins [4-7,161-167,181-186]. Alzheimer's disease is responsible for a reported 84,747 [35], and possibly the underlying cause of as many as 503,000 premature deaths annually [190], while Parkinson's disease is responsible for 25,196 deaths/year [35]. However, odds ratios for the effects of *Cannabis* use on incidences of or mortality from these neurodegenerative diseases are not available. Cannabinoids have also proven effective in reducing or eliminating the seizures characteristic of treatment-resistant epilepsy [189]. Furthermore, anti-epileptic and anti-Parkinsonism drugs caused 1,717 fatal overdoses in 2010 [158]. DM deaths are also likely underreported causing underestimation of DM deaths prevented by *Cannabis* use [107,108].

Medical marijuana patients substitute *Cannabis* for prescription and illicit drugs [10-12,194-199]. Drugs involved in overdose deaths include opioids, benzodiazepines, antidepressants, antiepileptic and antiparkinsonism drugs, antipsychotic and neuroleptic drugs, acetaminophen, barbiturates, NSAIDS, and muscle relaxants [158]. Recently, Bradford and Bradford [12] showed that prescriptions for drugs used to treat pain, anxiety, nausea, psychosis, seizures, sleep disorders, depression, and spasticity decrease following legalization of medical marijuana [12], yet data are not available for effects of legalization of MMJ on overdose deaths from drugs used to treat these conditions, other than opioids. Illicit use of *Cannabis* most likely reduced mortality rates from driving fatalities and overdoses prior to legalization, as the effects of *Cannabis* use on these causes of death only became visible when legal access increased the pool of people using *Cannabis*. Finally,

homicides and assaults are down in Colorado following legalization of recreational marijuana [178], although this most likely arises from cessation of prohibition rather than from *Cannabis* use itself. The present work therefore almost certainly significantly underestimates the number of premature deaths prevented by *Cannabis* use in the U.S. If so, further decreases in the mortality rate are expected with improved legal access.

Table 5

Scenario	Deaths prevented	Deaths prevented
	Lower estimate	Upper estimate
12.2% user rate, under current medical policies	**17,400**	**38,500**
12.2% user rate, with legal medical MJ nationwide	**23,500**	**47,500**

Table 5: Summary of the meta-analysis: Estimated lives saved per year by *Cannabis* use, from all causes. 'Current medical policies' includes states with legal access to medical marijuana in 2015, while 'legal medical MJ nationwide' gives estimates assuming legal MMJ in all states.

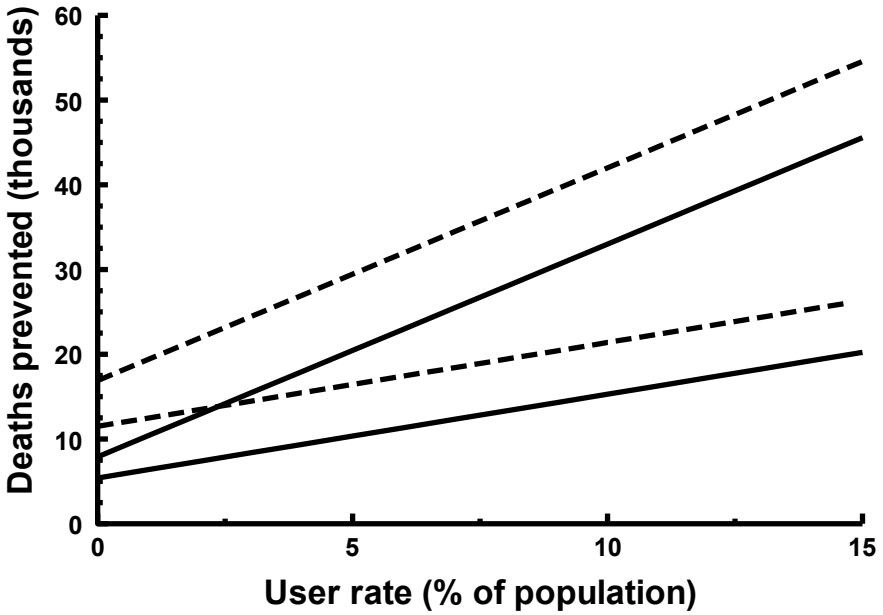

Figure 4: Estimated annual numbers of premature deaths prevented by *Cannabis* use in the United States. The solid lines show estimated premature deaths prevented by *Cannabis* use under current medical marijuana policies (as of 2015). At the Y intercept are the deaths prevented by medical marijuana, while the slope represents the additional deaths prevented by "recreational" use as a function of the percent of the

population using *Cannabis*. The dashed lines show the number of premature deaths that would be prevented by *Cannabis* use if medical marijuana were legal nationwide, with the Y intercept the deaths prevented by medical marijuana alone and the slope showing the additional effects of recreational use, as above.

Summary of the risk of bias across studies:

Prior reviews, by including only adverse effects of *Cannabis* use and ignoring beneficial effects, have grossly misrepresented the public health impact of *Cannabis* use in the U.S. This has fed misconceptions of the public health impact of *Cannabis* use that have influenced research priorities and government policies.

Estimation of the numbers of deaths caused by *Cannabis* prohibition:

If *Cannabis* reduces the mortality rate, a hypothesis strongly supported by the analysis above, and assuming that prohibition decreases the number of people using *Cannabis*, then prohibition must increase the mortality rate. Evidence that prohibition decreases the number of people using *Cannabis* is clearly seen in changes following legalization of medical marijuana, and in Colorado following legalization of recreational marijuana. The current analysis shows that the difference in deaths from opioid overdose, driving fatalities, and alcohol-related causes in states that have legalized medical marijuana (MMJ) and those that have not is an estimated 6,100 to 9,000 deaths/year. These deaths can be directly attributed to prohibition. Note that these deaths can be attributed to prohibition even if prohibition has no effect on the "recreational" user rate. We can add to this number the increased deaths from cancer, diabetes mellitus, and traumatic brain injury that occurred because prohibition caused people to abstain who would otherwise use *Cannabis*. Each 1% decrease in the proportion of the population using *Cannabis* results in an estimated 989 to 2,511 additional premature deaths each year. The amount by which the user rate is decreased by prohibition is not known. If, however, prohibition causes a 3% decrease in *Cannabis* use (from 15.2 to 12.2%), and deaths from lack of access to MMJ are included, prohibition is responsible for an estimated 9,100 to 16,500 deaths each year, in the range of the mortality rate from opioid overdose (16,235) or homicides (16,121). A 7% decrease in the user rate would cause more deaths than Parkinson's disease (25,196) [31](Figure 5). These calculations are almost certainly underestimates of the effects of prohibition, for reasons described above. Furthermore, prohibition has also almost certainly prevented the development of life-saving medicines and significant refinements in the medical use of *Cannabis* leading to additional deaths.

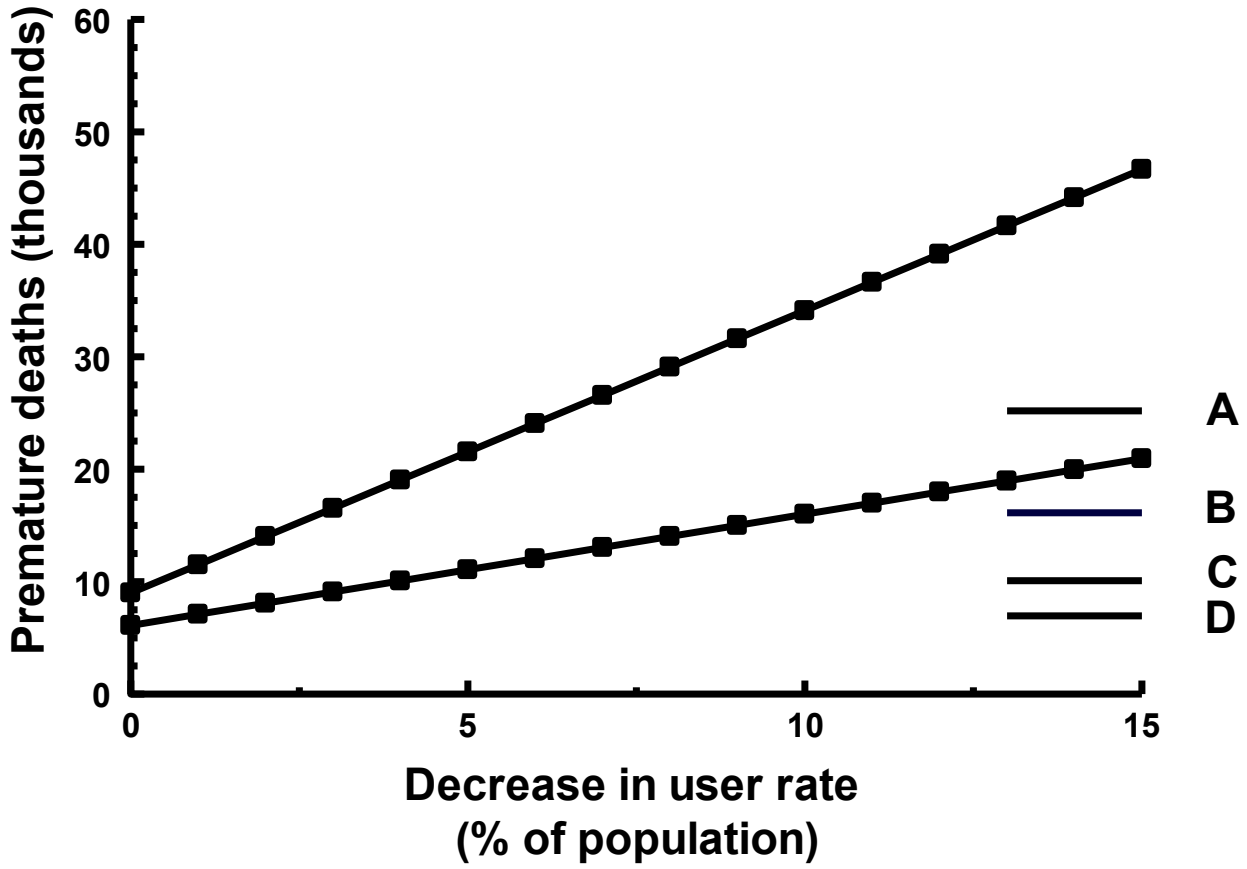

Figure 5: Annual estimates of premature deaths due to prohibition. The decrease in the percent of the population using *Cannabis* represents the effectiveness of prohibitionist policies. The Y-intercept shows the lower and upper estimates of the deaths attributed to lack of access to medical marijuana under current policies (as of 2015). The slopes of the lines are the 989to 2,511 additional deaths that occur each year from cancer, DM, and TBI for each 1% decrease in the user rate. The X- axis is the decrease in the proportion of the population using *Cannabis* in response to prohibition. The dashed lines show the numbers of deaths in 2010 from (A): Parkinson's disease, (B): homicides or opioid overdose, (C): drunk driving, and (D): HIV.

Conclusions:

This initial attempt to estimate the overall public health impact of *Cannabis* use, including both beneficial and harmful impacts on health, using published data, clearly suggests that *Cannabis* use is associated with a substantial decrease in the premature death rate.

Based on the results of this extensive review of the evidence, it is time to change the discussion, from determining how much harm is caused by *Cannabis* use, to determining how many deaths are prevented by *Cannabis* use. This does not, of course, mean that *Cannabis* has no harmful

effects, just that beneficial effects may outweigh harmful effects on physical health. The most important determinant of health status is continued survival, and the results of this investigation strongly support the hypothesis that *Cannabis* use is associated with improved survival.

The results of this analysis differ significantly from other recent studies that attempt to determine the public health impact of *Cannabis* use [18-21]. The current work includes factors (DM, cancer, TBI, MMJ) for which *Cannabis* use is associated with decreased mortality, effects that were either not known at the time, [19] or were not included [20,21] in prior analyses. The current analysis is also at odds with a number of studies that fail to detect changes in health or emergency room visits with *Cannabis* use [22-27]. The most likely cause of this discrepancy is that these longitudinal studies did not follow subjects long enough, as the longitudinal studies to date follow younger cohorts for 15 – 20 years, into their mid-thirties or early middle age [22-23]. Decreased mortality from obesity-related diseases and cancer in *Cannabis* users would most likely not become apparent until later in life. For example, the decrease in rates of diabetes mellitus observed by Rajavashiseth et al. [76] was only apparent in subjects aged 40 – 59, and death from obesity-related conditions such as diabetes mellitus may take many years after onset of the disease.

The results of the current analysis strongly suggest that *Cannabis* prohibition is a significant failure of public health policy, causing more harm than benefit. In addition to increasing the mortality rate, prohibition contributes to the largest per capita prison population in the world, interferes with pursuit of promising medical research, results in the loss of billions in potential tax revenues, empowers violent drug cartels thus destabilizing governments of neighboring countries, and causes extensive economic and electoral disenfranchisement of the most vulnerable U.S. communities. Furthermore, evidence available at this time suggests that prevention of *Cannabis* use by football players, people who are pre-diabetic or diabetic, people who may develop or have cancer, people suffering from chronic pain, epilepsy, Parkinson's disease, multiple sclerosis, Alzheimer's disease, and people who have been exposed to violence decreases their quality of life and/or increases their risk of death. This would seem to be a violation of basic human rights, especially as *Cannabis* is objectively less toxic than the widely used over-the-counter analgesic acetaminophen and many prescription drugs [158]. At present, prohibition creates the appearance that the criminal justice system is using taxpayer money to protect the profits of the pharmaceutical and private prison industries, in the process contributing to the systemic racism and voter disenfranchisement plaguing this country [223,224]. It is time to demand that politicians and the criminal justice system justify, if they can, the continuing harm caused to society by *Cannabis* prohibition when recent polls show that the majority of Americans support legalization.

Limitations of this study:

This study focuses on effects on premature death rates and does not claim that *Cannabis* has no harmful effects on individual health or society. Causes of morbidity that do not directly increase the death rate, such as *Cannabis* use disorder, are outside the scope of the study. The study focuses on population-level effects, which are by effects on the average user, rather than the worst outcomes arising in individuals with the highest levels of use. Estimates of impact of legalization of medical marijuana are based on average decreases across states and do not consider differences in population or demographics of individual states. The estimates are based on existing data revealed during extensive database searches, and these searches may have missed important data. Estimates of effects of *Cannabis* on the mortality rate from causes including neurodegenerative diseases and neurotoxins, epilepsy, those cancer types responsible for 30% of cancer diagnoses and 39% of cancer deaths, overdose deaths from prescription drugs other than opioids, and violence associated with *Cannabis* prohibition were not encountered during the search and were not included. The study is thus likely to underestimate significantly the actual impact of *Cannabis* use on the premature death rate. The numbers provided are thus rough estimates based on existing data, and it is anticipated that more refined analyses of more complete data will provide more accurate values. This study does not consider the indirect health effects of decreased life-long income due to the impact of drug law violations or *Cannabis* use on educational or employment opportunities.

Declarations:

Ethics approval and consent to participate: The analysis used published data, so ethics approval and consent to participate are not applicable.

Consent for publication: not applicable.

Availability of data and material. A summary of the cancer data used in the analysis are available in the supplemental excel file. The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Abbreviations:

MMJ; medical marijuana.
TBI; traumatic brain injury
OR; odds ratio
RR: relative risk
HR: hazard ratio
DM; diabetes mellitus
THC: Δ^9-tetrahydrocannabinol
CBD: Cannabidiol
CB_1 and CB_2: classes of cannabinoid receptors
HNSCC: head and neck squamous cell carcinoma
US; United States
LDL; low density lipoproteins
HDL; high density lipoproteins
COPD: chronic obstructive pulmonary disease
FEV_1: Forced expiratory volume, 1 second.

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