Responses to reviewer comments.

Cannabis use is associated with a substantial reduction in premature deaths in the United States.

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Preamble.

Summary of the editorial decision process at BMC Public Health, reviewer comments, and author's responses:

1. Initial decision: accepted pending minor revision.
An earlier version of this paper was deemed suitable for publication upon minor revision. The reviewer's comments are included below:

Reviewer 1: "The manuscript was interesting and well conducted from a methodological point of view. I have some comments: Row 128: to correct PRIZMA in PRISMA. Also in all other part of the text where reported. Row 156: Authors stated that studies should have a reasonable sample size. There was a minimum sample size criteria to enter into the review? Row 325-330: This methodological aspect should be reported in statistical methods. Row 398 (and other rows): to report the standard deviation for an Odds-ratio is not a diffuse practice. Only exact estimation together with the confidence interval should be reported."

Reviewer 2:
"Thank you for asking me to review the study on "Systematic review and meta-analysis indicates that Cannabis use substantially reduces the premature death rate in the United States". It is recommended to summarize the results of multiples studies in the form of forest plot. Moreover, some minor changes are also recommended which are given below; * In abstract, page 2 line 48, give full form of MMJ. * Frequent changes need in citation on various pages. For example, in page 33, line 836, 193,194,195,196,197 need to be written as 193-197. In page 35, line 875, citation from 206,207,208,209,210,211 need to be written as 206-211. Correction needed in most the places"

Author response: The forest plot was included and the other changes were made. Upon completing these revisions, I returned the revised manuscript. I received an email from the editorial staff with the statement below.

Editorial staff: “Your manuscript "Systematic review and initial estimate of the impact of Cannabis use on premature death rates in the United States" (PUBH-D-16-02309R1) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in BMC Public Health, once you have carried out some essential revisions suggested by our reviewers”.

2. The initial decision is reversed.

Now here is where it gets interesting. Normally, by standard editorial practice, this response from the editors implies that the paper can now be considered “in press”. I made the suggested revisions and returned the revision. However, the editors apparently became concerned about the political ramifications of the paper. Four months after the revised manuscript was returned, I still had not heard anything about the status of the manuscript, so I contacted the editors for an explanation. They did not respond, but the next day, the status of the manuscript changed on the website, to “reviews received”. Two days later, the editorial staff notified me that they were seeking additional advice, and then sent the manuscript out to another set of reviewers. These reviewers recommended rejection, based on the comments below. As you can see from my responses, I do not find their arguments compelling. However, the editors did not invite me to respond to these reviewer comments, and instead rejected the manuscript. The treatment of this manuscript by the editorial staff of BMC Public Health was clearly unprofessional and unscientific. The reviewers also appear to question my integrity as a scientist and lack a basic understanding of the scientific process. They also did not appear to read the manuscript carefully and showed an inability to look at the data and get past their preconceived ideas.

***Preamble: The theoretical basis for the study*.**
In contrast to the reviewer’s assumptions, the study was initiated based on theoretical insights from the ecology of plant-animal interactions. These insights led to the hypothesis that *Cannabis* evolved its signature chemical profile in a mutualistic relationship with animals. Such a relationship leads to the prediction that these chemicals will have net beneficial effects. This prediction is clearly supported by the myriad therapeutic benefits of *Cannabis*, and leads to the hypothesis that *Cannabis* use will reduce the premature death rate. This hypothesis is supported by the results of the study.

This study arose from insights gained from basic ecological and evolutionary theory, and came into focus during studies on the effects of SSRI’s on the feeding behavior of larval mosquitos. Plants defend themselves against herbivores using a variety of strategies, including chemical defenses. These defenses include toxins, anti-nutritive compounds that interfere with

digestion or absorption, and anti-feeding compounds that reduce appetite and/or induce nausea. Many plants have evolved psychotropic secondary compounds that influence the nervous system. Most examples of these are clearly defensive compounds. The sap of the opium poppy is deadly. Stimulants such as those from the coca plant increase locomotion and inhibit appetite. Nicotine from the tobacco plant is toxic, inhibits appetite, and induces nausea. Mescaline from various cacti species inhibits appetite and is packaged with compounds that induce vomiting. Similarly, in arthropods and mammals, serotonin inhibits appetite and serotonergic neurons predominate in the alimentary canal. A number of plants produce chemicals that alter serotonin levels or interact with serotonin receptors. LSA from seeds of members of the morning glory family, including *Ipomoea*, *Corymbosa*, and *Argyreia,* acts through serotonin receptors, inhibits appetite, and is packaged with compounds that induce nausea. SSRI's produced by *Sceletium tortuosum* would inhibit appetite via actions on serotonin. MAOIs inhibit the breakdown of monoamines, including serotonin, and have been used pharmacologically to treat depression. A number of plants, including *Pegalum harmala, Banisteriopsis caapi,* and *Passiflora incarnate*, produce MAOIs that would increase serotonin levels and inhibit appetite. Thus, some psychotropic plants are toxic and many if not most psychotropic plants inhibit appetite and induce nausea or vomiting. These effects make perfect sense as strategies to defend the plants against herbivores, as they would reduce the damage of herbivory on the plant leading to increased evolutionary fitness.

In contrast to these examples, the psychotropic compounds of *Cannabis* are non-toxic, stimulate appetite, and inhibit nausea and vomiting. This is not consistent with a defensive anti-feeding strategy characteristic of compounds used by other psychotropic plants in defense against herbivores. Why would a plant stimulate the appetite of the animals that are eating it? Instead, stimulation of appetite and inhibition of nausea, together with the wide range of known therapeutic benefits, are more consistent with a mutualism, a completely different type of plant-animal interaction in which both the plant and the animal benefit. Classic examples include plant-pollinator and fruit-frugivore interactions. In these, the plant develops rewards in the form of a concentrated nutrient source, and advertises the rewards with odors and bright colors. In the case of fruits, the colors and odors are only expressed when the seeds are ready to pass through the digestive tract. The animals, when taking the rewards, increase genetic diversity of the seeds by pollination or spread the seeds through the environment through frugivory.

The cannabinoids produced by *Cannabis* provide a number of rewards, as they are analgesic, promote euphoria, and inhibit inflammation and cancer. Furthermore, their role in the biology of the plant is also consistent with a mutualism. These active compounds are produced primarily in the female plant, particularly when she has not been pollinated. At the same time as she increases production of the rewards, she begins to produce odorants – in other words, as predicted by the mutualism hypothesis, the plant produces a combination of rewards and advertisement, and this is associated with sexual reproduction, just as in plant-pollinator or plant-frugivore interactions. The exact context in which these advertisements and rewards evolved is unclear.

These considerations of fundamental theory of plant-animal interactions led to the hypothesis that *Cannabis* evolved its pharmacopoeia in the context of a mutualistic relationship with animals, possibly as a back-up pollination plan. This led in turn to the hypothesis that *Cannabis* use would reduce the mortality rate. This hypothesis is strongly supported by the

analysis in the manuscript.

3. Reviewer comments, and author's responses, to the revised manuscript. Note this is the second set of reviewers, after the first set had recommended publication upon minor revision.

Reviewer 1:

Reviewer: The author presents a review and meta-analysis of evidence that cannabis exposure is associated with a variety of diseases and causes of death in the US, and then attempts to estimate the total net effect of cannabis use on mortality. He performs separate analyses of many different types of cancer, diabetes, brain injury, cardiovascular disease, lung disease, liver disease, suicide, opiate overdose, driving, and alcohol use. Along with an overall decrease in cancer rates, the author concludes that cannabis use prevents at least 13-41 thousand premature deaths, and that lack of access is causing many thousands of deaths as well in the US. While the issue of cannabis use is topical and important, and the review presented here is extensive in scope, I am uncomfortable with the attempt to cover so many different topics, I'm unclear on some of the methods utilized, and don't feel like the modeling effort (to explain deaths presented) is described in enough detail to be credible.

Author response: I agree that this is an initial, rather rough estimate of the impact on the premature death rate, and is not meant to provide exact numbers. I thought that was clear from the manuscript. However, the published evidence is clearly consistent with association of *Cannabis* use with a decrease in the premature death rate. This is the key take-home point of the paper, and is an important point that has not been made in other studies.

The published data on the health impact of *Cannabis* use clearly show that future arguments should take the form of "*how many lives are saved by Cannabis use", not the current argument of "how harmful is Cannabis use"*. At present, available reviews on the topic are still focused on how harmful *Cannabis* is, and by failing to include evidence for beneficial effects, thus misrepresent the net public health impact of *Cannabis* use.

This paper attempts for the first time to summarize the available data, in order to open discussion of the data. This is a basic principle of science – you go with what the available data are telling you. Seriously, do you have a valid reason for rejecting the available data other than that they do not support your underlying assumptions? When your assumptions do not fit the data, the next step is to examine your assumptions.

Reviewer comment: 1) The author attempts to cover the impact of cannabis on so many different diseases that I don't believe it's possible to do any one of them justice in this format.

Author response: It is necessary to cover all of the potential causes of death influenced by *Cannabis* use in order to arrive at an initial estimate of the numbers of deaths caused or prevented by *Cannabis* use. The main point of the paper, which may have gotten lost in the amount of information cited attempting to put the data in context, was to estimate the impact of *Cannabis* use on the premature death rate. The summary measures of the quantitative

analysis were to identify data that could be used to estimate the overall impact of *Cannabis* use on deaths. All of the other cited works and information were to provide context background for understanding the data showing the impact on premature death.

Reviewer comment: 2) There is some attempt to acknowledge the role that confounding may play, and to limit studies to those that at least control for smoking tobacco, I still believe that this issue is woefully underemphasized in the write up and interpretation of results. Without an extremely careful attempt to adjust for confounding, observational studies of marijuana use are going to be very hard to interpret in terms of causal inference.

Author response: There is a strong theoretical underpinning and extensive experimental evidence from laboratory studies to support the conclusions from the observational studies on cancer, DM, and TBI.

The manuscript was revised to clarify the adjustments; in summary, the data chosen were from fully adjusted models, including tobacco, but in addition sex, age, race, socioeconomic factors etc. were generally included. The data used are now summarized, with the adjustments used, in the supplemental excel file.

Reduced alcohol use, driving fatalities, and opioid use following legalization of medical marijuana are also supported by a number of studies on the behavior of medical patients given access to medical marijuana, including Lucas et al. 2013 and 2015, Bradford and Bradford 2016, Bachhuber et al, 2014, Anderson et al. 2013 etc. The paper by Santaella-Tenorio et al., published since the revision was completed and supporting the conclusions reached, were also added to the manuscript.

Reviewer: 3) Given the concerns about causal inference, trying to estimate causal effects and estimate impact of legalizing marijuana and such seems quite premature.

Author's response: I have made every attempt to provide causal inferences in the paper, citing a number of laboratory studies that support the conclusions of decreased deaths from cancer, DM, and brain injury. I have revised the paper to make the causality more obvious to the reader, for example, by including a number of references citing anti-tumor properties of cannabinoids, and the association of Cannabis use with reduced obesity rates.

I assessed over 1300 papers in preparing this manuscript, so my conclusions are hardly premature. I found there to be enough data available at this time to provide an initial, rough estimate of premature deaths prevented.

Do you have any concrete reasons to make the claim that we cannot make estimates with existing data, or is this your subjective opinion? How is your objection consistent with the basic scientific practice of analyzing the available data to reach conclusions?

Reviewer: 4) I am still a bit unsure of whether the authors actually used pre-post data before and after legalization efforts to do any estimation of causality with quasi-experimental design. I thought this was coming, but then it seemed that the legalization data was only used to make estimates about prevalence and usage? I may have missed this.

Author response: You most certainly missed this, as pre-post data was used for each of the medical marijuana topics; alcohol use, opioid OD fatalities, and driving fatalities. For alcohol, usage data pre-and post legalization was used, and the decrease in usage was used to estimate impacts on death. This is admittedly indirect, and the impact would presumably take years to manifest (many of the 25,000 deaths from direct toxic effects of alcohol would not be immediate for example). However, data on deaths from opioid OD and driving fatalities pre- and post-legalization were used to estimate immediate impacts on death rates.

Reviewer comment: 5) Even if the modeling effort was well described and executed, the results should not be presented in the abstract (or anywhere) without clear qualifiers ("we estimate that" or "we project that"; instead of "reveals that Cannabis prevents...").

Author's response: I thought that I had done this, but have revised the manuscript to make it more obvious. I will also round off the numbers from the modeling to make it more obvious that these are estimates.

Reviewer comment: 6) The manuscript was very long, and not well organized. Some paragraphs went on for over 2 pages without breaks, for example.

Author response: It was indeed very long, and included over 200 references. I fail to see what relevance this has for the scientific merit of the work. However, in revision I have attempted to improve the organization and the writing.

Reviewer comment: 7) The author clearly comes at this review with a point of view that is far from objective, noting prior bias against marijuana use and such; this makes me concerned that he may not treat the review with as much objectivity as is warranted.

Author's response: My analysis is highly objective. This study arose from insight into the ecological theory of plant-animal interactions, which led to the hypothesis that the cannabinoids arose in the context of a mutualism (see preamble above). This hypothesis in turn led to the prediction that moderate *Cannabis* use would have a net positive impact on health. The hypothesis was then tested with a careful examination of the literature for data that could inform impacts of *Cannabis* use on premature death rates. I surveyed over 1300 papers when preparing this manuscript. The published evidence, in the form of the low toxicity of cannabinoids together with their many therapeutic and life-saving effects, clearly support my hypothesis.

Is the reviewer arguing that I should base my conclusions on something other than the available, published data? What data should I invent to support the reviewer's preconceived views? That is not science. Is the reviewer claiming that I lack objectivity because the results of my analysis did not support their pre-conceived ideas? If so, it is the reviewer who lacks objectivity. A good scientist follows the data, and is able to examine and modify their assumptions when confronted with extensive data contradicting their assumptions.

Reviewer 2:

Reviewer comment: I appreciate that the author has put a great deal of work into this, and realize that this manuscript has been revised several times. However, this is my own first review of the manuscript. While I am generally inclined to agree with some of the author's viewpoints regarding the risks of cannabis when compared with other drugs and its legal status, I do not believe this manuscript holds up well to scientific scrutiny.

Author's response: It was indeed a lot of work, and took several years to find and assimilate the available information. That is probably why nobody else has done such an analysis yet, especially given the current climate of maximizing publication numbers.

Reviewer: I'll present my critique mostly in broad strokes, occasionally calling attention to specific examples in the manuscript.

1.) Meta-analyses of observational studies are of questionable value.
Observational cohort studies are generally attempts to establish the plausibility of an exposure being associated with an outcome. For example, if we see an association between obesity and heart disease after "adjusting" for measured confounders such as smoking, lack of exercise, family history and so on, we remain convinced of the plausibility of such a causal relationship, but it is still far from proven. The primary reason for this is that there are always unmeasured confounders and these generally bias the association estimate away from the null hypothesis. Thus, such measures of association are not causal estimates and to combine such estimates meta-analytically does not reduce the bias. It improves precision, but it does not improve accuracy. Moreover, an association measure that adjusts for X, Y, and Z is an estimate of something different than an association measure that adjusts for V, W and X. The two cannot be averaged to yield some interpretable parameters because each is confounded by a different set of unmeasured and/or unadjusted confounders.

Author's response: I agree that confounders are important. The data used are from the fully adjusted models in each case; the methods have been revised to emphasize this. However, the decrease in mortality from cancer, DM, and brain injury are predicted by theory as described in the preamble (admittedly the preamble describing the theoretical insight that led to the study was not in the original submission). They are supported by correlations in epidemiological studies, and further supported by extensive laboratory studies. When theory, epidemiology, and laboratory results are all telling you the same thing, at some point you have to consider that the data may actually reflect reality and demonstrate causality.

Furthermore, science depends on analyzing data. Are you saying that we cannot attempt to estimate the health impact of marijuana use, because we may be missing some important factor that influences the results? At some point, you must take the data you have and accept what it tells you. Furthermore, even if causality is not established, the data clearly show a correlation between *Cannabis* use and decreased premature deaths. This is clearly counter to claims that *Cannabis* use has a net harmful impact on health, though it does not demonstrate that *Cannabis* has no harmful effects. The reviewer is demanding a level of proof that is impossible to obtain in any scientific analysis – there is always the possibility that additional data

will come along and alter conclusions.

Reviewer comment: My recommendation would be to divide the manuscript as it stands into several narrative reviews, discussing the methods and measured confounders of each study and speculating about which direction the bias might go.

Author's response: I had considered breaking it up into several studies, but the ultimate goal of the study is to estimate the overall impact of *Cannabis* use on the premature death rate. Furthermore, while several studies would generate a greater publication rate, of benefit in annual evaluations, people are suffering and dying from lack of access to medical marijuana as we speak. Dividing the paper up would further delay publication and dilute the impact. It is the whole package with all causes of death addressed that will have the greatest impact.

Reviewer comment: The association between cannabis use and any health outcome is almost certainly dose-dependent, and cannot be captured with a single odds ratio.

Author's response: Anything in excess is harmful. Even such beneficial activities as exercise can be harmful when done to excess. Sugar in excess is far more harmful than *Cannabis*. What is most important for population based studies such as this one is the health effects of average or typical usage. Just as most alcohol users do not stay drunk all day, most Cannabis users do not stay high all day long every day (though such users certainly exist). It does not really matter if using a quarter ounce of *Cannabis* each day is harmful, if almost no users consume that much. What is more important for public health is the overall health impact of all use. I chose the data that seemed to best represent that usage amount.

Furthermore, I did include dose-dependence where available. Cancer rates across low, medium, and heavy users (0-1, 1-10, and 10+ joint-years) were analyzed to determine the dose dependence. These data are presented in Fig. 3. The low and medium user groups both showed significantly decreased rates of cancer relative to never users. Furthermore, the evidence for dose-dependence in the relationship between cannabis use and obesity/BMI were added to the manuscript during revision.

Reviewer comment: On lines 179-180, the author states that when "[odds ratios for] a variety of different usage patterns [were reported], the odds ratio for ever users versus never users (reflecting average or tyical use) was used if available. " First, the average or typical user would probably be one who uses a few dozen times in their lifetime, primarily in college, and possibly not at all during their working years. There is no biological plausibility that such sporadic use has large protective effects against cancers (OR=0.726 reported on line 287).

Author's response: The data used were clarified in the supplemental file, and included the best measures of effects of use. For a number of data points, ever users excluded experimenters. In other studies, current vs. never users were compared. For yet others, the average OR across usage groups (>0 – 60+ joint-years) was used. Many of the data sets gave OR for a number of usage groups, and the ever vs never values fell in the midst of these user groups. For example, Hashibe et al. 2006 gave data for users ranging from >0 to 60+ joint-years; ever vs never users

resembled those of the other usage groups. Furthermore, for a number of studies and cancer types, all usage groups from > 0 to 60+ joint-years showed OR < 1. There is strong evidence from a number of studies that demonstrate that cannabinoids have anti-cancer properties, triggering apoptosis in cancer cells without cytotoxicity to healthy cells, and curing cancer in experimental animals. For many studies, data across user groups could be compiled into low, medium, and high usage groups. Both the low and moderate use (0-10 joint-years of exposure) show decreased rates of cancer (Fig. 3), and generating values similar to those of the overall ever use vs. never use. Low usage: OR 0.76, moderate usage: OR 0.76. These were not significantly different from the ever use vs. never use OR. This strongly supports biological plausibility. Your concern that data from ever users were from people whose exposures were limited to a few trials, years earlier, does not hold up to scrutiny.

Reviewer's comment: One is reminded of the classic paper by Shedler & Block that found a U-shaped relationship between marijuana use and psychological problems among high-school students. Never-users were more anxious and socially isolated, occasional users were normal, and heavy users had other psychological problems. Likewise with alcohol, we find much lower mortality risk among people who drink on rare occasions than those who never drink. It is not plausible that a drink every two months has important cardioprotective effects, rather it seems that those who indulge on rare occasions are healthier than both heavy drinkers and never-drinkers. Which leads me to the next problem with the "ever vs. never" approach: it assumes a linear dose-response relationship between cannabis use and the outcome, which is very hard to justify.

Author's response: Note that the observed decrease in the premature death rate is driven primarily by impacts on diabetes mellitus, a disease that is strongly correlated with obesity. A number of articles, including Le Strat and Le Foll 2011, Rajavashiseth et al. 2012, and Meier et al. 2016, have all showed clear dose-dependent decreases in BMI or obesity with increased *Cannabis* use. Other diseases associated with obesity include cancer and Alzheimer's disease. Individuals who used cannabis more than 5x per month showed ½ the rate of obesity of non-users in the study by Rajavashiseth et al. (2012). I also showed in the manuscript (Fig. 3) that the available cancer data showed a different relationship, with the decrease in cancers among low and moderate users disappearing in the heavy usage group. This is consistent with multiple factors at play, such as the combination of anti-cancer and cancer-causing agents known to be found in *Cannabis* smoke.

Reviewer's comment: The reviewed / meta-analyzed studies are heterogeneous.
The author wants to put a single number on deaths caused by cannabis / cannabis prohibition, but combines two very different types of studies to do so. The first is the observational cohort study, discussed above. The second is studies of policy, which are more quasi-experimental, but are also subject to their own sets of biases. By analyzing differences in outcomes across states and over time, the policy studies attempt to deal with unobserved confounders in a manner that typical observational studies cannot. But there are still many shortcomings to such studies. There is a great deal of debate about how medical marijuana policy should be "coded;" for example, California is an medical cannabis state in which 2% of the adult population holds a

license because cannabis is approved for every indication under the sun. In contrast, medical licenses are quite rare in other states, so treating CA as being in the same category as NJ is questionable.

The second issue is that even quasi-experimental policy studies are subject to bias because states that have adopted medical cannabis policies are different than those that did not. This is why Anderson, Rees & Sabia found that medical cannabis availability was associated with decreased suicide rates: The subsequent paper that refuted their findings showed that states that adopted medical cannabis policies had growing minority populations (minorities have much lower suicide rates) and tended to adopt more progressive public health policies (also associated with lower suicide rates). The point, however, is that these studies are in a different family of studies than observational cohort studies and should probably not be evaluated in the same work.

Author's response: I agree completely that the overall effects of policy are likely to be driven by large states such as CA. They are likely to be quite different in states with liberal access and states with restricted access, and to be influenced by differences in the inhabitants of the different states as well. The data presented by Santaella-Tenorio et al. (2017) clearly show an immediate drop in overall numbers of driving fatalities in states legalizing medical marijuana, even though increases in fatalities were seen in a couple of states. California, the largest state in the study, experienced a drop of 16%, below only New Mexico. The overall drop in fatalities, of 10.8%, was driven by large states such as CA rather than small states. I welcome more thorough analyses of these issues that take into account differences among states; that was not the goal of this study.

The reviewers appear to be simultaneously criticizing the study for attempting to do too much, and for not doing enough. In the meantime, however, I fail to see why it is inappropriate to publish an analysis of available data to provide an initial estimate of impacts on premature deaths, especially given strong evidence for causality (see the response to the next reviewer comment below).

Reviewer's comment: Wrong assumptions are made about a drug and drug policy. The abstract states (lines 47-48) that prohibition is currently responsible for a certain number of deaths because it presumably keeps people from using cannabis, which would reduce their rates of premature death. Obviously, the first assumption made here is that these are all causal estimates, which they are clearly not.

Author's response: Actually, the evidence strongly supports the interpretation that the majority of these effects are causal. For DM, cancer, and brain injury, we have observational data that is supported by extensive laboratory experimental evidence, giving strong support for causality. For alcohol, driving fatalities, and opioid overdose, we have multiple lines of evidence all telling us the same thing – access to medical marijuana reduces alcohol and opioid use due to substitution, leading to decreased deaths.

Reviewer's comment: Secondly, however, even if the evidence for protective effects of cannabis

on mortality were stronger, we would hesitate to "recommend" cannabis use for those who do not currently use – and that is essentially what is being assumed when one asserts that prohibition causes death. (Prohibition probably does cause death because of its social consequences, but that is a separate question from presumed medical benefits). Again, consider the much more well-studied alcohol/mortality literature and the robust "J-shaped" association between alcohol use and mortality. Despite volumes of evidence that limited quantities of alcohol may protect against premature death, doctors are still cautioned from "prescribing" alcohol to their non-drinking patients because it has many other indirect effects – and because there is still debate about causality.

Author's response: First of all, you are mistaken as some doctors recommend a glass of red wine with supper. It is not too difficult to tell patients that a small amount is beneficial, and more is not better. Secondly, for cancer, DM, and brain injury, causality is strongly inferred from the combination of observational studies and laboratory studies. In the revision, the justification for causality has been added to the meta-analysis for each cause of death.

Secondly, why do you assume that laying out the available evidence is promoting *Cannabis* use? The purpose of scientific research is to analyze available data and draw inferences. Are we supposed to suppress the science, and continue to lie about the harms caused by *Cannabis*, for fear that more people will use it? Why are we singling out *Cannabis* here for suppressing evidence? Poor diet choices, soft drinks, and playing football are far more harmful than marijuana – in fact, available evidence demonstrates clearly that *Cannabis* use reduces the harm from these activities! It is a poor doctor indeed who will not honestly discuss the relative harms and benefits of their patient's lifestyle choices.

The use of alcohol to make a point about why we cannot tell the truth about *Cannabis* seems misguided at best, because alcohol is far more harmful than *Cannabis* by any objective measure, causing an estimated 88,000 deaths/year according to government estimates. *Cannabis* is nothing like alcohol, as it provides far more therapeutic and preventative benefits and is far less toxic in both acute and chronic exposures. A better analogy would be exercise. Exercise has a number of harmful effects, especially when done to excess, including joint damage, potential for cardiovascular accidents (myocardial infarctions, strokes) during exercise in people with pre-existing conditions, muscle tears, falling, etc. It can even be addictive for some people. Nevertheless, an objective analysis of the relative harms and benefits leads to the acknowledgement that exercise is beneficial.

The reviewer's comments only reinforce my impression that the public health community refuses to objectively analyze the relative harms and benefits of *Cannabis*, even when presented with the data. The reviewer's comments suggest that they wish to avoid an honest discussion because they fear it will promote *Cannabis* use. This is propaganda, not science.

Reviewer comment: In the case of cannabis, the author dismisses the clinical significance of cannabis use disorder (lines 83-84).

Author's response: I am certain you do not mean to imply that *Cannabis* use disorder is more harmful than death. That would be idiotic. You can recover from CU disorder, not from death, and people with the disorder would most likely tell you that being under the influence of *Cannabis* all the time is better than being dead. It is difficult to take your other comments seriously when you so obviously lack perspective.

Agosti et al. showed that 90% of people with *Cannabis* dependence had an underlying psychiatric disorder that drove their dependence. These disorders included PTSD, demonstrated by Neumeister et al. (2013) to be characterized by a disruption of the endocannabinoid system. In fact, the changes in the endocannabinoid and glucocorticoid signaling pathways were sufficiently consistent among patients to allow diagnosis of PTSD with 85% accuracy! Given the poor access to mental health care in the U.S., especially in lower income people, it is almost certain that many heavy users are self-medicating. This is supported by the reduction in use of anti-depressants, anti-anxiety, and anti-psychotic meds upon legalization of medical marijuana, as described by Bradford and Bradford (2016). Thus, cannabis use disorder is consistent with a mental health issue, but it is not clear at this time whether it is actually caused in healthy individuals by *Cannabis* use or is a symptom of other mental health issues.

Reviewer's comment: The calculations ignore the many more complicated pathways through which heavy cannabis use might lead to premature death. For example, cannabis use associated with impaired short-term memory and such impairment lasts for some time after cessation of use. (Even the most strident defenders of cannabis in the research community acknowledge this). Thus, it seems likely that if students use cannabis, it will impede their educational progress. This in turn could lead to many adverse life consequences including early mortality – as educational attainment is a strong predictor of mortality (and this is certainly causal, at least in part).

Author's response: It does no service to the discussion to focus only on the heaviest usage rate. It is true that memory impairments are the most commonly cited adverse side effect of medical marijuana, and these effects are most significant for verbal memory and are well supported in the literature. It is best to avoid regular marijuana use if you are trying to get into medical school by memorizing reams of information. However, not all students are trying to get into medical school. Many users claim that *Cannabis* use helps with focus and stimulates creativity, a claim supported by Carl Sagan, a successful individual by any measure.

Regarding decreased educational attainment in users, the results of recent studies suggest that Cannabis use has no real impact on educational attainment. Multiple recent studies have failed to demonstrate such an effect after accounting for confounding factors.

The following is from Mokrysz et al. 2016.

"There is much debate about the impact of adolescent cannabis use on intellectual and educational outcomes. We investigated associations between adolescent cannabis use and IQ and educational attainment in a sample of 2235 teenagers from the Avon Longitudinal Study of

Parents and Children. By the age of 15, 24% reported having tried cannabis at least once. A series of nested linear regressions was employed, adjusted hierarchically by pre-exposure ability and potential confounds (e.g. cigarette and alcohol use, childhood mental-health symptoms and behavioural problems), to test the relationships between cumulative cannabis use and IQ at the age of 15 and educational performance at the age of 16. After full adjustment, those who had used cannabis ⩾50 times did not differ from never-users on either IQ or educational performance. Adjusting for group differences in cigarette smoking dramatically attenuated the associations between cannabis use and both outcomes, and further analyses demonstrated robust associations between cigarette use and educational outcomes, even with cannabis users excluded. These findings suggest that adolescent cannabis use is not associated with IQ or educational performance once adjustment is made for potential confounds, in particular adolescent cigarette use. Modest cannabis use in teenagers may have less cognitive impact than epidemiological surveys of older cohorts have previously suggested."

See also the papers by Jackson and Grant, which failed to detect impacts of *Cannabis* use on educational attainment in twins discordant for *Cannabis* use.

Grant, Julia D., et al. "Associations of Alcohol, Nicotine, Cannabis, and Drug Use/Dependence with Educational Attainment: Evidence from Cotwin-Control Analyses." *Alcoholism: Clinical and Experimental Research* 36.8 (2012): 1412-1420.

Jackson, Nicholas J., et al. "Impact of adolescent marijuana use on intelligence: Results from two longitudinal twin studies." *Proceedings of the National Academy of Sciences* 113.5 (2016): E500-E508.

Furthermore, note that the argument you are making is a double-edged sword. You state, regarding your hypothetical decrease in educational attainment due to *Cannabis* use, "This in turn could lead to many adverse life consequences including early mortality – as educational attainment is a strong predictor of mortality (and this is certainly causal, at least in part)." Note that a drug conviction will reduce access to student loans, a major impediment to educational success. It will also greatly reduce employment opportunities for people with convictions, who have to "check the box" for the rest of their lives. This is very clearly summarized in Michelle Alexander's book, "The New Jim Crow". I did not include increased mortality of these people in the estimation of the deaths due to prohibition, just as I did not include hypothetical impacts of marijuana use on educational attainment, though I should note that the impact of prohibition on educational attainment is much better supported than the impact of *Cannabis* use itself. For example, the American Academy of Pediatrics concluded that the impact of interaction with the criminal justice system is more harmful than the negative effects of *Cannabis* use itself (The Impact of Marijuana Policies on Youth: Clinical, Research, and Legal Update. COMMITTEE ON SUBSTANCE ABUSE and COMMITTEE ON ADOLESCENCE. (doi: 10.1542/peds.2014-4146)

In summary, I restricted the estimates used in the analysis to topics for which I had data, and did not include speculative numbers from assumptions about other topics, especially when these assumptions are not well supported by the data.

Reviewer's comment: In short, cannabis is a drug – even if it does have beneficial effects. Most drugs have desired and undesired effects. To suggest that failure to administer a drug (through legalization) leads to death means that cannabis use is the "default" in terms of health. Such an assumption is dubious.

Author's response: First of all, after reading this comment, I find it ironic that this reviewer questions *my* objectivity. I acknowledge in the article that *Cannabis* has harmful effects; I thought this was obvious. However, the whole point of the paper is that you must weigh the harms and the benefits of a substance to arrive at an objective understanding of the net public health impact of its use. The reviews to date attempting to address the public health impact of *Cannabis* use fail to do so by ignoring beneficial effects.

Secondly, it is not clear what the reviewer means by "drug".

Thirdly, the reviewer seems ignorant of basic toxicology and pharmacology. Anything taken in excess is harmful, including water, food, oxygen, and exercise. It does not matter whether these are drugs or not. What is critically important is the relationship between the amount consumed and the amount that causes harmful effects. For *Cannabis*, the acute toxicity is extremely low, similar to that of water. Moderate usage reduces odds of major causes of death and illness associated with obesity, including DM and cancer, while the harmful effects are generally not fatal even at high levels of use, and if so, typically only after years of exposure. Furthermore, fundamental ecological and evolutionary theory predicts that *Cannabis* would act differently to other drugs as its biology is consistent with evolution in the context of a plant-animal mutualism, as described in the preamble (admittedly, this was not included in the manuscript sent to the reviewer).

An extensive analysis of the literature reveals that marijuana is a drug that obviously has enormous potential, not only for therapeutic use, but also for prevention of some of the most serious diseases our society faces. Note in particular the serious diseases related to obesity. For example, diabetes mellitus is responsible for 15.7% of all deaths. The evidence for reduced obesity and DM in *Cannabis* users is clear and solid, consisting of both observational and experimental studies. In fact, *Cannabis* has even been proposed as a therapeutic treatment for DM (Le Foll et al. 2013, Medical Hypotheses 80: 564-567). Are you seriously claiming that reducing the numbers of patients with DM does not improve public health? I am unable to follow your logic that, because it is a drug, it must be harmful and therefore, reducing its use cannot lead to improved public health.

The reviewer states: "To suggest that failure to administer a drug (through legalization) leads to death means that cannabis use is the "default" in terms of health. Such an assumption is dubious."

Author's response: This is absurd. I will use the analogy of vaccinations to help make my point. Vaccines are generally accepted by the medical community to save lives, by preventing a number of diseases. Parents are strongly urged to have their children vaccinated. In recent

years, the anti-vaxxer movement has emerged leading to outbreaks of measles and other diseases that were assumed to be under control. Reduced vaccination rates will obviously increase the premature mortality rate. Now imagine if d public policy was to arrest people producing or administering vaccines. Couple this with years of propaganda about the harms of vaccinations. Do you accept that rates of vaccinations would decrease, and this would result in increased deaths?

While use of vaccinations as an analogy is obviously hyperbole, the point remains. Reducing an activity that saves lives will increase deaths. This is glaringly obvious and I do not know why I have to explain it.

Reviewer's comment: The agenda is obvious.

Author response: If it is not, I will spell it out. The study is based on a hypothesis that arose from a consideration of the basic theory of the ecology and evolution of animal-plant interactions, as detailed in the preamble above. The hypothesis was tested by identifying and summarizing the data that can be used to estimate the effects of *Cannabis* use on premature death, then use those data to perform an initial, rough estimate of such effects. During the course of the investigation, as I became familiar with the data on obesity-related illnesses and neuroprotection, the impact of medical marijuana was included to give a complete estimation of impacts of *Cannabis* use on premature death. As the analysis progressed, and the overall picture of a substantial reduction in premature deaths attributable to *Cannabis* use came into focus, several additional agenda items emerged – to save lives, improve medical care, and keep people out of prison.

Reviewer's comment: The conclusion of the paper is an eloquent critique of drug policy, much of which I agree with. However, the review / meta-analyses should be about the health risks or benefits of cannabis and the strength of the evidence behind the conclusions about such risks/benefits. The review would have far more impact if it remained objective about moral, ethical, and legal matters.

Author's response: Maybe so. I find that difficult to do because I live in a state without legal access to even medical marijuana, and many people in the state could benefit from medical marijuana. I have acquaintances who have children with epilepsy, have fibromyalgia, and an acquaintance whose wife has MS, and another with serious anxiety issues. I have been contacted by medical refugees who would love to return to Indiana but are unable to do so due to the legal climate, as they are afraid of being treated as criminals for seeking medical help. Indiana is also in the midst of obesity and opioid overdose epidemics, and the research clearly shows that recreational *Cannabis* use and legalization of medical marijuana can reduce both of these causes of death. At some point a conscientious person has an moral obligation to state the obvious and stand up for improving health care and survival of people in need.

Reviewer's comment: The calculations are not accurate. I've already discussed reasons that the mortality calculations are inaccurate: They unjustifiably assume causality. They ignore more complex pathways through which heavy cannabis use might impact health and mortality.

Author's response: These are initial, rough estimates, and are not meant to give precise numbers. The reviewer appears to be criticizing the manuscript for failing to do something it was never meant to do. The data is not really there to do such an analysis anyway, as deaths from DM may be vastly underreported, and we have no data on effects on mortality rates from other causes of death such as Alzheimer's, Parkinson's, etc. that laboratory studies suggest would benefit from *Cannabis* and cannabinoids. We have no data on the impact of *Cannabis* use on overdose deaths from non-opioid drugs such as anti-anxiety and anti-depressants even though Bradford and Bradford clearly show that prescriptions for these drugs decline following legalization of medical marijuana.

This impact of *Cannabis* on premature death should certainly be studied further, and continue to be studied as more evidence accumulates. In the meantime, the literature is still dominated by reviews that address only the harmful impacts, despite repeated studies that failed to find any increase in mortality or hospitalizations or injuries in users. These reviews continue to ignore the beneficial effects, even when these are well supported in laboratory studies, as in cancer, brain injuries, and DM. This paper makes a critical contribution to the field by pointing this out and demonstrating that the data are consistent with a substantial reduction in the premature death rates with cannabis use.

Perhaps I did not explain the evidence for causality clearly enough. The conclusions regarding impacts on physical health (cancer, DM, brain injury) are supported by experimental studies in the laboratory, and based on the fundamental ecological and evolutionary theories of plant-animal interactions. For example, multiple studies have shown that cannabinoids shrink or cure carcinomas in laboratory animals, acting on a wide variety of cancer types. The predominant mechanism appears to be triggering of apoptosis in cancer cells without cytotoxic effects on healthy cells, thus leaving non-cancerous cells unharmed. For DM, laboratory studies in a mouse model have clearly shown substantial decreases (from 86% to 30%) in the incidence of DM in a strain of mice genetically predisposed to get DM when given cannabinoids. There is abundant evidence that cannabinoids have neuroprotective effects, and are also potent antioxidants and anti-inflammatory agents. Following brain injury, one of the greatest risks is spread of oxidative damage from the original site of injury leading to an expanding area of necrotic tissue progressing after the initial injury. Another is swelling and edema of the nervous tissue. Furthermore, a clinical trial (Knoller et al.) demonstrated improved outcomes following closed head brain trauma upon administration of a synthetic cannabinoid. For opioid overdose deaths, studies show significant benefits of Cannabis in treatment of pain, and multiple studies have shown patients reducing opioid use when they initiate medical marijuana. Their reduced use of alcohol provides a causal explanation for the observed decrease in driving fatalities. I would assert that causality can be justifiably assumed for the reduction in premature deaths observed for each of these.

The article has been revised to include a summary of the justification for causality to the meta-analysis for these causes of death, and additional articles for the anti-tumor and anti-obesity impact of *Cannabis* use have been included.

Complex dose-response relationships are not the subject of this paper. However, there

is no question that the highest usage rates are harmful. On the other hand, it seems obvious to the author that even heavy use, by itself, is less harmful than cancer or DM. After all, someone who uses heavily can always quit before significant health problems arise. Furthermore, a number of recent studies have followed *Cannabis* users for decades and failed to find the emergence of any significant health problems. See for example Meier et al. 2016 JAMA Psychiatry or Fuster et al. 2014 J Gen Intern Med. Meier et al. further showed that the lack of effect was not due to users being in better health at the beginning of the study, but was instead due to the complete absence of any effect.

The calculations do not ignore dose-response relationships. I have absolutely no doubt that heavy cannabis use is harmful. Anything in excess is harmful, even water, food, or exercise. The point I am making is that you must consider both harmful and beneficial effects to determine the net health impact, and that from a public health perspective, typical use is more important than extremes. Consider exercise, for example. If one considered only the harmful effects, one would see knee injuries, muscle sprains and tears, cartilage damage, risk of CVA episodes during exercise, pain, risk of being hit by a car when jogging or biking, etc. However, people are strongly urged to exercise because benefits are greater than the harms.

Reviewer's comment: An additional problem is the calculations use odds ratios and risk ratios interchangeably, which can lead to serious error in the case of common exposures such as cannabis use. In fact, in these situation, the odds ratio is generally higher than the risk ratio. This is very basic epidemiology.

Author's response: They are indeed different. However, both an OR and a RR below 1 indicates that rates are lower in users. Most of the data are in the form of OR, and the difference between OR and RR is not huge, so while inclusion of a few RR will change the mean relative to using all OR, it will not change the overall conclusion that the risk is lower in users. This is very basic math.

Reviewer: In conclusion, I admire the great deal of work that the author has put into this manuscript. I agree with the author that the literature is probably biased in terms of emphasizing the harmful effects of cannabis. (Though, to some degree this is justified because – just as with pharmaceutical drugs – we start with the assumption that drugs are harmful). I am concerned about funding and publication biases resulting in an overstatement of cannabis-associated risk and that findings will be used to justify an immoral drug policy that is not based on evidence. I agree that cannabis is far less harmful than our legal drugs. However, the way to counter the myths and biases surrounding cannabis is through objective and dispassionate science.

Author's response: I have made every effort to be objective. I searched databases for studies that contained data that could be used to estimate effects of *Cannabis* use on premature mortality. Those data lead to the conclusions that I express in the paper. I did not base conclusions on data that do not exist, or leave out data to support my hypothesis. I am offended that both reviewers appear to be questioning my integrity as a scientist rather than examining their assumptions by evaluating the data that I have presented. They also fail go back to the

original papers to evaluate the data for themselves to see whether they can rebut my claims. Instead they assume that I lack objectivity because my results do not meet their preconceived ideas or support their assumptions. This epitomizes the bias evident in the field, as expressed in numerous review articles detailing the harmful effects of *Cannabis* while neglecting to include any mention of its beneficial effects.

Reviewer's comment: My recommendation to the author (depending on what the editors ultimately decide about the current version) is to break the work into several narrative reviews focusing on specific diseases or disease classes, discuss biological plausibility weight the strengths and weakness of each individual study, and evaluate potential biases in both directions.

Author's response: I have certainly considered breaking this study up into a series of minimal publishable units, thereby increasing my publication rate. However, as the main point of the study was to estimate the effects on premature death rates, I believe that would change the whole purpose of the study. The additional material was included to allow interpretation of the data, to provide justification for causality, and to give an overview of the science in each area addressed by the paper. I agree that the paper is too large to be easily digestible, as is clear from the reviewer's comments, and that leads to the potential failure of readers to assimilate the main points. I therefore tried to express the main points in the Meta-analyses for each topic.