MEDICINAL CANNABIS, CHRONIC PAIN AND SLEEP: EFFICACY AND SAFETY, PATIENTS' PERSPECTIVES, AND PATTERNS OF USE

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Medicinal Cannabis, Chronic Pain and Sleep: Efficacy and Safety, Patients' Perspectives, and Patterns of Use

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ABSTRACT

Chronic pain and sleep problems are two prevalent conditions frequently reported by the general population. Despite limited evidence, in recent decades, there has been a rapid rise in the use of Medicinal Cannabis (MC) for managing these two health conditions. Cannabis is increasingly used for therapeutic purposes by Canadians; however, this therapeutic option has largely emerged as a result of legal challenges instead of high-quality empirical evidence establishing that the benefits exceed the harms. Furthermore, complicating the use of cannabis as a therapeutic product is its' recreational use. Canada is the leading per capita consumer of cannabis for recreational use, which has raised concerns among some healthcare providers that patients may seek authorization to use MC for non-medical purposes.

Therefore, the current thesis has examined three areas to inform the use of MC based on rigorous quantitative and qualitative approaches. It begins with investigating the efficacy and safety of MC and cannabinoids for impaired sleep through conducting a systematic review and meta-analysis of randomized clinical trials. Subsequently, it explores patients' perspective towards MC use for chronic non-cancer pain (CNCP) using a qualitative approach and finally, it assesses declared rationale for cannabis use before and after legalization for recreational use for therapeutic purposes in Canada.

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DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis is a “sandwich thesis”, which combines three individual projects submitted for publication in peer-reviewed journals. This work is original research, and I am the principal contributor and first author of all the manuscripts included in this dissertation. The detail of my contributions (Mahmood AminiLari) in all papers included in this dissertation is as follows:

***Chapter 1*: Medical Cannabis and Cannabinoids for Impaired Sleep: A Systematic Review and Meta-Analysis of Randomized Clinical Trials:**

This chapter is published in the “Sleep Journal”.

Jason Busse and Mahmood AminiLari conceptualized and designed the study; Mahmood AminiLari, Jason Busse, and Li Wang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Literature search: Rachel Couban and Mahmood AminiLari.

Acquisition, analysis, or interpretation of data: Mahmood AminiLari, Jason Busse, Li Wang, Samuel Neumark, Candidate; Taranah Adli and Aidan Giangregorio.

Clustering outcome measures: Colleen E. Carney, Jason Busse and Mahmood AminiLari.

Statistical analysis: Li Wang

Drafting of the manuscript and critical revision of the manuscript for important intellectual content: Mahmood AminiLari, Jason Busee, Li Wang, and Colleen Carney.

All authors reviewed or critically revised the manuscript.

Supervision: Jason Busse.

Chapter 2: Patients' Perspectives of Medical Cannabis for Managing Chronic Pain: A Qualitative Study:

This chapter has been submitted to the "Pain Medicine" Journal and is currently under revision based on the journal request.

Mahmood AminiLari, Patricia Strachan and Jason Busse designed the study.

Mahmood AminiLari drafted the proposal.

Jason Busse, Patricia Strachan, James Mackillop, and Li Wang provided their feedback on the drafted proposal.

Jason Busse and Patricia Strachan approved the proposal.

Mahmood AminiLari and Natasha Kithulegoda conducted the interviews (9 and 4 interviews respectively), performed qualitative data analysis, and extracted the primary codes and themes, and reported the results.

Jason Busse, Patricia Strachan, James Mackillop, and Li Wang provided their feedback on the primary codes and themes.

Sushmitha Pallapothu and Samuel Neumark audiotaped and transcribed verbatim the interviews and Sushmitha Pallapothu, Samuel Neumark Sangita Sharma, Jagmeet Sethi, Ramesh Zacharias, Allison Blain, Lisa Patterson helped with patient's recruitment.

Mahmood AminiLari drafted the manuscript and Jason Busse, and Patricia Strachan provided their feedback on the manuscript.

All authors reviewed or revised the manuscript.

Supervision: Jason Busse.

***Chapter 3*: Declared Rationale for Cannabis Use before and after Legalization for Recreational Use: A Longitudinal Study of Community Adults in Ontario:**

This chapter has been submitted to Cannabis and Cannabinoid Research and is currently under review.

James MacKillop led the original study.

Jasmine Turna provided the data and general guidance.

Mahmood AminiLari, James MacKillop, and Jason Busse designed the study.

Mahmood AminiLari drafted the proposal, performed data analysis, and drafted the manuscript.

James MacKillop, and Jason Busse provided their feedback on the proposal, analysis report and manuscript.

CHAPTER 1: INTRODUCTION OF THE THESIS

Chronic pain and sleep problems are two prevalent conditions frequently reported by the general population. It is estimated that the prevalence of chronic pain ranged from 6% to 15%, [1-3] and sleep problems ranged between 17% and 25%. [1,2,4,5]

According to the International Association for the Study of Pain (IASP), chronic pain is defined as a widely prevalent pain condition persisting more than three months and frequently accompanied by distress, demoralization, and functional impairment.[6] In North America, approximately 1 in 5 individuals are living with chronic pain.[5,7] Chronic pain affects different aspects of patients' health and significantly reduces their quality of life.[8,9]

Sleep disorders are the other frequent conditions in which patient experiences some problems in initiating or keeping sleep leading to irritability or fatigue during the day. Insomnias or sleep-disruptive events, along with commonly related discomforts such as snoring and sleep apnea are the most frequent problems among various types of sleep disorders.[10] The results of a survey of 2000 Canadians over 18 years old indicated that approximately 20% of the respondents were not satisfied with their sleep and 40% were suffering from insomnia**.** [11] Studies also indicated that individuals with sleep disorders are at greater risk of developing anxiety disorders and depression.[12]

Evidence shows that impaired sleep is highly frequent among chronic pain patients.[13] Approximately 2 out of 3 people living with chronic pain in the general population encounter some difficulties in sleep due to pain. [14] The results of a meta-analysis suggested a high prevalence of clinically diagnosed sleep disorders among people living with chronic pain regardless of the type of diagnosis.[15] A recent review also

indicated that compared to patients with pure chronic pain, patients with concurrent chronic pain and sleep disturbances have higher levels of pain severity and longer duration of pain, and are more likely to suffer from depression, catastrophizing, anxiety, and suicidal ideation.[16] Emerging evidence also indicates a significant reciprocal relationship between sleep disturbance and chronic pain,[17-20] that is, a higher level of sleep disturbance during the night is associated with greater pain intensity during the day and vice versa.[20-22] This simultaneous experience of sleep disturbance and chronic pain can make the treatment of both conditions increasingly challenging.[23] Therefore sleep problems should be considered as a presumable goal of the treatment for a variety of chronic diseases including pain, and a systematic approach in managing chronic pain should account for such pain-related conditions. [24,25] Furthermore, given the high prevalence and the proven association between these two conditions, it is necessary to investigate the new approaches to chronic pain and resultant sleep disorders.[23]

Cannabis is one of the oldest documented medicines in history, prepared from the plant Cannabis sativa with a wide range of chemical compounds.[26] Among over 100 psychoactive compounds called “cannabinoids”, Delta 9-tetrahydrocannabinol (Delta 9-THC) and Cannabidiol (CBD) are the most well-characterized components. Both THC and CBD have psychoactive and analgesic effects while CBD has minimal psychoactive impacts.[27] Medicinal cannabis (MC) refers to the therapeutic use of herbal cannabis and its components.[28]

Despite limited empirical evidence, MC is promoted for many conditions with two of the most common being chronic pain and impaired sleep. The results of an

international cross-sectional survey completed by 953 respondents from 31 countries indicated that chronic pain and sleeping disorders were among the top five conditions for which cannabinoid-based medicines were used.[29] According to the Canadian Alcohol and Drug Use Monitoring Survey, the summary of results for 2011, 17.7% of 10,076 respondents aged 15 years and older endorsed cannabis use for medicinal purposes with half of them using it for chronic pain such as arthritis and back pain.[30] The results of another survey of 209 Canadian patients with chronic non-cancer pain (CNCP) conducted over a period of 6 weeks revealed that 35% of the respondents reported having used cannabis and 15% of the total sample had used it for pain relief.[31] The analysis of self-reported data collected from 10,269 authorized cannabis users in Ontario, Canada (from 2014 to 2016) also revealed that although patients used cannabis for treating a wide range of medical conditions, the majority of respondents (two-third) sought cannabis for managing chronic pain.[32] The results of a survey among 1000 individuals accessing cannabis through adult-use markets in the United States indicated that 74% reported using cannabis to improve their sleep and 84% of this population found it very or extremely helpful leading to significant reductions or discontinuations of the over-the-counter or prescribed sleep medications.[33]

Several systematic reviews have investigated the impact of MC and various cannabinoids on chronic pain and sleep problems; however, the results are controversial. A systematic review of 5 high-quality trials suggests that despite some uncertainty about specific indications, ideal doses, and adverse effects, low-dose MC is supposed to have potential treatment effects in pain management.[34] The results of another systematic

review found that cannabinoids may reduce chronic treatment-resistant neuropathic pain and improve sleep quality.[35] Limited evidence was found by another review on the potential benefits and harms of cannabis use among chronic pain patients. This review suggests that cannabis with an exact amount of THC–CBD (mostly 1:1 to 2:1 ratios) may improve neuropathic pain related to various health conditions; however, the strength of the evidence is low due to including small studies with methodological problems and unclear long-term effects.[8] Another review of 18 trials showed that commonly used cannabinoids have a modest analgesic effect which can allow patients with CNCP to have a safe and reasonable alternative treatment for managing chronic pain. This review also suggests significant improvements in sleep reported by several included trials. [36]

One systematic review that specifically examined the effectiveness of cannabis on sleep has found mixed and diverse effects of MC,[37] and an additional review suggests no sufficient evidence to support the therapeutic effects of cannabinoids for managing sleep disorders due to the lack of high-quality clinical studies.[38] The results of the most recent and high-quality systematic review and meta-analysis indicated that based on moderate to high certainty evidence non-inhaled MC compared to placebo, contribute to a small to a very small increase in the proportion of patients with cancer or noncancer pain experiencing a clinically important improvement in pain relief and sleep quality, in addition to several transient adverse effects.[39]

Studies also described uncertainty regarding the efficacy and safety of cannabis by considering several harmful and potentially dangerous side effects.[40] Sedation, vertigo, dizziness, increased heart rate, fluctuations in blood pressure, euphoria (excitement),

anxiety, decreased ability to think and remember things and tolerable neurocognitive adverse effects are some possible physical and psychological side effects of cannabis reported by patients with chronic pain.[34,39,41]

For many years prohibition has been the main approach for managing cannabis use in most countries; however, new reforms including decriminalization and legalization have recently been adopted by some countries.[42] In Canada, in March 2014, a new regulation on marihuana/cannabis use for medical purposes called Canada Medical Marihuana Access Regulations (MMAR) was released and replaced with the previous one established in 2001. [26] Based on this new rule, instead of the government, authorizing a patient as a medical cannabis user needed to be confirmed by a doctor through examining and endorsing that cannabis is 'therapeutically' beneficial.[42] On October 17, 2018, the production, distribution, and consumption of cannabis at the national level was also legalized in Canada;[43] however, little is know about the possible changes in patterns of cannabis use among all users in general and medical cannabis users in particular post legalization. Furthermore, complicating the use of cannabis as a therapeutic product is its' recreational use. Canada is the leading per capita consumer of cannabis for recreational use, which has raised concerns among some healthcare providers that patients may seek authorization to use MC for non-medical purposes. Studies indicated that many MC users concurrently use cannabis for recreational purposes. The results of a survey conducted among 348 American users who had the authorization to use cannabis legally and medically demonstrated that 55.5% used cannabis for both recreational and medical

purposes.[44] A recent national survey in the US found that only 22.5% of those who endorsed MC use exclusively used cannabis for medical purposes and most of the respondents (77.5%) used cannabis for both medical and recreational purposes.[45] Overlapping patterns of recreational and medical use also has been reported in one self-assessment study of a large community sample of Canadian cannabis users.[46]

To sum up, cannabis is increasingly used for therapeutic purposes by Canadians;[47] however, this therapeutic option has largely emerged as a result of legal challenges instead of high-quality evidence establishing that the benefits exceed the harms. Although the increasing legal availability of MC has provoked upturned research into the impact of cannabinoids for sleep disorders,[48] due to lack of empirical evidence, the efficacy of MC for impaired sleep has remained uncertain. Only two systematic reviews[37,38] specifically assessed the impact of MC on sleep; however, both reviews suffer from methodological limitations.

In addition, numerous studies have examined cannabis for therapeutic purposes using a quantitative lens, and little is known about the efficacy of MC for chronic pain from patients 'perspectives using a qualitative approach. Finally, Cannabis has established recreational effects and therapeutic potential, but until 2018 was only legal for medical use in Canada. This may have resulted in some patients acquiring recreational cannabis through medical access.

This thesis, therefore, has explored three areas to inform the use of MC:

- What is the evidence for the use of medical cannabis for the management of impaired sleep?
- What are the perspectives of people living with chronic pain towards medical cannabis?
- What has the impact of legalization of recreational cannabis been on patterns of use among self-declared medical cannabis users?

Outline of the thesis

This is a sandwich thesis of three papers presented in chapters 2 to 4 covering a range of topics on the Medicinal Cannabis for Chronic Pain and Sleep: Efficacy, Patients' Perspectives and Changes in Patterns of Use Pre-and Post-Legalization. We intended to better understand the current efficacy and safety of medical cannabis use in the management of chronic pain and impaired sleep.

In chapter 2, given the paucity of well-done systematic reviews on the effectiveness of medicinal cannabis for impaired sleep, we used a state-of-the-art methodology to inform evidence-based management of sleep problems using MC. We conducted a rigorous systematic review and meta-analysis of all published randomized clinical trials including human participants and assessing the impaired sleep following the administration of medicinal cannabis or cannabinoids for any condition. The results of this review can help inform physicians working in the fields of sleep or/and chronic pain who prescribe medical cannabis for managing impaired sleep.

In chapter 3, we applied a qualitative approach to be among the first few studies exploring the effectiveness of medicinal cannabis from patient perspectives who are living with chronic non-cancer pain. We applied thematic analysis and used an inductive thematic approach for the coding in which data collection and analysis occur simultaneously.

In chapter 4, we characterized patterns of cannabis use among participants who endorsed using cannabis for medical purposes and the changes in participant status over the course of cannabis legalization for recreational purposes in Canada.

Finally, in chapter 5 we summarized the key findings and the implications of the thesis with direction for opportunities in the future.

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CHAPTER 2: MEDICAL CANNABIS AND CANNABINOIDS FOR IMPAIRED SLEEP: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

Medical Cannabis and Cannabinoids for Impaired Sleep: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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ABSTRACT

Study Objectives: We conducted a systematic review to explore the effectiveness of medical cannabis for impaired sleep.

Methods: We searched MEDLINE, EMBASE, CENTRAL and PsychINFO to January 2021 for randomized trials of medical cannabis or cannabinoids for impaired sleep vs. any non-cannabis control. When possible, we pooled effect estimates for all patient-important sleep-related outcomes and used the GRADE approach to appraise the certainty of evidence.

Results: Thirty-nine trials (5,100 patients) were eligible for review, of which 38 evaluated oral cannabinoids and 1 administered inhaled cannabis. The median follow-up was 35 days, and most trials (33 of 39) enrolled patients living with chronic cancer or noncancer chronic pain. Among patients with chronic pain, moderate certainty evidence found that medical cannabis probably results in a small improvement in sleep quality versus placebo (modeled risk difference [RD] for achieving the minimally important difference [MID], 8% [95% CI, 3 to 12]). Moderate to high certainty evidence shows that medical cannabis vs. placebo results in a small improvement in sleep disturbance for chronic non-cancer pain (modeled RD for achieving the MID, 19% [95% CI, 11 to 28]) and a very small improvement in sleep disturbance for chronic cancer pain (WMD of -0.19cm [95%CI, -0.36 to -0.03cm]; interaction p=0.03). Moderate to high certainty evidence shows medical cannabis, versus placebo, results in a substantial increase in the risk of dizziness (RD 29% [95%CI, 16 to 50], for trials with ≥3 months follow-up), and a

small increase in the risk of somnolence, dry mouth, fatigue, and nausea (RDs ranged from 6% to 10%).

Conclusions: Medical cannabis and cannabinoids may improve impaired sleep among people living with chronic pain, but the magnitude of benefit is likely small.

INTRODUCTION:

The prevalence of sleep disorders in the general population is approximately 20%,[1] and cannabis is increasingly promoted as a management strategy to improve sleep.[2] A US survey of 1,000 adults attending a cannabis dispensary found that 74% reported using cannabis to improve sleep and 84% of this population reduced or discontinued their sleep medication.[3] An international survey completed by 953 participants from 31 countries indicated that sleep disorders were among the top-five conditions for which they used medical cannabis.[4]

There are two systematic reviews that have assessed the effect of cannabinoids on sleep;[5,6] however, neither conducted meta-analyses to pool effect estimates nor evaluated the overall certainty of evidence,[5,6] and the literature search of one review was outdated [5]. We conducted a systematic review of the effect of medical cannabis and cannabinoids on impaired sleep that addressed these limitations.

METHODS

We registered our review on PROSPERO (CRD42018103266) and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. [7]

Data Sources and Searches

We searched MEDLINE, EMBASE, CENTRAL and PsychINFO from inception to January 19, 2021, using search strategies designed by an academic librarian (Appendix

2.A). We reviewed reference lists of relevant systematic reviews and all included studies to identify additional eligible trials.

Eligibility Criteria

We included randomized controlled trials (RCTs), in any language, evaluating the effect of medical cannabis or cannabinoids on sleep. Trials were eligible if they: 1) enrolled patients aged 18 or older with impaired sleep; 2) randomized them to any form of medical cannabis or cannabinoid vs. a non-cannabis control, and 3) collected outcome data ≥14 days after treatment. We excluded open-label trials, trials that enrolled individuals using cannabis for recreational purposes, and studies exploring treatment for cannabis use disorder or cannabis withdrawal.

Study selection and data extraction

Paired reviewers screened titles and abstracts of identified citations and reviewed full texts of all potentially eligible studies, independently and in duplicate. The same pair of reviewers extracted data, independently and in duplicate, including patient characteristics, intervention details, effects on sleep quality, sleep disturbance, other sleep-related outcomes, and all adverse events reported by ≥5 trials.

Risk of Bias Assessment

Two reviewers assessed risk of bias among eligible trials, independently and in duplicate, using a modified Cochrane risk of bias instrument.[8,9]

Data Analysis

We used the adjusted kappa (κ) statistic to assess the interrater agreement for inclusion of trials at the full-text screening stage. Our included studies used various instruments to measure sleep quality and sleep disturbance, with the most reported measure being the 10cm visual analogue scale (VAS). To facilitate statistical pooling in natural units, we converted other measures of sleep quality or sleep disturbance to a 10cm VAS, as long as they had ≥4 categories of response options, according to the method of Thorlund et al.[10] We re-scaled measures, when necessary, to ensure that higher scores indicated worse sleep quality or sleep disturbance. When possible, we pooled effects across trials using random-effects models and the DerSimonian-Laird method.

We reported pooled effect estimates of continuous outcomes as both the weighted mean difference and, when possible, the modeled risk difference (RD) of achieving the minimally important difference (MID) to optimize interpretability.[11,12] The MID is the smallest amount of improvement that patients recognize as important,[13] and is approximately 1cm for the 10cm VAS for sleep quality and sleep disturbance.[14] We reported the pooled effects on binary outcomes as relative risks and RDs. For all meta-analyses, we used change scores from baseline to the end of follow-up to account for interpatient variability. If change scores were not reported, we calculated them using the baseline and end-of-study scores and the associated standard deviation (SD) using a correlation coefficient derived from the largest trial at the lowest risk of bias that reported a change score.

When treatment effects were reported simply as non-significant without accompanying data, we contacted study authors to request these data. If unsuccessful, we addressed the risk of overestimating the magnitude of effect by imputing a weighted mean difference (WMD) of 0 or a relative risk (RR) of 1 for missing effect estimates. We derived the associated variance for missing non-significant results with the hot-deck approach.[15] When individual studies did not provide data that allowed for their inclusion in meta-analysis, we explored the consistency of their findings with pooled effects. Stata statistical software version 15.1 (StataCorp) was used for all analyses, and comparisons were 2-tailed using a $p \leq .05$ threshold for statistical significance.

Subgroup analysis, meta-regression and sensitivity analysis

We used Cochran's chi-squared test and the I-square statistic to examine statistical heterogeneity of pooled treatment effects.[16] We tested the following a priori subgroup hypotheses that larger treatment effects for beneficial outcomes were associated with: (1) shorter vs. longer length of follow-up; (2) noncancer vs. cancer-related chronic pain; (3) high tetrahydrocannabinol (THC) vs. THC and cannabidiol (CBD) vs. high CBD products; and (4) high vs. low risk of bias on a component-by-component basis.
We made the same assumptions for harm outcomes, except we anticipated greater harms with longer vs. shorter follow-up. We conducted subgroup analyses only if there were two or more studies in each subgroup. We assessed the credibility of subgroup effects using ICEMAN criteria.[17] We performed meta-regression for length of follow-up, duration of treatment, and loss to follow-up.

We also conducted post hoc sensitivity analyses to assess the robustness of our results by excluding studies in which the WMD for non-significant effects was imputed.

Assessing certainty of evidence

We used the GRADE approach to summarize the certainty of evidence for all outcomes,[18] and followed GRADE guidance for communicating our findings.[19] We assessed for small-study effects when there were at least 10 studies available for meta-analysis by visual assessment of asymmetry of funnel plots for each outcome, and Egger's test [20] for continuous outcomes and Harbord's test[21] for binary outcomes. If no credible subgroup effect was found for risk of bias components, then we pooled all trials and did not rate down for risk of bias. If a credible subgroup effect was found, then we only reported the pooled estimate of effect among trials at low risk of bias. If a subgroup effect for risk of bias could not be explored for a given outcome, due to <2 trials per group, we rated down for risk of bias if the relative contribution of trials at high risk of bias to the pooled effect estimate was >20%.

We considered pooled effects for continuous outcomes imprecise if the associated 95% CI included ½ the MID, which equates to approximately a 10% RD, and binary outcomes if the associated 95%CI included both benefit and harm. We also rated down significant effects for imprecision if they were informed by <300 patients for continuous outcomes or <300 events for binary outcomes.[22] We did not rate down the same effect estimate twice for both inconsistency and imprecision.

RESULTS

Among 2,510 citations identified, 136 articles were reviewed in full text and 38 publications reporting 39 RCTs[23-60] with 5,100 enrolled patients met eligibility criteria. (Figure 1). Agreement between reviewers regarding eligibility of full-text articles was substantial ($\kappa = 0.78$).

Study Characteristics

The median of the average age of participants enrolled among included trials was 53 years

(interquartile range, 48-58 years) and 53% (2,726 of 5,100) of patients were female. Twenty-five trials enrolled patients with chronic noncancer pain, 8 with chronic cancer related pain, 2 with Parkinson's disease, and single trials enrolled patients with PTSD, sleep apnea, anorexia nervosa and multiple sclerosis. Only one trial administered inhaled cannabis;[33] the remaining 38 trials administered oral formulations of cannabinoids (i.e., drops, capsules, sprays). The median follow-up duration was 35 days (IQR, 28-56 days). Most trials, 29 (74%) were fully or partially funded by industry. (eTable 1 in Appendix 2.D)

Risk of Bias

The proportion of trials at low risk of bias for each domain was as follows: adequately generated randomization sequence (82%); adequately concealed allocation (92%); blinded patients (100%); blinded caregivers (100%); blinded data collectors

(100%); blinded outcome assessors (97%); and low (≤20%) missing outcome data (67%). (eTable 2 in Appendix 2.D)

Outcomes for medical cannabis vs. placebo

Sleep Quality

Moderate certainty evidence from 16 RCTs (2,052 patients)[24-27,31-33,37,40,43,44,49,55,57,58,60] suggests that, compared to placebo, medical cannabis and cannabinoids result in a small increase in the proportion of patients experiencing an improvement in sleep quality at or above the MID (modeled risk RD 8% mean difference [95% CI, 3 to 12]; based on a WMD of -0.43 cm on a 10cm VAS [95% CI -0.18 to -0.67]; Table 1, Figure 2**)**.

Consistent with these results, four studies[35,36,54,56] that did not report data suitable for pooling all found medical cannabis significantly improved sleep quality, compared with placebo (eTable 3 in Appendix 2.D).

Sleep Disturbance

Use of cannabinoids showed a small increase in the proportion of patients reporting improved sleep disturbance compared to placebo (modeled RD for achieving the MID 13% [95% CI 7 to 20]); however, we found a significant subgroup effect for chronic noncancer vs. cancer pain (test of interaction p=0.001; Figure 3). We also found a subgroup effect based on loss to follow-up; however, this was of only low credibility (eTable 5a in Appendix 2.D) and was almost completely confounded with study

population in those trials of chronic cancer pain patients also reported the highest amount of missing data.

High certainty evidence (Table 1) from 11 RCTs[23,27,28,30,38,40,41,48,50,51,59] of people living with chronic noncancer pain (n=906) showed that, compared to placebo, cannabinoids increased the proportion reporting reduced sleep disturbance (modeled RD for achieving the MID 19% [95%CI 11 to 28]; based on a WMD of -0.99 cm on a 10cm VAS [95%CI -0.57 to –1.41]. Moderate certainty evidence from 5 RCTs[39,45,47,53] of people living with chronic cancer pain (n=1,249) found medical cannabis results in a very small improvement in sleep disturbance, versus placebo (WMD -0.19 cm on a 10cm VAS [95%CI -0.03 to -0.36]; Table 1).

Our sensitivity analysis excluding two studies [23,41] for which the WMDs for non-significant effects were imputed, found no important difference in results. (eFigure2 in appendix 2.B).

One placebo-controlled study that did not contribute to our pooled analyses showed consistent results. Low certainty evidence from this study suggests that palmitoylethanolamide may reduce sleep disturbance among patients with chronic pain due to carpal tunnel syndrome (42 patients).[56] (eTable 3 in Appendix 2.D)

Other sleep-related outcomes

Low certainty evidence from one trial (73 patients) suggests that nabilone, versus placebo, may reduce the frequency and intensity of nightmares among PTSD patients

(mean change in the clinician administered PTSD scale [CAPS], -3.6 ± 2.4 vs. -1.0 ± 2.1), but may provide no benefit for total sleep time or numbers of awakenings each night.[23]

Very low certainty evidence from one trial (56 patients) suggests that nabilone, compared to placebo, may not improve sleep among patients undergoing radiotherapy for head and neck carcinomas.[42]

Low certainty evidence from one trial (73 patients) suggests dronabinol, versus placebo, may reduce sleepiness among patients with moderate to severe obstructive sleep apnea at a dose of 10mg/day (mean change in the Epworth Sleepiness Scale, 2.3 ±1.2, p=0.05), but not at a lower dose of 2.5mg/day.[46]

Low certainty evidence from one trial (42 patients) suggests ultra-micronized palmitoylethanolamide, versus usual care, may increase continuous sleep time among patients with chronic carpal tunnel syndrome.[56]

Adverse Events

Nausea

Medical cannabis or cannabinoids increased the risk of nausea (RD 5% [95% CI, 3 to 8]), and longer use was associated with greater risk (test of interaction p=0.03, eFigures 3&3.1 in Appendix 2.C). High certainty evidence from 4 RCTs[24-26,28] (1,163 patients) that followed patients for ≥3 months shows that medical cannabis and cannabinoids, versus placebo, results in a larger increase in the risk of nausea (RD 10% [95% CI, 5 to 17]) compared to trials that followed patients for <3 months (RD 3% [95% CI, 1 to 6]; 18 RCTs[27,30,32,33,35,37-41,43,45,49,51,53,55,57,60] [2,380 patients]). (Table 1)

Dizziness

Use of medical cannabis or cannabinoids increased the risk of dizziness (RD 13% [95% CI, 9 to 20]); however, the risk was greater with longer use (test of interaction p=0.007; eFigures 4 &4.1 in Appendix 2.C). High certainty evidence from 5 RCTs[25,26,28,36,44] (1,824 patients) that followed patients for ≥3 months shows that medical cannabis or cannabinoids, versus placebo, results in a large increase in risk of dizziness (RD 29% [95%CI, 16 to 50]), compared to trials with <3 months follow-up (RD 8% [95% CI, 4 to 12]; 19 RCTs[27,30-33,37-41,43,45,49,51,53,55,57,58,60] [2,481 patients]) (Table 1).

Diarrhea

High certainty evidence from 12 RCTs[24,26,28,30,35,37,38,45,50,55,57,60] (1,777 patients) shows that cannabinoids probably slightly increase the risk of diarrhea, compared with placebo (RD, 2% [95% CI, 0% to 5%]; Table 1, eFigure 5 in Appendix 2.C)

Disturbance in Attention

Moderate certainty evidence from 7 RCTs (1,086 patients)[24,26,30,37,38,55,60] indicates that cannabinoids, compared to placebo, probably slightly increases the risk of disturbance in attention (RD, 2% [95% CI, 0% to 7%]). (Table 1, eFigure 6 in Appendix 2.C)

Vomiting

Moderate certainty evidence from 9 RCTs (1,538 patients)[24,26,30,32,33,38,43,45,55] showed that medical cannabis or cannabinoids may slightly increase the risk of vomiting (RD, 2% [95% CI, 0% to 6%]). (Table 1, eFigure 7 in Appendix 2.C)

Headache

Moderate certainty evidence from 14 RCTs (1,819 patients)[24,26-28,30,32,33,35,37,38,44,49,55,60] showed medical cannabis or cannabinoids vs. placebo may make little to no difference in the risk of headache (RD, -1% [95% CI, -3% to 2%]). (eTable 6 in Appendix 2.D, eFigure 8 in Appendix 2.C)

Fatigue

High certainty evidence from 13 RCTs[24-26,28-30,37,38,44,49,50,55,60] (2,087 patients) found that cannabinoids increases the incidence of fatigue compared to placebo (RD, 6% [95% CI, 3% to 11%]) (eTable 6 in Appendix 2.D, eFigure 9 in Appendix 2.C)

Dry mouth

Our results showed that medical cannabis and cannabinoids increases the risk of dry mouth compared with placebo (RD 7% [95% CI, 3 to 12]), (eFigure 10 in Appendix 2.C); however, studies with longer follow-up showed greater risk. High certainty evidence (eTable 6 in Appendix 2.D) from 5 RCTs[24-26,36,44] (1,829 patients) that followed patients for ≥3 months showed that medical cannabis or cannabinoids, versus placebo, results in a larger increase in the risk of dry mouth (RD 10% [95% CI, 5 to 17]) than trials that

followed patients for <3 months (RD 4% [95% CI, 0 to 10]; 10 RCTs [27,30,32,33,38,45,49,51,57,60] [905 patients]) (test of interaction p=0.04; eFigure 10.3 in Appendix 2.C).

Somnolence

High certainty evidence from 14 RCTs[24-26,28,30,37-40,43,45,49,51,55] (2,753 patients) shows that cannabinoids, versus placebo, increases the risk of somnolence (RD 6% [95% CI, 3% to 9%]). (eTable 6 in Appendix 2.D; eFigure 11 in Appendix 2.C)

Constipation

Low certainty evidence from 8 RCTs (1,659 patients)[24,32,39,41,45,53,57,60] suggested no significant association between cannabinoid use and the risk of constipation (RD -1% [95% CI, -2 to 2]). (eTable 6 in Appendix 2.D and eFigure 12 in Appendix 2.C)

Outcomes for medical cannabis vs active comparators

Medical cannabis vs. amitriptyline

Low certainty evidence from one trial (32 fibromyalgia patients) suggests that nabilone, compared to amitriptyline, may provide greater improvement in symptoms of insomnia (mean difference on the insomnia severity index 3.25 [95%CI, 5.26 to 1.24]) and a slightly more restful sleep (mean difference on the Leeds Sleep Evaluation Questionnaire [LSEQ] 0.48; 95%CI 0.01 to 0.95).[29]

Medical cannabis vs. opioids

Low quality evidence from one trial (96 patients with chronic neuropathic pain) suggests that nabilone may make little to no difference in sleep interruptions compared to dihydrocodeine (mean difference on a 0-10cm VAS, 0.2 [95%CI, -0.1 to 0.5]; p=0.20).[34]

Medical cannabis vs. diazepam

Low quality evidence from one trial (11 female patients) suggests that THC may improve sleep disturbance versus diazepam for anorexia nervosa (-2.09 vs. -1.91 [p=0.004] on the Hopkins Symptom Checklist).[52]

Four studies eligible for our review did not report data suitable for pooling. Three reported responder analyses instead of the mean change on continuous outcome measures [35,36,54], and one reported results on a 3 category scale.[56] We describe their findings in eTable 3, Appendix 2.D. No additional subgroup analysis or meta-regression were credible apart from those reported above (eTables 4&5 in Appendix 2.D and Appendices 2.B & 2.C).

DISCUSSION

Moderate to high certainty evidence shows that, compared to placebo, medical cannabis or cannabinoids result in small improvements in sleep quality among patients living with chronic cancer or noncancer pain, small improvements in sleep disturbance among patients living with chronic noncancer pain, and very small improvements in sleep

disturbance among chronic cancer pain patients. Compared to placebo, use of medical cannabis or cannabinoids shows small increases in the risk of dizziness (and large increases in risk with more prolonged use), somnolence, dry mouth, fatigue, and nausea, but not vomiting, constipation, or headache.

Nabilone might be more effective for symptoms of insomnia than amitriptyline, and equivalent to dihydrocodeine for reducing sleep interruptions; however, these findings were supported by only low certainty evidence. Our results were restricted to 2 to 16 weeks of treatment and, almost exclusively, to non-inhaled cannabinoids.

The most recent systematic review of cannabinoids for the management sleep disorders only included 3[23,29,46] of the 39 RCTs that we identified.[6] In part, this was due to their eligibility criteria, which excluded sleep disorders secondary to a primary condition unless the trial used a sleep-related outcome as their primary outcome measure. An earlier systematic review of cannabinoids for sleep identified 19 of 39 trials in our review.[5] Neither review conducted meta-analyses nor assessed the overall certainty of evidence. Both concluded that further research was needed to establish the role of cannabinoids for sleep disorders. Our review extends these findings by substantially increasing the evidence considered by prior reviews, quantifying treatment effects, and assessing the certainty of evidence on an outcome-by-outcome basis.

Strengths and limitations

This systematic review is the first to statistically pool treatment effects of medical cannabis and cannabinoids on impaired sleep. When possible, we converted all significant

pooled mean effects to RDs to facilitate interpretation and used the GRADE approach to appraise the certainty of evidence on an outcome-by-outcome basis. We explored causes of heterogeneity among pooled effects and assessed the credibility of all subgroup effects.

Our review has several limitations including: 1) most evidence we found was for non-inhaled cannabinoids provided to people living with chronic pain, and our findings may not be generalizable to smoked or vaporized forms of cannabis or to patients without chronic pain; 2) the evidence for cannabis or cannabinoids vs. active comparators was only low to very low certainty; 3) although the 10cm VAS was the most frequent measure used among trials eligible for our review, there are better validated measures of impaired sleep (e.g. insomnia severity index [ISI][61]); 4) we could not explore the association between dose and effect estimates as most trials (28 of 39; 72%) allowed for post-randomization titration by patients; 5)we calculated change scores, when not reported, using a correlation coefficient from the largest trial at lowest risk of bias. An alternate approach would be to use a correlation coefficient of 0.5 and then conduct a sensitivity analysis using extreme ranges (0.1 and 0.9); however, we believe that our approach, which uses data from studies eligible for our review, is likely to generate plausible correlation coefficients; 6) eligible trials did not report on concurrent use of other medications that may interact with medical cannabis; and 7) trials in our review followed patients for relatively brief periods of time (median of 35 days), which precludes confident inferences about long-term use of medical cannabis on sleep. One recent observational study has found use of medical cannabis may improve sleep in the short-

term, but that long-term use is associated with problems initiating and maintaining sleep.[62]

CONCLUSIONS

We found moderate to high certainty evidence that, when compared to placebo, use of medical cannabis or cannabinoids results in small improvements in sleep quality among patients living with chronic pain; small improvements in sleep disturbance among patients living with chronic noncancer pain, very small improvement in sleep disturbance among chronic cancer pain patients, and small increases in several adverse side effects (with a large increase in dizziness with longer treatment). The effects of medical cannabis and cannabinoids on impaired sleep, compared to active treatment, is uncertain as the evidence is only low to very low certainty.

Figure 2.1. Flow diagram of database searches and articles included in the systematic review and meta-analysis

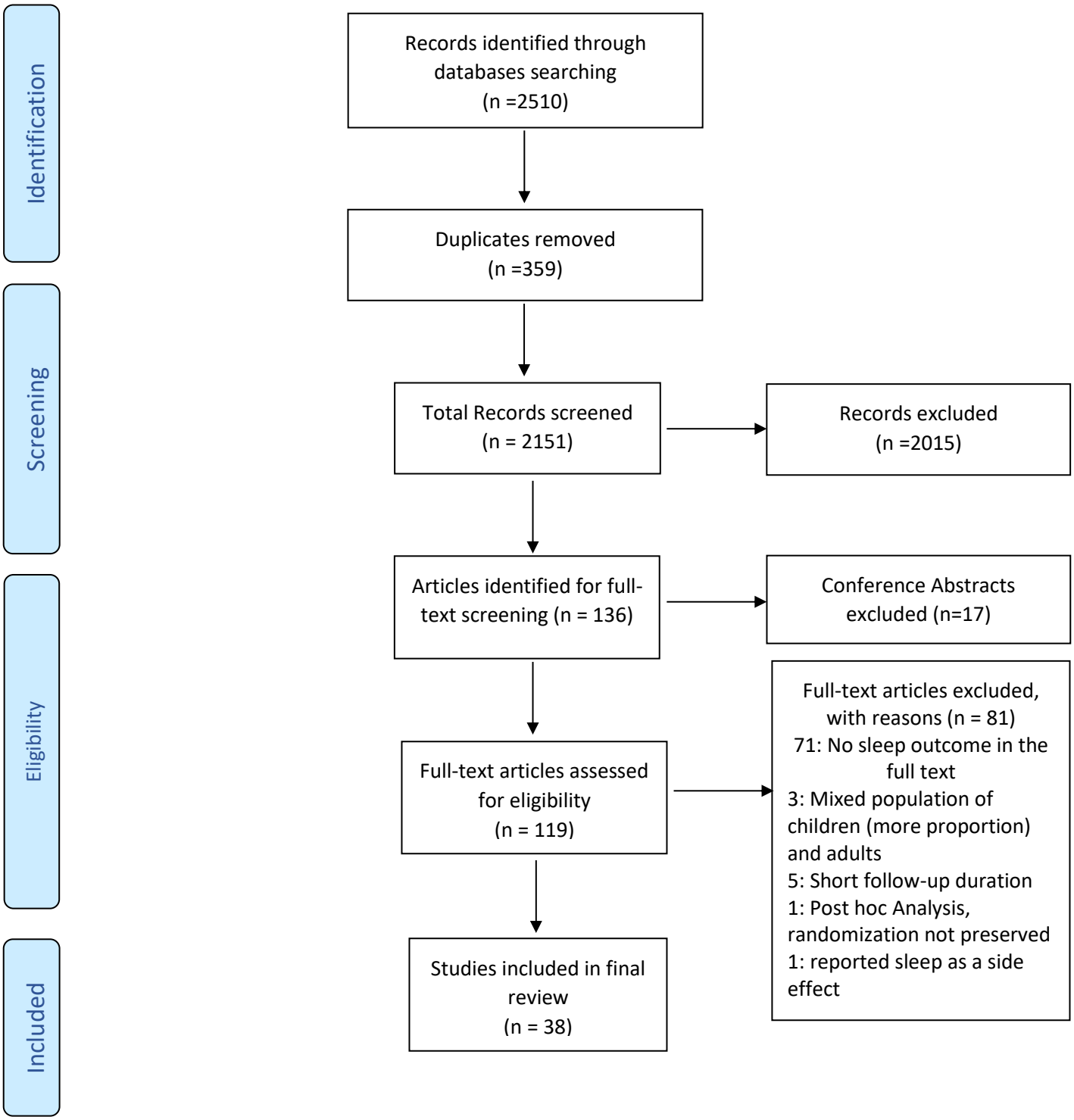


Figure 2.2. Forest plot showing sleep quality on a 10-cm visual analog scale among people living with, predominantly, chronic pain who received medical cannabis vs placebo

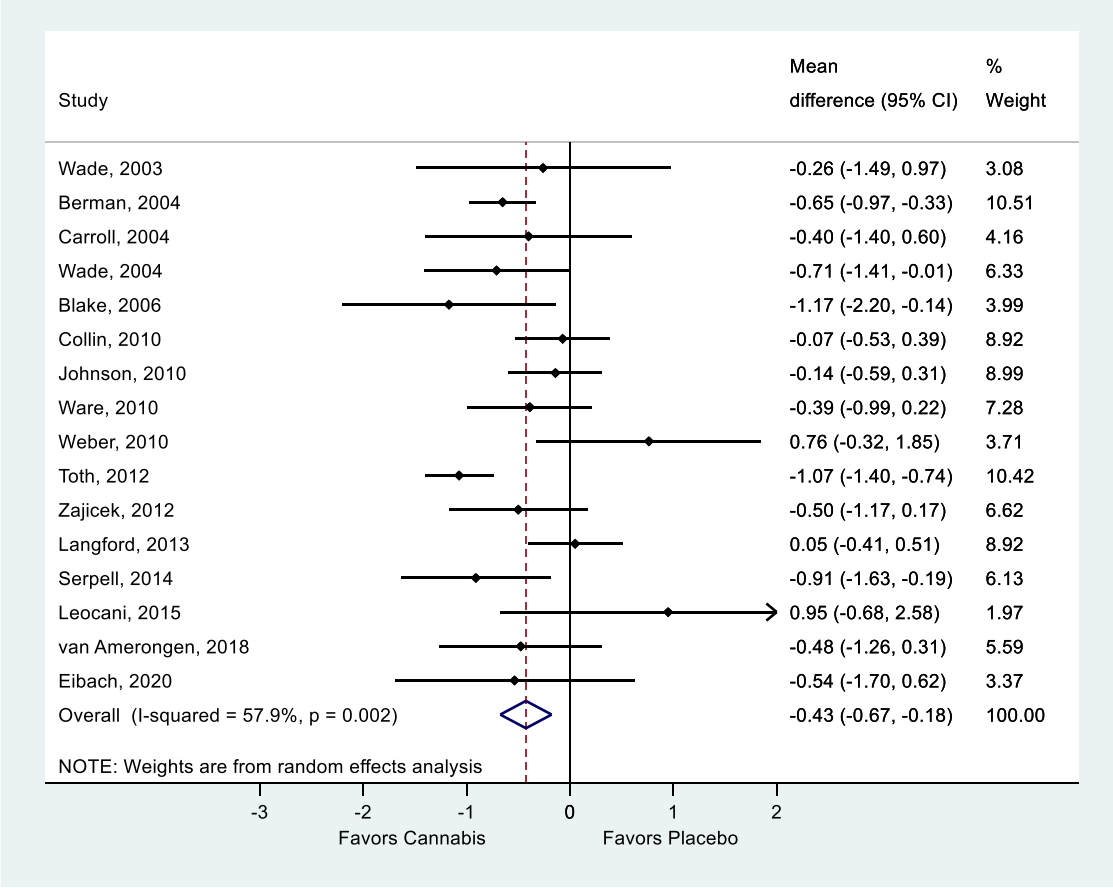
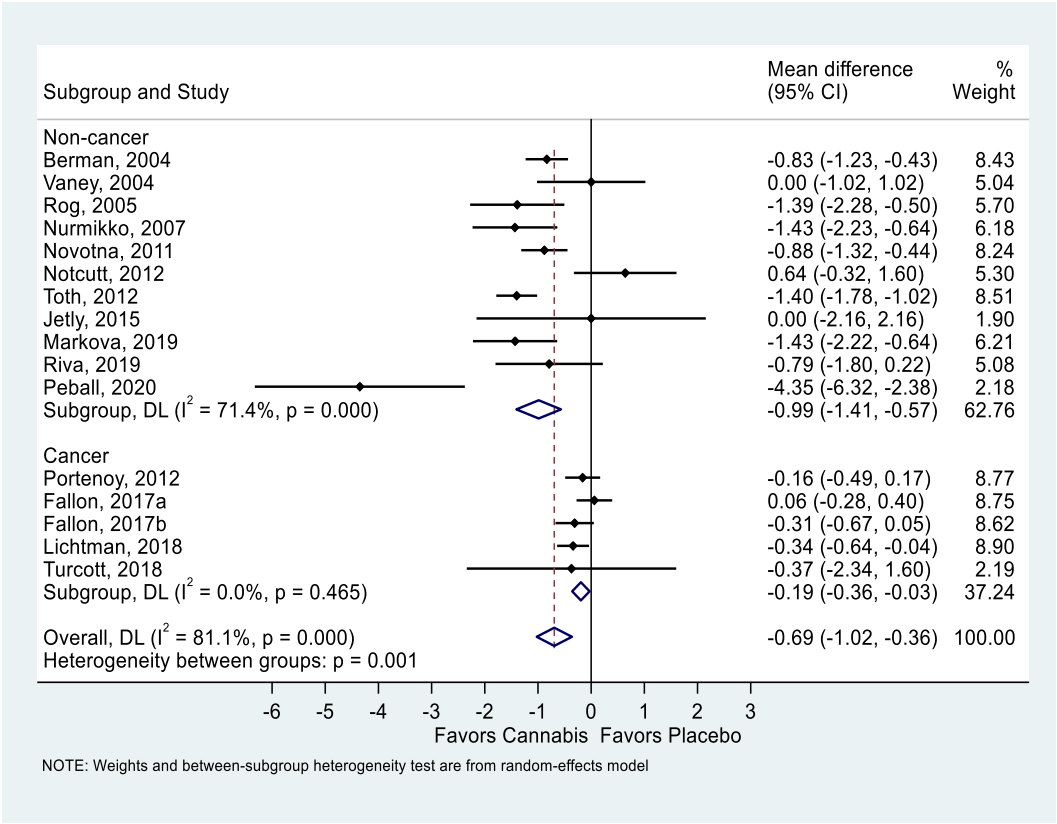


Figure 2.3 Forest plot showing subgroup analysis of sleep disturbance for cancer vs non cancer pain



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Table 2.1. GRADE Evidence Profile of Medical Cannabis and Cannabinoids vs Placebo Predominantly for Patients with Chronic pain Included in Randomized Clinical Trials *

Outcome	No. of patients (trials)	Follow-up range in weeks	Risk of Bias [a]	Inconsistency [b]	Indirectness [c]	Imprecision	Publication Bias [d]	Risk Difference for Achieving the MID (95% CI)	WMD-RR (95% CI)	Quality of Evidence
Sleep Quality (VAS: 0 to 10 cm)	2052 (16 RCTs)	2-14	not serious [e]	not serious I-squared=57.9%	not serious	serious [f]	Undetected (p = 0.22)	8% (3 to 12)	MD 0.43 lower (0.18 lower to 0.67 lower)	Moderate
Sleep Disturbance (Non-Cancer Patients) (VAS: 0 to 10 cm)	906 (11 RCTs)	2-12	not serious [e]	not serious I-squared=71.4%	not serious	not serious	Undetected (p = 0.88)	19% (11 to 28)	MD 0.99 lower (0.57 lower to 1.41 lower)	High
Sleep Disturbance (Cancer Patients) (VAS: 0 to 10 cm)	1249 (5 RCTs)	5-8	serious [g]	not serious I-squared= 0%	not serious	not serious	Uncertain: only five trials	no baseline data available	MD 0.19 lower (0.03 lower to 0.36 lower)	Moderate
Nausea (RCTs ≥3 months follow-up)	1163 (4 RCTs)	12-14	not serious [e]	not serious I-squared= 0%	not serious	not serious	Uncertain: only four trials	10% (5 to 17)	RR 2.64 higher (1.83 higher to 3.80 higher)	High
Nausea (RCTs <3 months follow-up)	2380 (18 RCTs)	2-8	not serious [e]	not serious I-squared= 0%	not serious	not serious	Undetected (p = 0.28)	3% (1 to 6)	RR 1.49 higher (1.11 higher to 1.98 higher)	High
Dizziness (RCTs ≥3	1824 (5 RCTs)	13-16	not serious [e]	not serious I-squared=59.7%	not serious	not serious	Uncertain: only five trials	29% (16 to 50)	RR 4.28 higher (2.76 higher to 6.65 higher)	High

months follow-up)										
Dizziness (RCTs < 3 months follow-up)	2481 (19 RCTs)	2-4	not serious [e]	not serious I-squared= 0%	not serious	not serious	Undetected (p = 0.72)	8% (4 to 12)	RR 2.03 higher (1.60 higher to 2.58 higher)	High
Diarrhea	1777 (12 RCTs)	2-14	not serious [e]	not serious I-squared=0%	not serious	not serious	Undetected (p = 0.06)	2% (0 to 5)	RR 1.74 higher (1.07 higher to 2.82 higher)	High
Disturbance in attention	1086 (7 RCTs)	2-14	serious [h]	not serious I-squared=0%	not serious	not serious	Uncertain: only seven trials	2% (0 to 7)	RR 4.7 higher (1.77 higher to 12.5 higher)	Moderate
Vomiting	1538 (9 RCTs)	2-14	not serious [e]	not serious I-squared=0%	not serious	serious [i]	Uncertain: only nine trials	2% (0 to 6)	RR 1.56 higher (0.97 lower to 2.49 higher)	Moderate

*22 studies of medical cannabis for chronic non-cancer pain, 7 for chronic cancer pain, one for multiple sclerosis and one for Parkinson disease.

a. We used a modified Cochrane risk of bias instrument for assessing risk of bias.
b. An I^2 value between 75% and 100% may demonstrate considerable heterogeneity.
c. We considered the evidence indirect if, among contributing trials, the intervention, patients, or outcomes were different from our review question.
d. We assessed symmetry of the funnel plot and used Egger's test to assess publication bias when there were at least 10 studies available.
e. We did not rate down for risk of bias as subgroup analysis showed no significant difference in low vs. high risk of bias on a component-by-component basis, or the relative contribution of trials at high risk of bias to pooled estimate was < 15% (eTable 7 in Appendix 2.D).
f. The 95%CI includes ½ the MID
g. Four out of five studies (Fallon et al, 2017a; Portenoy et al., 2012; Turcott et al., 2018; Lichtman et al., 2018) had a high loss to follow up (26%, 27%, 36% and 27%, respectively), the result of meta-regression for loss to follow-up was significant ($p<0.001$) and the relative contribution of trials at high risk of bias to pooled estimate was greater than 20%.
h. One study (Serpell, 2014) reported high loss to follow-up (30%) and the relative contribution of this trial to pooled estimate was 23%.
i. Confidence intervals include benefit and harm.

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CHAPTER 3: PATIENTS' PERSPECTIVES TOWARDS MEDICAL CANNABIS (MARIJUANA) FOR CHRONIC PAIN: A QUALITATIVE RESEARCH STUDY

Patients' Perspectives Towards Medical Cannabis for Chronic Pain: A Qualitative Research Study

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ABSTRACT

Objective. Although there is a growing interest in medical cannabis for chronic pain, little is known about patients' perspectives. We explored perceptions of people living with chronic pain regarding benefits and concerns surrounding their use of medical cannabis.

Setting. A hospital-based clinic in Hamilton and two community based interdisciplinary pain clinics in Burlington, Ontario, Canada.

Methods. In this qualitative descriptive study, we conducted semi-structured interviews with 13 people with chronic pain who used medical cannabis for managing pain, living in Ontario, Canada. We used thematic analysis and drew upon an inductive thematic approach for the coding with data collection and analysis occurring concurrently.

Results: People living with chronic pain reported financial costs and stigma as important barriers to use of medical cannabis. Moreover, while many perceived important benefits associated with use of medical cannabis, including substitution for prescription medication, most patients also acknowledged harms, and there was considerable variability in patient experiences.

Conclusion. Evidence-based guidance that incorporates patients values and preferences may be helpful to inform the role of medical cannabis in the management of chronic pain.

Key words: medical cannabis; chronic pain; patient attitudes; qualitative research

INTRODUCTION:

In July 2001, Canada enacted the Medical Marihuana Access Regulations (MMAR) [1], which allowed patients to legally acquire cannabis for therapeutic purposes [2]. The 2011 Canadian Alcohol and Drug Use Monitoring Survey, based on telephone interviews with 10,076 Canadian residents aged 15 years and older (46% response rate), found that 17.7 % reported use of cannabis for medical purposes, with half endorsing use for chronic pain [3]. As of March 2021, approximately 420,000 Canadians had authorization from Health Canada to use cannabis for medical purposes [4]. Despite interest regarding cannabis for management of chronic pain, the evidence to support this practice is limited [5]. Further, adverse events are associated with medical cannabis use, including sedation, vertigo, and dizziness [5, 6]

Cannabis is also used for recreational purposes, and on Oct. 17, 2018, the Cannabis Act came into effect, legalizing the sale and use of non-medicinal cannabis across Canada [7]. Patients who manage their symptoms with medical cannabis may therefore be subject to scrutiny regarding their motives, and prior surveys, reviews and qualitative studies conducted among patients with various conditions have documented the perception of stigma from law enforcement personnel [8], friends and relatives [1, 9], employers [9, 10] and health care providers [9-12]. To understand this more fully exclusively among patients living with chronic non-cancer pain, we explored the perceptions of patients regarding benefits and concerns surrounding their use of medical cannabis.

METHODS

This study employed a qualitative descriptive design [13, 14]. This approach provides a summarized, comprehensive, and coherent description of a phenomenon of interest [15] using language similar to participants' own words [13]. We followed the consolidated criteria for reporting qualitative research (COREQ) checklist in reporting our findings [16].

Participants

We recruited participants from a hospital-based clinic in Hamilton and two community based interdisciplinary pain clinics in Burlington, Ontario, Canada between April 2019, and October 2020. Potentially eligible patients were identified by their physician, who briefly introduced the study and asked permission for a member of our study team to contact them for additional details and determine their interest in participating. Eligible patients were adults (≥20 years of age) using medical cannabis for management of chronic noncancer pain, who provided written informed consent. We used a non-probability, purposive sampling strategy to recruit participants with experiential fit with the study phenomenon [17, 18]. We stopped recruiting once we had interviewed sufficient participants to achieve the thematic saturation of codes and themes regarding use of medical cannabis [19, 20]. Before being interviewed, each participant was provided with an information letter outlining the purpose of the study, the length of the interview and how confidentiality would be maintained. Participants were compensated for their participation with a $10 gift card.

Data collection

We conducted one-on-one, in-depth, semi-structured interviews with all participants using an interview guide with open-ended questions (Appendix 3). The interview guide was informed by the literature [21, 22] and discussions with content experts in the field of cannabis and chronic pain. We also engaged two people living with chronic pain who used medical cannabis to review our interview guide for clarity and `completeness, and we modified the wording of two items based on their feedback. Two members of our study team with training in qualitative interviewing (MA, NK) conducted all patient interviews.

Prior to the COVID-19 pandemic, nine interviews were conducted in-person in a private room in the pain clinics. We conducted the remaining four interviews by videoconference after public health measures were enacted to reduce spread of COVID-19. Interviews took between 25 to 50 minutes to complete, and we reached saturation of code and meaning after interviewing 13 participants [20].

Prior to each interview, participants provided demographic information (e.g., age, education, race, income, duration of chronic pain, method of cannabis consumption). All interviews were audiotaped and transcribed verbatim. To ensure confidentiality, all data were de-identified, and each participant was assigned an identification number in all transcribed documents and interview notes. The interviewers recorded field notes to highlight personal reflections and emotions during data collection. We did not return transcripts to participants, nor did we conduct follow-up interviews. The Hamilton Health Sciences-McMaster Research Ethics Board approved our study (Project no. 5007).

Data Analysis

We used thematic analysis and drew upon an inductive thematic approach for the coding with data collection and analysis occurring concurrently [23]. The same two team members who conducted the interviews (MA and NK) manually coded and aggregated transcribed text into meaningful themes and subthemes independently. Our approach was guided by recommendations by Braun and Clarke: (1) reading the transcripts several times to become familiar with the data; (2) generating initial codes and the relevant data; (3) identifying the potential themes and sub-themes based on the codes; (4) reviewing the identified themes and labelling them by considering the overall story revealed from the analysis; and (5) selecting representative quotes for themes and sub-themes [24]. All team members reviewed the results and confirmed the main themes and subthemes of our study findings, which were accompanied by supporting quotes.

RESULTS

We contacted a total of 15 patients who referred by physicians and 13 agreed to be interviewed. Our participants included 7 men and 6 women, with a median age of 53 (interquartile range 45 to 64). The majority were white (62%), 38% were divorced, and most patients (46%) reported an annual household income of <$50,000 CAN. Most (46%) had acquired a college diploma, were retired (46%), and the majority (69%) had lived with chronic pain for more than 10 years. Participants reported various types of chronic pain including neuropathy, arthritis, chronic injuries, ulcerative colitis, and carpal

tunnel syndrome. Most described their pain as debilitating, leading to decreased functioning and overall quality of life, and sometimes resulting in suicidal thoughts. Some reported marital tension because of limitations associated with their pain, as well as negative attitudes towards their condition.

Six participants were attending a hospital-based pain clinic, and seven were receiving care at a community-based pain clinic. Before receiving physician authorization to access medical cannabis, almost all of our participants (11 of 13) were using cannabis; two exclusively for medical purposes and nine exclusively for recreational purposes. Since receiving medical authorization, 12 participants reported cannabis use for exclusively medical purposes, and one for both recreational and medical purposes. Most had received authorization for medical cannabis after they initiated a discussion with their primary care physician. Most respondents (46%) administered their medical cannabis both through inhalation and ingestion (e.g., oil-filled capsule, edibles), and the majority (54%) were receiving disability benefits (Table 1). Eleven participants were paying for medical cannabis out-of-pocket, and two participants were re-imbursed for the costs of their medical cannabis by Veterans Affairs Canada.

Main themes

Three key themes were identified that described perceptions of people living with chronic pain regarding benefits and concerns surrounding their use of medical cannabis: 1) financial barriers to use of medical cannabis, 2) stigma associated with use of medical cannabis, and 3) effectiveness of medical cannabis for chronic pain.

Table 3.1. Respondents' characteristics

Characteristic		Frequency/percentage
Sex	Female	6 (46%)
	Male	7 (54%)
Marital Status	Single	1 (8%)
	Married	6 (46%)
	Divorced	5 (38%)
	Common-Low	1 (8%)
Race	White	8 (62%)
	Black	1 (8%)
	Aboriginal	1 (8%)
	Caucasian	1 (8%)
	Other	2 (15%)
Receiving Disability Benefits	Yes	7 (54%)
	No	6 (46%)
Living with	Spouse/Partner	7 (54%)
	Children	3 (23%)
	No one	3 (23%)
Annual Household Income	Less than 25k	4 (31%)
	25k to 49999	2 (15%)
	50k to 74999	1 (8%)
	75K to 99999	3 (23%)
	100K to 150k	2 (15%)
	More than 150 k	1 (8%)
Educational Level	High School	5 (38%)
	College	6 (46%)
	University	2 (15%)
Employment Status	Employed full-time	3 (23%)
	Employed part-time	1 (8%)
	Unemployed	3 (23%)
	Retired	6 (46%)
Duration of Chronic Pain	Less than 5 years	2 (15%)
	5- 10	2 (15%)
	11- 15	2 (15%)
	16- 20	2 (15%)
	21- 25	2 (15%)
	More than 26	3 (23%)
Method of administration of Medical Cannabis	Orally (e.g., oil-filled capsule, edibles)	4 (31%)
	Exclusively smoking or inhaling	3 (23%)
	A combination of oral and inhaled use	6 (46%)

Financial barriers

Most participants noted out-of-pocket costs of medical cannabis as a major concern, due to lack of coverage from the government or insurers. For example, one participant (a middle-aged female) stated:

"I *still have to stretch it out because the cost is prohibitive. And I don't want to buy it on the street because you don't know what you're going to get...Yeah. So, when I tried it, I started with the oil. But that became too expensive so I switched to vaping it, because Ontario disability support program will pay for the vaporizer, but they won't pay for the medical marijuana, even if it's prescribed… right now, I'm not using it as often as I should, part of that is the cost, and I have to spread it out as much as possible."*

To reduce costs, some participants reported purchasing medical cannabis through an online distributor, rather than a dispensary or licensed producer. One participant noted they continued using opioids to manage their chronic pain because they could only afford some of the amount of cannabis recommended by their physician:

"*Oxycodone? Ya, still five milligrams twice a day. Yeah. I never changed that one. I tried to wean myself off of that one, but I can't do it. I need it too badly. I can't afford the marijuana. That's the biggest deal for me with the marijuana. The insurance companies don't cover it. And I can't afford seven hundred dollars a month. I'm only on a small disability pension so I can only afford one third of what's prescribed to me most months."*

In contrast, one participant with higher annual income than most others interviewed, explained that cost was not a major concern for them:

"The cost is a little bit high. But can you put a price on your happiness? ….. you cannot put a price on it. That's my happiness I'm dealing with. So, I've spent a lot more on dumb things in my past. So, this is my future this is my happiness so I can't put a price on that so I'm going to continue to pay for it until somebody says that the government might pick up the tab."

Stigma associated with use of medical cannabis

According to patients' experiences, stigma arose from different sources which can be categorized as follows: (1) family, (2) healthcare providers, (3) general population, and (4) the older generation. Participants described strategies they used to cope with stigma from others, and how negative feedback was associated with participants' unwillingness to discuss their use of medical cannabis.

Stigma from healthcare providers

Several participants perceived stigma from healthcare providers regarding their use of medical cannabis, with one advising they feared healthcare providers viewing them as a "drug addict". One participant stated:

"… there was a good 5, 6, 7 years there where I was run around by doctors all over the place. My general practitioner in particular, and it got to the point where it was like, no, I'm on my team. And I need to do what's best for me. And I don't really care who that upsets... Because I have to do what's best for me and my pain."

Stigma from family

Participants had mixed experiences with their families. Some participants reported that their families were understanding and accepting, particularly if other family members were also using medical cannabis:

"*But my family, you know, because some of my family are using it as well. My sister, my, you know, my niece, that sort of thing. So, I do have discussions with them. And they have nothing negative to say about it."*

Other participants reported their family's discomfort with their use. One participant hid their cannabis use from their children for more than 20 years, and another described hiding their use of medical cannabis, even after it was legalized, from their mother and father-in-law for several years because of perceived stigma:

"*I know that my mother-in-law and my father-in-law, even if it's legalized, they still disagree with it completely. They say even if it's legalized, we don't agree with it. We don't think that you should be using it. So yeah, I've had to hide it from them*."

Two participants were raised in religious families and cited their fear of openly using medical cannabis due to perceived judgment from members of their religious community. This led to guilt surrounding the use of cannabis and, for one participant, reluctance to access their religious spaces due to fear of judgment from others. However, another participant described being open about their use of cannabis to their fellow churchgoers, particularly those who also lived with chronic pain.

Stigma from the public

Most participants reported experiencing stigma because of medical cannabis use. One noted that their friends who used cannabis recreationally, viewed their use of medical cannabis as a "joke." Others felt looked down on in public, feeling they were viewed as using a recreational drug rather than a medicine. One participant noted they only used cannabis in public when also using a walker so as to avoid suspicion of recreational use. A middle-aged female explained:

"…. *Some people look down on you and so there's a very negative energy coming from them.*

…. They view it very much as a drug in the same category as say heroin. Some people are very open to it. I find that the more chronic pain someone has the more open they are to it, because people without chronic pain sometimes don't realize just how much chronic pain negatively affects your life."

Another participant (older aged male) stated:

"*Even after legalization there are still those same kind of thoughts out there, and I don't see it as often, but they still treat you like a leper almost because you use marijuana for medical purposes you know. "Don't go talk to him, he uses marijuana he's probably crazy." *laugh* Yeah, that's not as bad as it used to be but it's still there for sure.*"

Stigma from the older generation

Several participants explained that older individuals in their lives viewed cannabis negatively, even after legalization. Some participants perceived this stigma arising from beliefs that medical cannabis is an illegal and addictive substance:

"*So, a lot of people my age, I would say, and in their 30s are very accepting of if … especially because it's medical. So, they understand a lot, but I would say more like older generations. Yeah, they don't really understand. You know, why I'm taking it or, you know, maybe they'll think that it's because I'm using it recreationally.*"

Strategies for addressing stigma

Participants' struggle with stigma was evident throughout the interviews, as they described discomfort they had endured because of others' views. Participants also reported that indicating to others that their use of cannabis was for medical purposes would sometimes help to alleviate criticism. For instance, a young female stated:

"*People are, I think if they had an opinion about it, I think maybe a negative opinion, I think maybe their negative opinion has changed somewhat since just hearing my story in regard to what I used and how I get through life right now."*

Some participants wanted more education directed at the general population regarding use of medical cannabis for chronic pain. Moreover, participants believed that some healthcare providers were inadequately prepared to appropriately offer medical cannabis to patients and reflected on the need for education among healthcare providers:

"*I think family doctors maybe need to be more onboard, more educated, because they can then, you know. Patients are willing to accept their, their opinions, right? Especially like me, my doctor, I've been with her for 17 years. So, she says to me, I think this is good. And that's why I'm trying it because I respect her opinion.*"

Effectiveness of medical cannabis for chronic pain

Many participants reported benefits associated with medical cannabis, including reduced pain, improved sleep, appetite, energy, nausea, and overall mood. Medical cannabis was also described by most of the participants as a more natural substance than other opioids. Some noted that use of cannabis had allowed them to reduce use of prescription medications, with better overall results. A middle-aged male stated that:
"*....my marriage and my family life were terrible when I was on Duloxetine ... and then when I started using CBD oil which literally gave me the opportunity to start getting off Duloxetine…it's brought me a whole new thing, a whole new life and you know what there's a lot of harmony in my home right now which I give a lot of credit to CBD oil."*

Others reported that medical cannabis was insufficient on its' own but allowed them to reduce their use of prescription medication. For example:
"*I'm taking amitriptyline 75 milligrams, also, oxycocet. I take half the tablet when my pain reaches 10 and the medical marijuana won't, like help the pain because sometimes I have like 10 on 10 pain, where I'm crying, and I'm bent over. So, I have to take like half a*

tab of the oxycocet to really make it go away…. I don't think I can only take marijuana because there's other things going on too."

Two participants felt their medical cannabis provided no additional pain relief however, both continued to use small amounts due to enthusiasm of their treating physician. Many participants reported adverse effects associated with medical cannabis, including lung irritation and coughing, forgetfulness, weight gain, dizziness, dry mouth, headache, and sedation. However, almost half of participants felt that medical cannabis had fewer side effects than prescription medications they had used (or were using). It is noteworthy that these participants continued to use MC regardless of their views towards side effects. Three participants also reported no side effects associated with medical cannabis.

DISCUSSION

In this study, people living with chronic pain reported the cost of medical cannabis and lack of coverage by governmental agencies and insurers as a barrier to use. Another significant barrier was the experience of stigma from healthcare providers, family members, and the general public – in particular, members who participants viewed as the "older generation."

Experiences regarding effectiveness of medical cannabis for chronic pain were variable. While many associated improvements across a range of outcomes and reduction in some prescription medications, there was consensus that medical cannabis was insufficient on

its own. Two participants did not perceive benefits but continued their use of cannabis to appease their treating physician. Although many acknowledged modest side effects of cannabis use, the benefits were felt to exceed the harms, and adverse effects were often less than those associated with prescription medications.

Participants' financial concerns of medical cannabis use are supported by prior qualitative studies exploring the experience of older adults with chronic conditions [10, 12, 25]. An American study reported that patients living with chronic pain who used medical cannabis also noted costs as the primary negative theme [12].

Most of our participants perceived stigma towards use of cannabis: a previous qualitative study of patients using cannabis for therapeutic purposes in Canada noted similar issues [9]. They suggested that the illegal status of recreational cannabis may be a contributory factor. In contrast, our interviews were conducted after legalization of non-medical cannabis which suggests that patients were focused on experiences prior to legalization or that stigma may persist despite legalization. However, it is also noteworthy that the majority of our participants were using cannabis for recreational purposes prior to obtaining medical authorization, and one continued with recreational use after medical authorization. The need for education around therapeutic use of cannabis for both healthcare providers and the general public has also been identified by other investigators [10, 25].

Most of our participants advised that medical cannabis as an adjunct to prescription medication was helpful for their chronic pain, and they believed that cannabis was safer compared with medication. Similarly, other qualitative studies have found that people

living with chronic pain perceive that cannabis is effective in reducing their symptoms, improving quality of life, and allowing for reduction in prescription medication use [26, 27,12, 25]. Further, that medical cannabis is associated with fewer side effects than prescription medications commonly used for chronic pain [10]. However, while observational studies show large beneficial effects of medical cannabis, moderate to high certainty evidence from randomized trials demonstrate a high non-specific effect and very modest risk differences for improvement in pain, sleep quality and physical functioning versus placebo (risk differences of 10%, 6% and 4% for achieving the minimally important difference, respectively) [5]. Further, most of our participants reported inhaling their medical cannabis with consequent respiratory complaints of cough, dry mouth, and lung irritation. Medical cannabis is available in non-inhaled forms (e.g. sprays, oral capsules) and it is unclear why clinicians would authorize cannabis products that are typically inhaled (e.g. dried flower) over modes of administration that would avoid pulmonary harms.

Strengths and limitations

We applied rigorous qualitative methodology to investigate attitudes of people living with chronic pain towards medical cannabis and recruited a range of participants to gather diverse perspectives. No members of our study team had any motivation to encourage positive or negative answers, thereby minimizing information bias during interviews. We did not implement member checking to verify our findings; however, two members of our team with training in qualitative research methods conducted open

coding and theme generalization, independently and in duplicate, to promote trustworthiness of our results.

There are limitations to our study. First, due to COVID-19 restrictions our recruitment efforts were stalled, and our four final interviews were conducted by videoconferencing instead of in-person. Second, our sample size (n =13) was not large; however, we sampled to thematic saturation which suggests that additional interviews would be unlikely to create further codes. Third, our study results are based on experiences and perspectives of patients living with chronic non-cancer pain attending a hospital-based and two community-based pain clinics in two Canadian cities and may have limited applicability to patients with other conditions and different settings.

CONCLUSIONS

People living with chronic pain in our study reported financial costs and stigma as important barriers to use of medical cannabis. Moreover, while many perceived important benefits associated with use of medical cannabis, including substitution for prescription medication, most patients also acknowledged harms, and there was considerable variability in patient experiences. Evidence-based guidance that incorporates patients values and preferences may be helpful to better clarify the role of medical cannabis in the management of chronic pain.

Declaration of Conflicting Interests

The authors declare no conflicts of interest with respect to the research, authorship, and publication of this article.

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CHAPTER 4: DECLARED RATIONALE FOR CANNABIS USE BEFORE AND AFTER LEGALIZATION FOR RECREATIONAL USE: A LONGITUDINAL STUDY OF COMMUNITY ADULTS IN ONTARIO

Declared Rationale for Cannabis Use before and after Legalization for Recreational Use: A Longitudinal Study of Community Adults in Ontario

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ABSTRACT

Objectives: To examine the proportion of medical cannabis users who reported recreational use after non-medical use of cannabis was legalized.

Materials and Methods: We acquired data from the Population Assessment for Tomorrow's Health Cannabis Legalization Surveillance Study (PATH-CANN) on a subpopulation of participants residing in Hamilton, Ontario, Canada, who reported using cannabis for medical purposes, 6-months before legalization of cannabis for recreational purposes. This same cohort was surveyed again 6-months after legalization about their rationale for using cannabis. We constructed a logistic regression model to explore the association between potential explanatory factors and endorsing only recreational use after legalization and reported associations as odds ratios (ORs) and 95% confidence intervals (95%CIs).

Results: Our sample included 254 respondents (mean age 33 ±13; 61% female), of which 208 (82%) reported both medical and recreational use (dual motives) of cannabis before legalization for recreational purposes, and 46 (18%) reported exclusively medical use. Only 25% (n=63) indicated they had medical authorization to use medical cannabis of which 37 (59%) were dual motives users. After legalization of non-medical cannabis, approximately 1 in 4 previously exclusive medical users declared dual use (medical and recreational), and approximately 1 in 4 previously dual users declared exclusively recreational use of cannabis. No individual with medical authorization reported a change to recreational use only after legalization.

Our adjusted regression analysis found that younger age, male sex and not having authorization for cannabis use were associated with declaring solely recreational use of cannabis after legalization. Anxiety, depression, sleep problems, pain and headaches were among the most complaints for which respondents used cannabis therapeutically. Most respondents reported using cannabis as a substitute for prescription medication at least some of the time, and approximately half reported using cannabis as a substitute for alcohol at least some of the time.

Conclusions: In a community sample of Canadian adults using cannabis for medical purposes, legalization of recreational cannabis was associated with a substantial proportion changing to either dual use (medical and recreational) or exclusively recreational use. Younger men without medical authorization for cannabis use were more likely to declare only recreational use after legalization.

BACKGROUND

Cannabis has psychoactive properties, primarily associated with the cannabinoid tetrahydrocannabinol (THC), and is widely consumed in Canada for both medical and recreational purposes.[1] The 2012 Canadian Community Health Survey found that 12% of Canadians (aged ≥15 years) reported using cannabis in the past year.[2] By 2019, the prevalence of past-year cannabis use among Canadians aged 15 and over had increased to 15%.[3] In general, individuals who endorse use of cannabis are more likely to be male and younger.[2-5]

Cannabis has been legal for medical use (for select indications) in Canada since 2001, [6] and in 2020 approximately 420,000 Canadians were authorized by Health Canada to acquire cannabis for medical purposes.[7] A 2019 systematic review found that chronic pain, anxiety and depression were the most common indications reported by patients for use of medical cannabis; [8] however, empirical support is limited and the effectiveness of cannabis as a therapeutic agent is uncertain for most indications for which it is commonly used.[9-13]

Allowing legal access to cannabis for medical purposes only may result in some recreational users acquiring access through this system. On October 17, 2018, the federal government of Canada legalized the acquisition of cannabis for non-medical purposes.[14] This provided an opportunity to conduct a natural study exploring whether declared rationale for use of cannabis among Canadians was associated with this change in legal status.

METHODS

Study Design and Participants

As of January 2021, all phases of the PATH-CANN study have been administered and data from 6 months before legalization (phase 1: September 16th - October 17th, 2018) and 6 months after legalization of recreational cannabis (phase 2: April 14th - May 14th, 2019) were used for this study. In each phase, participants were asked to report their cannabis use status over the past 6 months. We analyzed the data collected from a subpopulation of participants who reported using cannabis for medical purposes in the first phase (pre-legalization) to explore for changes to their declared rationale for use of cannabis after legalization.

Study Sample

The sample of interest was a subset of community adults (age 18-65 at recruitment), derived from the PATH-CANN cohort who reported use of cannabis for medical purposes, and provided internally consistent data at both phases 1 and 2 of the online PATH-CANN assessment. Participants who reported using cannabis only for recreational purposes were excluded. Specifically, the current study considered only cohort members that endorsed medical use of cannabis before legalization of recreational cannabis (i.e., exclusively medical use and medical + recreational use [dual motives users]) and their status six-months later.

Methods of Measurement and Outcome Measures

We acquired the following data collected through the PATH-CANN on-line survey: patients' demographic characteristics (age, gender, race, income, marital status, education, and employment status), reason(s) for using cannabis and the role of cannabis in managing disease/ symptoms measured using the Reasons for Using Medical Marijuana Questionnaire (RUMM).[15] To examine subjects' attributions about using cannabis for treating diseases or symptoms, we analyzed data related to the five most frequent diseases or symptoms for which respondents used medical cannabis, and the role of cannabis as a substitute for prescription medication or alcohol.

Analysis Plan

We reported the mean and standard deviation (SD) of continuous variables, and absolute and relative frequencies for categorical variables at pre-and post-legalization. We constructed a logistic regression model to examine the associations between age, sex, income and medical authorization for cannabis, and the probability of reporting only recreational use after legalization of non-medicinal cannabis. To explore for potential multicollinearity between covariates, we constructed a correlation matrix to identify unacceptably high correlations between independent variables and then calculated the variance inflation factor (VIF) of all variables included in our model. We consider a VIF > 5 to indicate problematic multicollinearity**.** The Goodness of fit for the models was also examined using the Hosmer-Lemeshow test. We presented results as odds ratios (ORs) with 95% confidence intervals (CIs). All analyses were performed using SPSS v25.0 (IBM SPSS Statistics ©) and all comparisons were 2-tailed using a $p \leq 0.05$ threshold for statistical significance.

RESULTS

Of the 1,480 members of the PATH-CANN cohort, 254 respondents who reported using cannabis for medical purposes before legalization of recreational cannabis, and correctly answered 3 out of 5 data quality questions, were eligible for this secondary study. (Figure 1 in Appendix 4) The mean age of our sample was 33±13 (range: 19 to 66), most were female (61%), and 68% were between the ages of 19 and 34. The majority were employed in either a full-time (53%) or part-time (24%) capacity, reported an annual household income of ≤$60,000/year, and had completed some college or university education (50%). (Table 1)

Table 4.1. Respondents 'characteristics

Characteristic		Frequency/percentage
Age, yr.	Mean ± SD	33±13
	≥ 65	4 (2%)
	45–64	43 (17%)
	35–44	34 (13%)
	25–34	74 (29%)
	19–24	99 (39%)
Sex Assigned at Birth	Female	156 (61%)
	Male	98 (39%)
Household Income	≤ $30 k	87 (34%)
	$31k to $45k	32 (13%)
	$46k to $60 k	29 (11%)
	$61k to $90k	43 (17%)
	≥ $91k	63 (25%)
Educational Level	Less than high school	15 (6%)
	High school graduate (or GED)	21 (8%)
	Some college/university	126 (50%)
	Associates degree completed	28 (11%)
	Bachelor's degree or higher	64 (25%)
Employment Status	Full Time	134 (53%)
	Part Time	61 (24%)
	Legally disabled	20 (8%)
	Unemployed	31 (12%)
	Retired	8 (3%)

Prior to legalization of recreational cannabis

Of 254 respondents, 25% (n=63) reported authorization from a health professional to use cannabis for medical purposes, of which 37 (59%) also endorsed recreational use of cannabis. Only 18% (n=46) reported exclusively medical use of cannabis over the past 6 months. The remaining 208 respondents (82%) reported both medical and recreational use of cannabis. (Table 2) Most respondents used cannabis to manage anxiety (67%; n=169) and/or depression (48%; n=122), and to assist with sleep (65%; n=165) and/or acute pain (48%; n=121). (Tables 3&4)

Table 4.2. Disclosed reason(s) for cannabis use before and after legalization of recreational cannabis

	6-months before legalization	Percentage	6-months after legalization	Percentage
Exclusively Medical user	46	18%	40	16%
Medical+ Recreational user	208	82%	140	55%
Exclusively Recreational user	-	-	52	20%
No use of cannabis	-	-	22	9%
Total	254	-	254	

Most respondents (62%) reported substituting cannabis for their prescription medication at least some of the time, and 30% did so most or all the time. Close to half (45%) endorsed substituting cannabis for alcohol at least some of the time, and 14% did so most or all the time. (Figure 2 in Appendix 4) Substitution of cannabis for illicit drugs (e.g., cocaine) was less frequent, and endorsed by only 20% of respondents.

After legalization of recreational cannabis

Following legalization of non-medicinal cannabis, the largest shifts in declared use were from solely medical to dual use (medical and recreational), and from dual use to solely recreational. After use of recreational cannabis was legalized, 24% of respondents who had reported exclusively medical use declared dual use. Among declared dual users prior to legalization, 24% changed their reported use to exclusively recreational. (Tables 2 and 5)

Patterns of use to manage clinical disorders and symptoms, as well as substitution for prescription medication, alcohol, and illicit drugs, were similar to what respondents reported before recreational cannabis was legalized. (Tables 3 and 4, Figure 3 in Appendix 4)

Table 4.3. Medical conditions for which respondents used medical cannabis

Disease	Pre-legalization (n=254)	Post-legalization (n=254)
	Frequency (%)	Frequency (%)
Anxiety	169 (67%)	120 (47%)
Depression	122 (48%)	98 (39%)
Arthritis	52 (21%)	40 (16%)
PTSD	46 (18%)	39 (15%)
Irritable bowel syndrome	44 (17%)	30 (12%)

Table 4.4 Symptoms for which respondents reported use of cannabis

Symptoms	Pre-legalization (n=254)	Post-legalization (n=254)
	Frequency (%)	Frequency (%)
Sleep problems	165 (65%)	119 (47%)
Acute pain	121 (48%)	81 (32%)
Headaches/migraines	133 (45%)	78 (31%)
Chronic non-cancer pain	92 (36%)	69 (27%)
Nausea/ vomiting	57 (22%)	52 (21%)

Table 4.5. Changes in cannabis use patterns at pre-and post-legalization (n=254)

	Pre-Legalization		Post-Legalization			%
	Medical	**Recreational**	**Medical**	**Recreational**		
Dual motives Users	Yes	Yes	Yes	Yes	129	62%
	Yes	Yes	No	Yes	50	24%
	Yes	Yes	Yes	No	13	6%
	Yes	Yes	No	No	16	8%
total					**208**	**100%**
Exclusively Medical Users	Yes	No	No	No	6	13%
	Yes	No	Yes	No	27	59%
	Yes	No	Yes	Yes	11	24%
	Yes	No	No	Yes	2	4%
total					**46**	**100%**

Predictors of becoming recreational users at post-legalization

Our adjusted regression analyses found three factors associated with declaring solely recreational use of cannabis after legalization: younger age (OR 0.64 for every decade increase from age 19, 95%CI 0.45 to 0.90), male sex (OR 2.35, 95%CI 1.22 to

4.50), and not being authorized by a healthcare provider to use medical cannabis (OR 3.52, 95%CI 1.29 to 9.57). (Table 6) The results of the Hosmer and Lemeshow test showed no evidence of over-fitting (Chi-square=12.66- df=8, P-value= 0.12), and there was no evidence of multicollinearity.

Table 4.6. Factors associated with declaring exclusively recreational use of cannabis after legalization (n = 254)

Independent factor	Univariable Analysis OR (95% CI)	p-value	Multivariable Analysis OR (95% CI)	p-value
Older age (by decade, from age 19)	0.65 (0.47 to 0.89)	0.007	0.64 (0.45 to 0.90)	0.01
Sex female male	 reference 2.31 (1.24 to 4.31)	 0.008	 reference 2.35 (1.22 to 4.50)	 0.01
Income ≤$60,000/year >$60,000/year	 reference 1.45 (0.78 to 2.68)	 0.24	 reference 1.66 (0.86 to 3.22)	 0.13
Medical authorization for cannabis yes no	 reference 3.71 (1.40 to 9.79)	 0.007	 reference 3.52 (1.29 to 9.57)	 0.01

OR = Odds Ratio
95%CI = 95% confidence interval

DISCUSSION

Our study of community adults who report use of cannabis for therapeutic purposes found that most endorse both medical and recreational use. Among this population, cannabis was commonly used to manage symptoms of anxiety, depression, pain, and impaired sleep, and often as a substitute for prescription medication. However, only a minority reported that their use of therapeutic cannabis was authorized by a healthcare

provider. After legalization of non-medical cannabis, approximately 1 in 4 modified their declared rationale for cannabis use to either dual use (medical and recreational) or exclusively recreational use. Younger age, male sex and not being authorized by a healthcare provider for medicinal cannabis use were associated with declaring solely recreational use of cannabis after legalization.

Our findings suggest that the 420,000 Canadians who have medical authorization to access cannabis for therapeutic purposes may considerably underestimate the actual number who use cannabis for medical purposes.[7] Reasons why most adults in our cohort used cannabis therapeutically without medical authorization are uncertain; however, reluctance by family physicians to authorize medical cannabis may be a contributory factor.[16] Moreover, our finding that 1 in 4 respondents changed their declared use to recreational after it was legal to do so suggests that some medical use prior to legalization may have been recreational.

Our results regarding therapeutic use of cannabis are very similar to a 2016 cross-sectional survey of 1,429 medical cannabis users in Washington State, where respondents endorsed pain (61%), anxiety (58%), depression (50%), headache/migraine (36%), nausea (27%), and muscle spasticity (18%) as the most frequently targeted symptoms.[17] As with our cohort, other studies have found managing psychiatric disorders is a common reason for using cannabis[18-20], however, the effectiveness and safety of cannabis for mental illness is uncertain.[21]

Replacement of prescription medications with medical cannabis has also been reported previously. A 2015 Canadian survey of 271 authorized medical cannabis users

found 63% reported substituting cannabis for prescription medications.[22] A survey of 2,774 Americans who reported having used cannabis at least once in the previous 90 days found that 46% reported using cannabis as a substitute for prescription drugs.[23] Another survey of 2,897 medical cannabis users revealed that 97% endorsed substitution for prescription opioids;[24] however, the opioid-sparing effects of medical cannabis remain uncertain due to very low certainty evidence .[25]

Strengths and Limitations

In terms of the strengths, our cohort had only 2% missing data and we administered validated instruments for capturing data on reason(s) for using cannabis and the role of cannabis in managing disease/ symptoms. Our study also has limitations. First, we asked respondents to recall their use of cannabis over the past 6-months, and results may be affected by recall bias. Second, the results of our study cannot be generalized to all patients who have authorization to use medical cannabis since most participants in our cohort endorsed both medical and recreational cannabis use and were not authorized by a health professional. Third, social desirability bias may have caused some respondents to fail to report recreational use of cannabis; however, this seems unlikely given that 82% of our sample reported non-medicinal use of cannabis prior to legalization.

CONCLUSIONS

In a community sample of Canadian adults using cannabis for medical purposes, legalization of recreational cannabis was associated with a substantial proportion changing to either dual use (medical and recreational) or exclusively recreational use.

Those individuals who were younger, male, and were not using medical cannabis under authorization by a healthcare provider were more likely to declare exclusively recreational use of cannabis after legalization.

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CHAPTER 5: CONCLUSIONS AND FUTURE DIRECTIONS

SUMMARY OF FINDINGS, CONCLUSIONS, AND FUTURE DIRECTIONS

This work presents three key findings on the use of medical cannabis for two major conditions including impaired sleep and chronic pain as well as the changes in patterns of cannabis use for medical purposes before and after the federal legalization of cannabis use for recreational purposes. The main findings can be summarized as follows:

The first thesis project was conducted to investigate the safety and efficacy of medical cannabis and cannabinoids for impaired sleep compared with placebo. This systematic review and meta-analysis included 39 randomized trials and 5056 patients with impaired sleep. Our study suggests that based on moderate to high certainty evidence use of medical cannabis or cannabinoids compared with placebo slightly improves subjective sleep quality, among patients with chronic pain, and subjective sleep disturbance among patients with chronic noncancer pain. Patients living with chronic cancer pain also show very small improvements in sleep disturbance. In addition, high certainty evidence indicates the association between medical cannabis or cannabinoids use with small increases in the risk of several adverse events including diarrhea, fatigue, somnolence, as well as dry mouth and nausea (greater with longer treatment), and a large increase in dizziness among trials that followed up patients for three months or longer. Given the only low to very low certainty evidence, there is uncertainty regarding the effects of medical cannabis and cannabinoids on impaired sleep, compared to active treatments.

Overall, our results suggest that medical cannabis and cannabinoids may improve subjective sleep quality and sleep disturbance among chronic pain patients; however, the magnitude of the effect is likely to be small.

As outlined above, most of the included trials (85%) in our study enrolled patients with chronic pain and limited number of trials enrolled patients with other conditions. Furthermore, the choice of outcome (i.e., subjective rating of sleep quality and disturbance) may limit interpretation as medicinal cannabis may worsen objective indices of sleep. Measures of sleep quality and disturbance also vary in their psychometric support and converting to a standardized index may have obscured important information about whether the data are reliable or valid.

Therefore, this evidence cannot fully support the clinical use of medical cannabis for treating a wide range of sleep disorders among patients with various conditions given the lack of high-quality large-scale trials that evaluate both objective and subjective indices of sleep measured using validated scales. Our study highlights the necessity of conducting high-quality research that assesses the direct impact of medical cannabis and cannabinoids on different aspects of sleep measured using standardized scales among patients living with different conditions.

To further exploring the therapeutic aspects of using medical cannabis we conducted a qualitative study to look at the safety and efficacy of medical cannabis from patients' perspectives. In this qualitative descriptive approach, three key themes were emerged based on analysis of 13 interview transcripts: 1) financial barriers to the use of medical cannabis; 2) stigma associated with MC use, and the effectiveness of medical cannabis for chronic pain. In general, participants described positive experiences with using MC, explaining it as a complementary and often substitute drug for managing

CNCP. However, participants also described barriers to MC use such as cost, and perceived stigma from various sources including family, healthcare providers, the general population, and the older generation.

The results of his study as an adjunct to clinical findings and evidence can help inform future treatment programming and policy development in the field of medical cannabis to empower patients using MC to manage the potential barriers of cannabis use. The life-enhancing benefits and drawbacks of medical cannabis explored in this study can also have implications for those health care providers dealing with CNCP patients to develop cannabis-related interventions. This study suggests that future studies include more participants from various contexts to better explore the other potential benefits or barriers of the use of medical cannabis for managing chronic pain. Furthermore, given the potential impacts of past cannabis use experience and the concurrent use of cannabis for both medical and recreational purposes, we suggest that researchers consider the following two main criteria including “the use of cannabis for exclusively medical purposes” and “no history of cannabis use in the past” among their study eligibility criteria when they want to recruit participants. This can help better explore patients’ pure experience in the use of medical cannabis for managing chronic pain. This study also suggests evidence-based guidance includes patients’ beliefs and preferences to better inform the therapeutic role of medical cannabis for chronic pain.

The third project sheds light on changes in patterns of cannabis use among individuals reporting cannabis for medical purposes over the course of cannabis

legalization for recreational use in Canada. The results of this study revealed that most of the respondents who reported using cannabis for medical purposes also endorsed recreational use at pre-legalization. Given this high proportion, our study suggests that for many people who use cannabis, there are no clear borders between medical and recreational use, and they may substantially change by changes in legal situation. This issue can also influence the therapeutic effects of cannabis which needs to be prescribed and monitored by a health professional. However, these implications are necessarily conjectured at this stage and warrant further investigation. In addition, further research on medical cannabis users needs to be exclusively conducted among those who have authorization from a physician to use cannabis for medical purposes in order to obtain robust findings.

Approximately 40% of the respondents in both dual motives users and exclusively medical users, changed their status after legalization. Therefore, we can conclude that participants' attributions about their cannabis use were relatively unstable over the course of legalization. We found high rates of concurrent recreational use at both pre-and post-legalization phases and notable transitions to recreational-only use following legalization. This implies that when recreational cannabis is illegal, individuals may be more likely to report using it for medical purposes in addition to recreational purposes.

More importantly, according to current data reported in the literature, there are about 420,000 Canadians who have authorization for using cannabis; however, this may considerably underestimate the actual number of those who use cannabis for medical

purposes as we found most adults in our cohort used cannabis therapeutically without medical authorization.

We also found that younger age, male sex and not being authorized by a healthcare provider for medicinal cannabis can be considered as the predictors of reporting cannabis use for only recreational purposes after legalization. Large-scale surveys and continued monitoring at the national level are suggested to continue to inform patterns of use among Canadians who use cannabis for medical purposes.

Appendices

Appendix 2.A: Literature search strategies

MEDLINE

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

---

1 sleep.mp. (202222)

2 exp sleep waking cycle/ or exp sleep disorder assessment/ or exp sleep parameters/ or exp sleep stage/ or exp night sleep/ or exp sleep hygiene/ or exp nonREM sleep/ or exp experimental sleep apnea/ or exp circadian rhythm sleep disorder/ or exp Leeds Sleep Evaluation Questionnaire/ or exp sleep induction/ or exp slow wave sleep/ or exp sleep therapy/ or exp sleep pattern/ or exp sleep disordered breathing/ or exp sleep walking/ or exp sleep/ or exp sleep spindle/ or exp benign neonatal sleep myoclonus/ or exp delta sleep inducing peptide/ or exp "International Classification of Sleep Disorders"/ or exp sleep arousal disorder/ or exp sleep quality/ or exp sleep deprivation/ or exp sleep medicine/ or exp sleep time/ or exp REM sleep deprivation/ or exp sleep disorder/ (146114)

3 exp sleep disorder/ (92169)

4 Sleep Wake Disorders.mp. (23226)

5 insomnia.mp. or exp insomnia/ (27104)

6 exp parasomnia/ (7603)

7 parasomnias.mp. (1227)

8 exp sleep deprivation/ (9820)

9 sleep deprivation.mp. (12942)

10 exp sleep disordered breathing/ (36657)

11 sleep apnea.mp. (45939)

12 exp SLEEP AIDS, PHARMACEUTICAL/ or exp "SLEEP INITIATION AND MAINTENANCE DISORDERS"/ or exp SLEEP APNEA, OBSTRUCTIVE/ or exp SLEEP MEDICINE SPECIALTY/ or exp SLEEP/ or exp SLEEP-WAKE TRANSITION DISORDERS/ or REM SLEEP BEHAVIOR DISORDER/ or exp SLEEP LATENCY/ or exp SLEEP AROUSAL DISORDERS/ or exp SLEEP HYGIENE/ or exp SLEEP APNEA SYNDROMES/ or exp SLEEP STAGES/ or exp SLEEP APNEA, CENTRAL/ or exp SLEEP DISORDERS, INTRINSIC/ or exp SLEEP DISORDERS, CIRCADIAN RHYTHM/ or exp SLEEP, REM/ or exp SLEEP BRUXISM/ or exp SLEEP WAKE DISORDERS/ or exp DELTA SLEEP-INDUCING PEPTIDE/ or exp SLEEP DEPRIVATION/ (153755)

13 exp "Sleep Initiation and Maintenance Disorders"/ or exp INSOMNIA, FATAL FAMILIAL/ (13811)

14 exp PARASOMNIAS/ (7603)

15 dreams.mp. or exp DREAMS/ (8843)

16 nightmare*.mp. (3124)

17 sleep apne*.mp. (46021)

18 sleep apnoe*.mp. (6571)

19 (upper airway resistan* adj2 syndrom*).mp. (267)

20 (obstruct* adj2 hypopn?ea*).mp. (670)

21 (sleep disorder* adj1 breathing).mp. (7209)

22 (sleep adj2 respirat* adj1 disorder).mp. (51)

23 osa.tw. (14922)

24 osas.tw. (4378)

25 osahs.tw. (1489)

26 ((mixed or central) adj4 apn?ea*).mp. (3659)

27 apn?e*-hypopn*.mp. (11507)

28 (nocturnal adj2 hypoxemia).mp. (510)

29 (sleep disorder* adj1 respirat*).mp. (109)

30 (nocturnal adj2 hypoxemia).mp. (510)

31 apn?eic.mp. (3572)

32 Sleep Apnea Syndromes/ or sleep apnea, central.mp. (16212)

33 or/1-10 (218627)

34 or/11-32 (172728)

35 33 or 34 (233251)

36 exp medical cannabis/ or exp Cannabis sativa/ or exp cannabis smoking/ or exp "cannabis use"/ or exp "Cannabis sativa subsp. indica"/ or exp cannabis derivative/ or exp cannabis addiction/ or exp cannabis/ or Cannabis.mp. or exp "Cannabis (genus)"/ (26806)

37 Cannabinoids.mp. or exp cannabinoid/ (13050)

38 cannabi$.mp. (44224)

39 36 or 37 or 38 (46597)

40 exp nabiximols/ or exp tetrahydrocannabinol/ or exp tetrahydrocannabinolic acid/ or THC.mp. or exp cannabis/ or exp cannabidiol/ (19124)

41 exp tetrahydrocannabinol/ or exp dronabinol/ (7162)

42 exp dronabinol/ or CBD.mp. (14206)

43 Cannabidiol.mp. (3582)

44 nabilone.mp. (353)

45 Cesamet.mp. (22)

46 dronabinol.mp. (7338)

47 Marinol.mp. (90)

48 nabiximols.mp. (283)

49 Sativex.mp. (199)

50 or/40-49 (25587)

51 (bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol).mp. (24218)

52 50 or 51 or 39 (63221)

53 35 and 52 (1288)

54 randomized controlled trial.pt. (521065)

55 controlled clinical trial.pt. (94023)

56 randomized.ab. (509034)

57 placebo.ab. (215236)

58 drug therapy.fs. (2270287)

59 randomly.ab. (350598)

60 trial.ab. (540071)

61 groups.ab. (2151910)

62 or/54-61 (4905665)

63 clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs. (5907830)

64 randomized controlled trial.pt. or randomized controlled trial.mp. (553836)

65 randomized controlled trial.pt. or randomized.mp. or placebo.mp. (945715)

66 63 or 64 or 65 (5925436)

67 62 or 66 (7707783)

68 53 and 67 (702)

69 limit 68 to ed=20200601-20210120 (54

EMBASE
Database: Embase <1974 to 2021 January 19>

Search Strategy:

---

1 exp sleep disorder/ (246743)

2 Sleep Wake Disorders.mp. (893)

3 exp primary insomnia/ or exp insomnia/ or exp Insomnia Severity Index/ or exp fatal familial insomnia/ (70702)

4 insomnia.mp. (77343)

5 exp parasomnia/ (7098)

6 parasomnias.mp. (1654)

7 exp sleep deprivation/ (16601)

8 sleep deprivation.mp. (19474)

9 exp sleep disordered breathing/ (54621)

10 Sleep Apnea Syndromes.mp. (962)

11 exp sleep disordered breathing/ (54621)

12 sleep apnea.mp. (69549)

13 or/1-12 (292612)

14 exp sleep medicine/ or exp "International Classification of Sleep Disorders"/ or exp sleep deprivation/ or exp sleep induction/ or exp night sleep/ or exp sleep waking cycle/ or exp Leeds Sleep Evaluation Questionnaire/ or exp circadian rhythm sleep disorder/ or exp slow wave sleep/ or exp central sleep apnea syndrome/ or exp experimental sleep apnea/ or exp sleep quality/ or exp sleep time/ or exp nonREM sleep/ or exp sleep walking/ or exp sleep arousal disorder/ or exp sleep parameters/ or exp sleep disorder assessment/ or exp sleep therapy/ or exp Pittsburgh Sleep Quality Index/ or exp sleep disordered breathing/ or exp sleep pattern/ or exp sleep spindle/ or exp sleep stage/ or exp

delta sleep inducing peptide/ or exp sleep disorder/ or exp REM sleep/ or exp REM sleep deprivation/ or exp sleep hygiene/ or exp benign neonatal sleep myoclonus/ or exp sleep/ (371942)

15 sleep.mp. (326772)

16 14 or 15 (425389)

17 13 or 16 (428685)

18 exp cannabis derivative/ or exp "cannabis use"/ or exp cannabis/ or exp cannabis smoking/ or exp "Cannabis (genus)"/ or exp "Cannabis sativa subsp. indica"/ or exp Cannabis sativa/ or exp medical cannabis/ (44376)

19 cannabis.mp. (52936)

20 exp cannabinoid/ (70199)

21 Cannabinoids.mp. (13349)

22 exp cannabis derivative/ or exp cannabis smoking/ or exp "Cannabis (genus)"/ or exp "Cannabis sativa subsp. indica"/ or exp Cannabis sativa/ or exp cannabis-induced psychosis/ or exp "cannabis use"/ or exp cannabis addiction/ or exp cannabis/ or exp medical cannabis/ (48757)

23 cannabi$.mp. (80738)

24 or/18-23 (89758)

25 exp tetrahydrocannabinol/ (6479)

26 tetrahydrocannabinol.mp. (13233)

27 exp dronabinol/ or exp cannabis/ or cannabidiol/ or exp tetrahydrocannabinol/ (47037)

28 CBD.mp. (12879)

29 exp cannabidiol/ (5344)

30 Cannabidiol.mp. (6194)

31 exp nabilone/ (1389)

32 nabilone.mp. (1446)

33 Cesamet.mp. (284)

34 exp dronabinol/ (8022)

35 dronabinol.mp. (8112)

36 Marinol.mp. (608)

37 exp nabiximols/ (755)

38 nabiximols.mp. (792)

39 Sativex.mp. (727)

40 exp nabiximols/ or exp tetrahydrocannabinol/ or exp cannabidiol/ or exp dronabinol/ or exp cannabinoid/ or exp cannabis/ (70199)

41 THC.mp. (11191)

42 or/25-41 (83074)

43 24 or 42 (102136)

44 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (28527743)

45 human/ or normal human/ or human cell/ (21973866)

46 44 and 45 (21907442)

47 44 not 46 (6620301)

48 17 and 43 (4721)

49 48 not 47 (4412)

50 random:.tw. or placebo:.mp. or double-blind:.tw. (1884023)

51 ((treatment or control) adj3 group*).ab. (913339)

52 (allocat* adj5 group*).ab. (35354)

53 ((clinical or control*) adj3 trial).ti,ab,kw. (444066)

54 or/50-53 (2638374)

55 49 and 54 (1207)

56 limit 55 to em=202024-202104 (78)

PsycInfo

Database: APA PsycInfo <1806 to January Week 2 2021>

Search Strategy:

---

1 sleep.mp. (80194)

2 exp sleep/ or nocturnal teeth grinding/ or sleep apnea/ or sleep deprivation/ or exp sleep disorders/ or sleep onset/ (52934)

3 exp dreaming/ (8027)

4 sleep apnea/ (3202)

5 (insomnia* or parasomnia* or dream* or nightmare*).mp. (43219)

6 (OSA or OSAS or OSAHs).mp. (2333)

7 (upper airway resistan* adj2 syndrom*).mp. (37)

8 (obstruct* adj2 hypopn?ea*).mp. (94)

9 ((mixed or central) adj4 apn?ea*).mp. (306)

10 apn?e*-hypopn*.mp. (1395)

11 (nocturnal adj2 hypoxemia).mp. (46)

12 apn?eic.mp. (248)

13 or/1-12 (111109)

14 exp cannabis/ or exp cannabinoids/ or tetrahydrocannabinol/ (13670)

15 marijuana/ or hashish/ or exp marijuana laws/ or marijuana usage/ (6301)

16 (cannabi* or sativa or sativex or THC or CBD or nabiximol* or tetrahydrocannabi* or dronabinol* or nabilon* or cesamet or marinol*or nabiximol*).mp. (18920)

17 (bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol).mp. (13257)

18 or/14-17 (28106)

19 13 and 18 (701)

20 (double-blind or random: assigned or control).tw. (496683)

21 clinical trials/ (11839)

22 (controlled adj3 trial*).mp. (47938)

23 (clinical adj2 trial*).mp. (41069)

24 (randomi?ed adj7 trial*).mp. (59083)

25 or/20-24 (552419)

26 19 and 25 (158)

27 limit 19 to ("therapy (maximizes sensitivity)" or "therapy (maximizes specificity)") (379)

28 26 or 27 (384)

29 limit 28 to yr="2020 -Current" (24)

Cochrane Library

Search Strategy:

Search Name: cannabis sleep

Date Run: 20/01/2021 12:36:59

Comment:

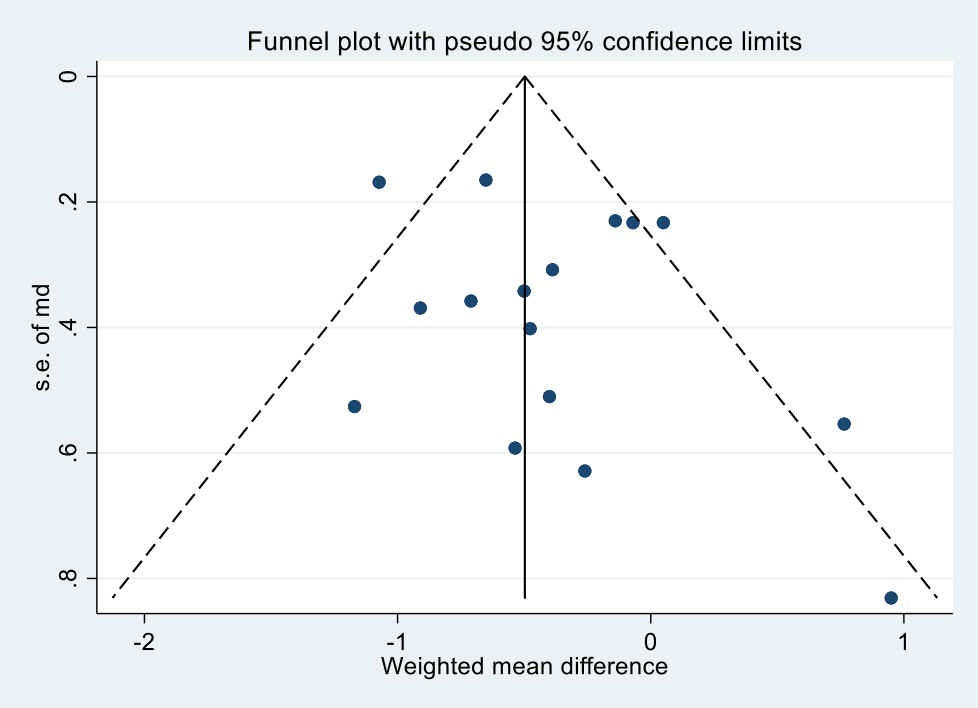
ID	Search Hits
#1	MeSH descriptor: [Cannabis] explode all trees 304
#2	MeSH descriptor: [Cannabinoids] explode all trees 831
#3	MeSH descriptor: [Endocannabinoids] explode all trees 51
#4	MeSH descriptor: [Endocannabinoids] explode all trees 51
#5	(Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*):ti,ab,kw (Word variations have been searched) 4765
#6	#1 or #2 or #3 or #4 or #5 4765
#7	MeSH descriptor: [Sleep Wake Disorders] explode all trees 8237
#8	MeSH descriptor: [Sleep Initiation and Maintenance Disorders] explode all trees 2472
#9	MeSH descriptor: [Parasomnias] explode all trees 812
#10	sleep deprivation 1791
#11	MeSH descriptor: [Sleep Deprivation] explode all trees 754

#12	MeSH descriptor: [Sleep Apnea Syndromes] explode all trees	2656
#13	(sleep*):ti,ab,kw (Word variations have been searched)	40020
#14	#7 or #8 or #9 or #10 or #11 or #12 or #13	40338
#15	#6 and #14 in Trials	322
#16	#15 with Cochrane Library publication date in the last 9 months	38

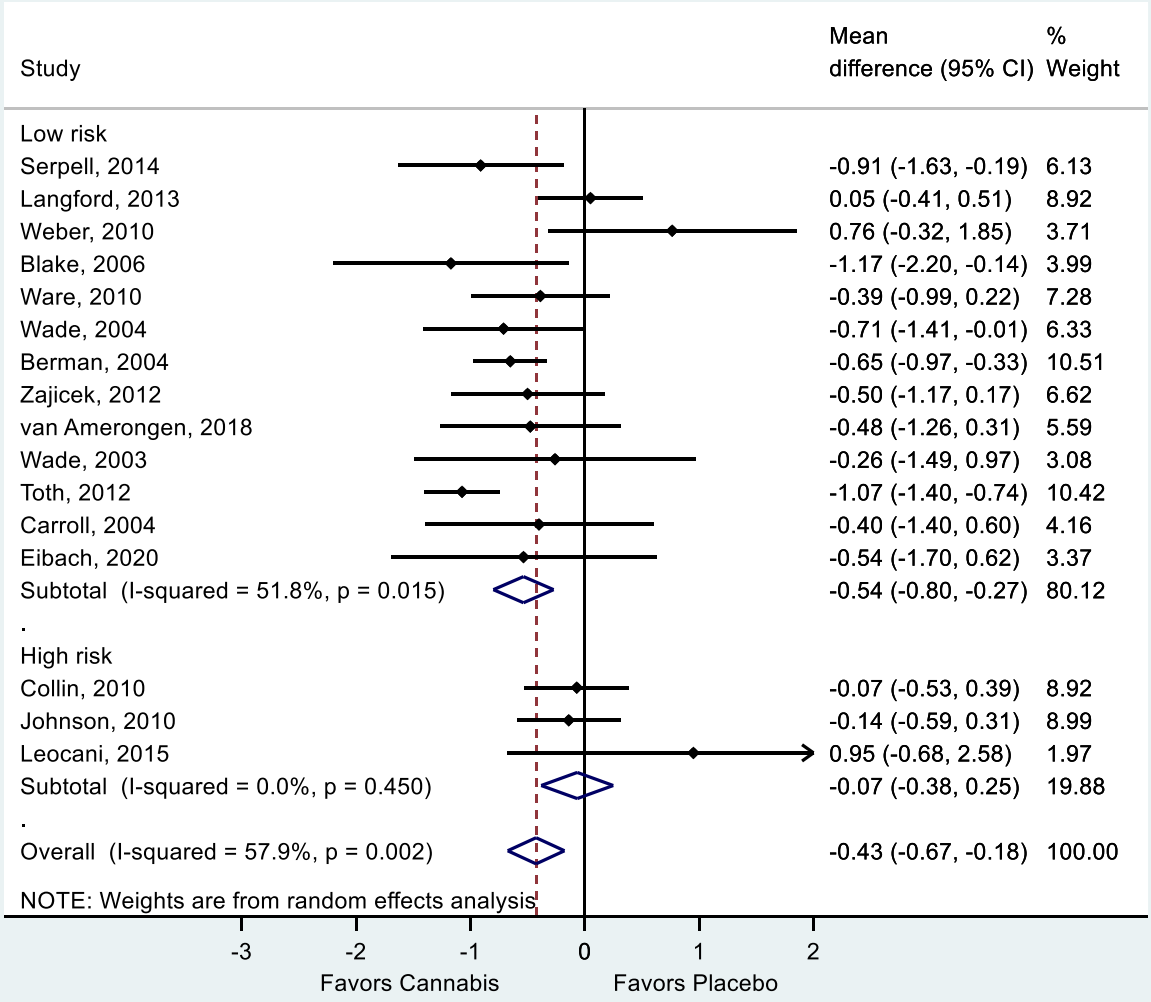
Appendix 2.B: Primary Outcomes

1. Sleep quality

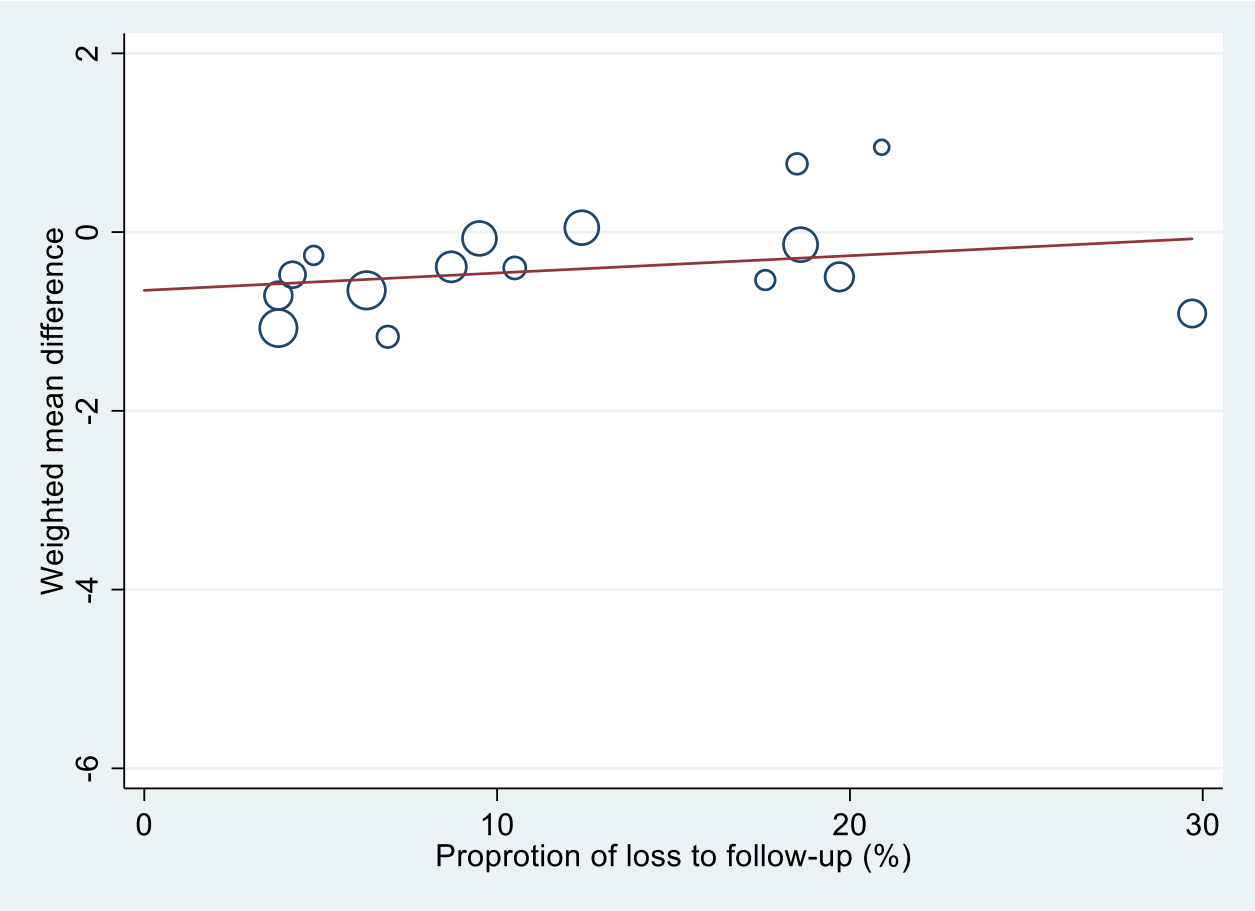
eFigure 1. Funnel plot of sleep quality (Egger's test p=0.22)



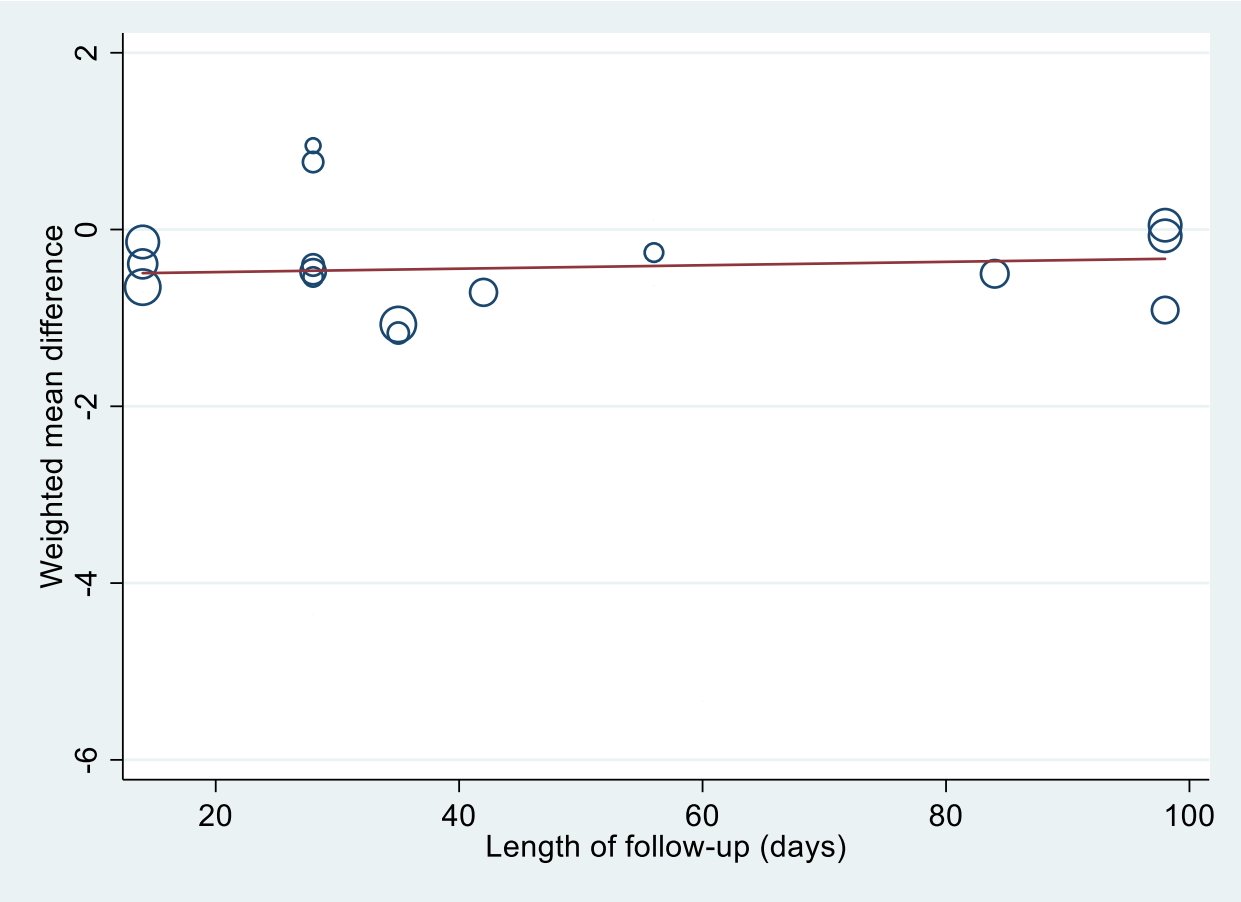
eFigure 1.0. Subgroup analysis of adequate vs. inadequate randomization (interaction p=0.08)



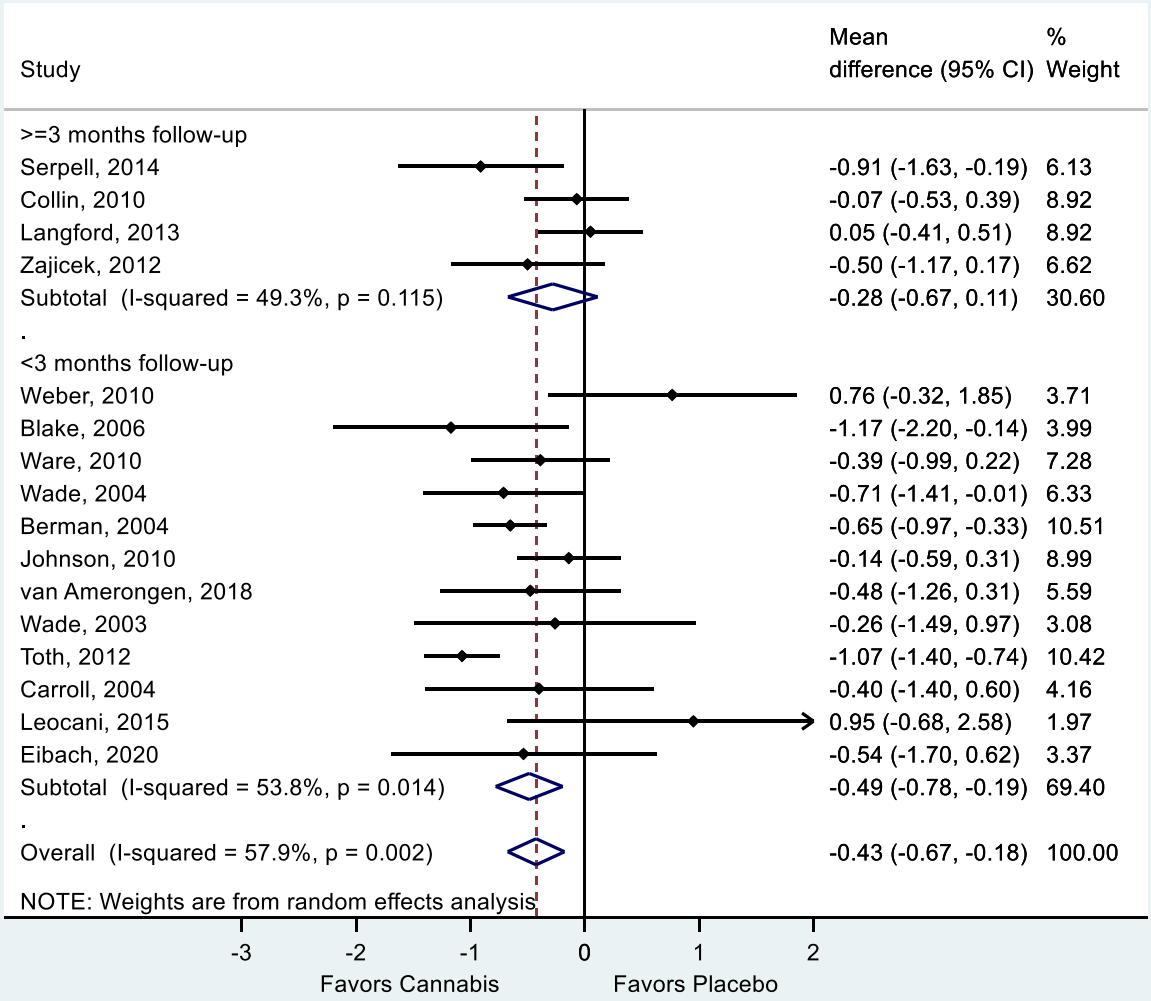
eFigure 1.1. Meta-regression of loss to follow-up and sleep quality (p=0.26)



eFigure 1.2. Meta-regression of length of follow-up and sleep quality (p=0.61)

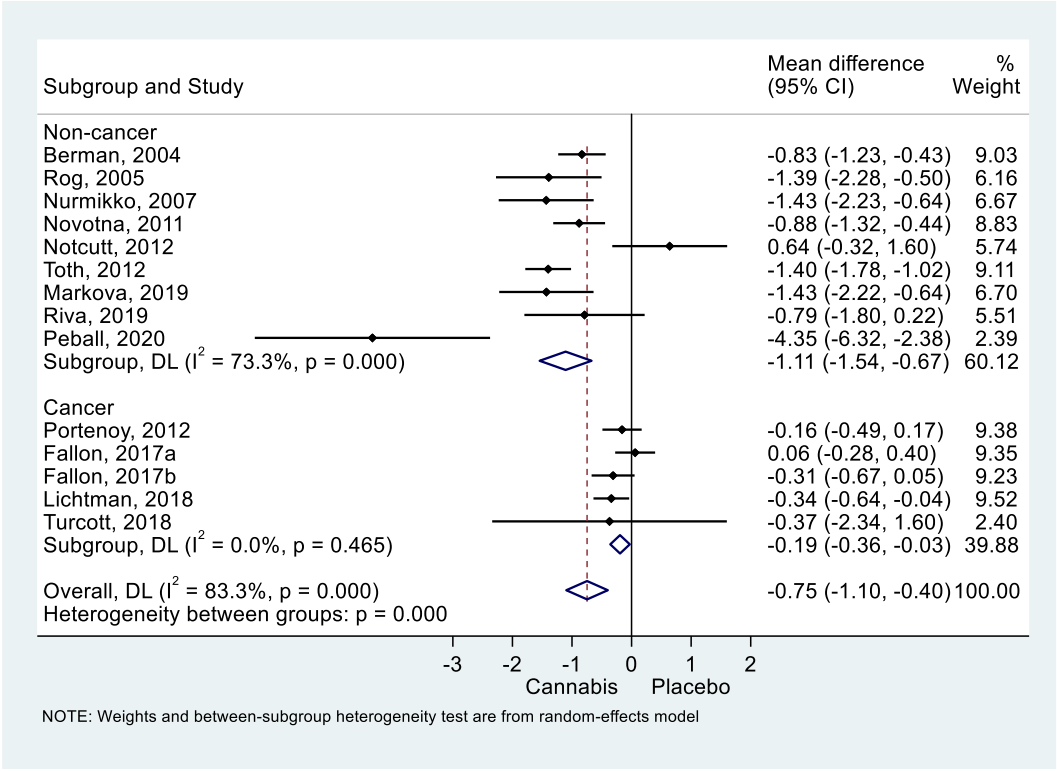


eFigure 1.3. Subgroup analysis of shorter vs longer follow-up (interaction p=0.45)



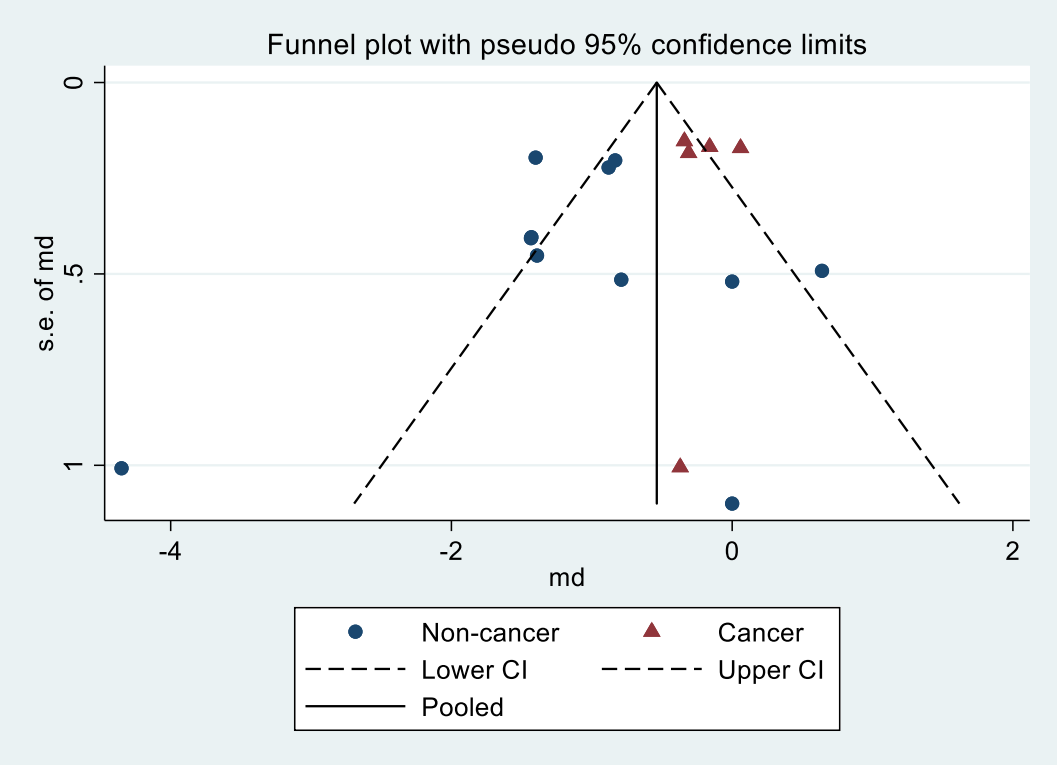
2. Sleep disturbance

eFigure 2. Sensitivity analysis excluding imputed data (interaction p<0.001)



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

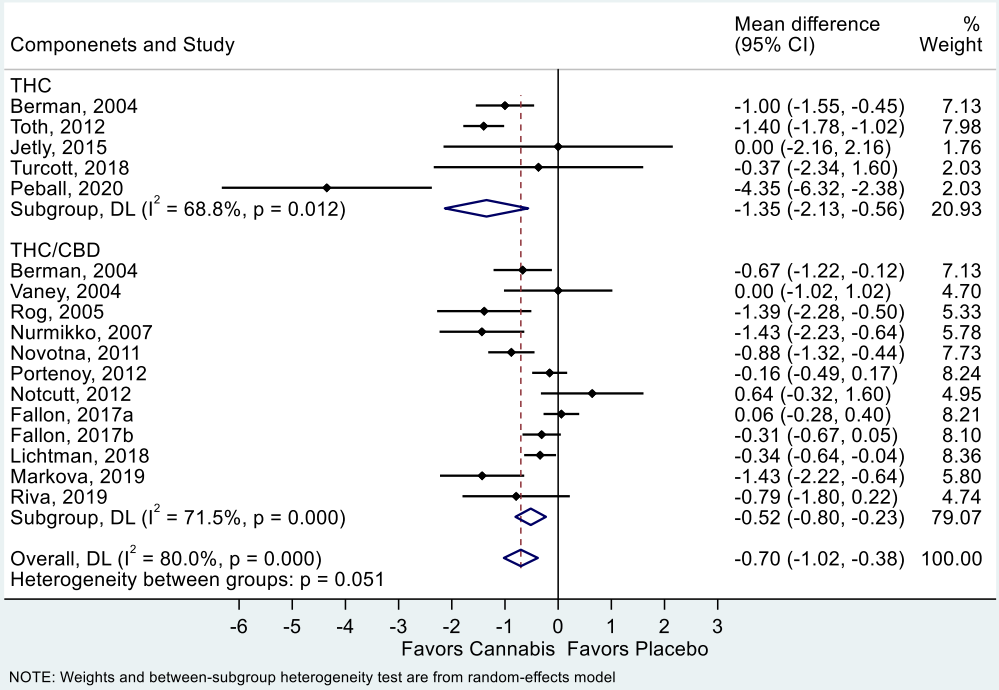
eFigure 2.0. Funnel plot for sleep disturbance



Overall Egger's test p = 0.23

p = 0.94 for non-cancer conditions among 11 studies

eFigure 2.1. Subgroup analysis for THC vs THC/CBD (interaction p=0.05)



eFigure 2.2. Subgroup analysis of adequate vs. inadequate randomization (interaction p=0.48)

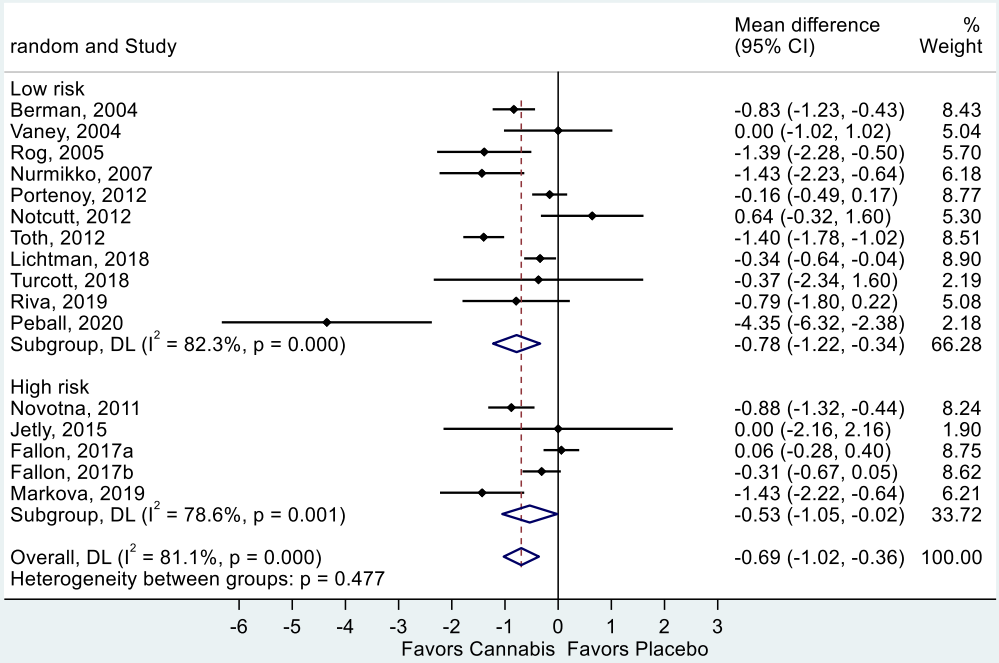


Figure 2.3. Subgroup analysis of adequate vs. inadequate allocation concealment (interaction p=0.14)

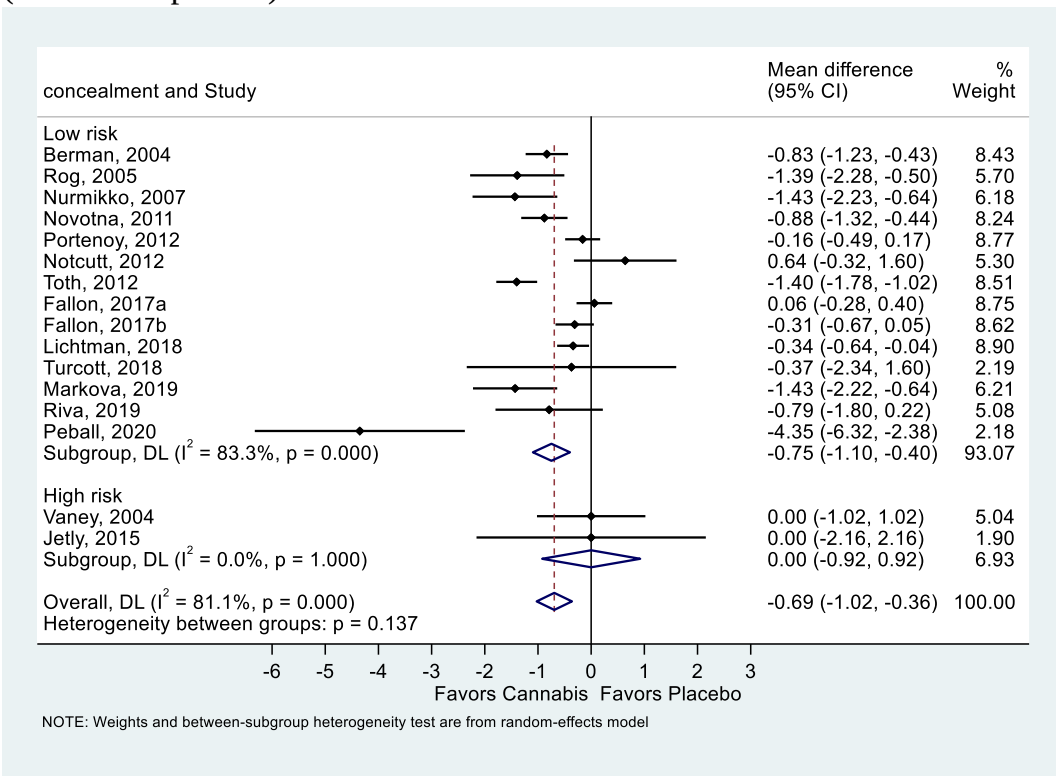


Figure 2.4. Meta-regression of loss to follow-up and sleep disturbance (p<0.001)

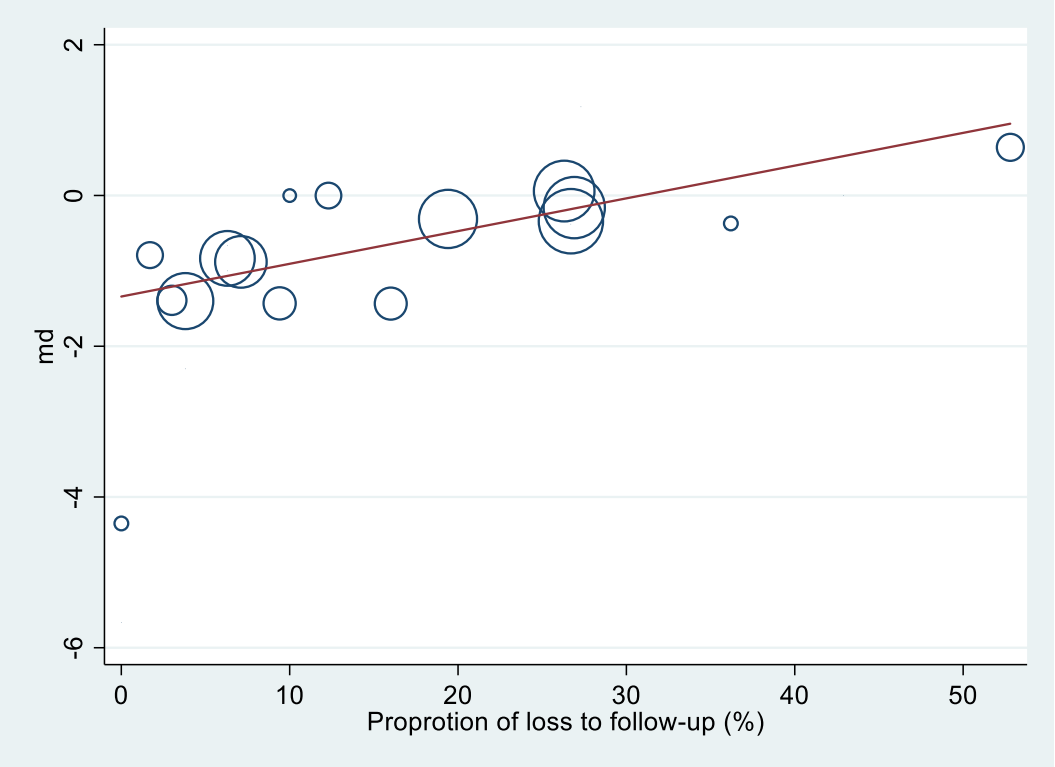


Figure 2.5. Subgroup analysis of lower vs. higher loss to follow-up (interaction p<0.001)

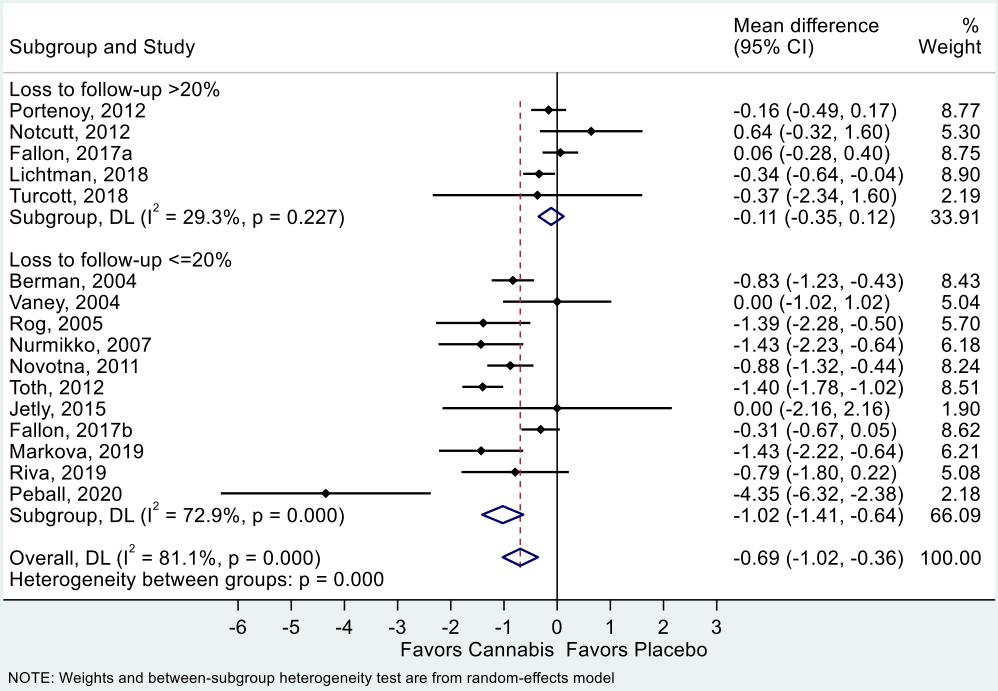


Figure 2.6. Meta-regression of length of follow-up and sleep disturbance (p=0.56)

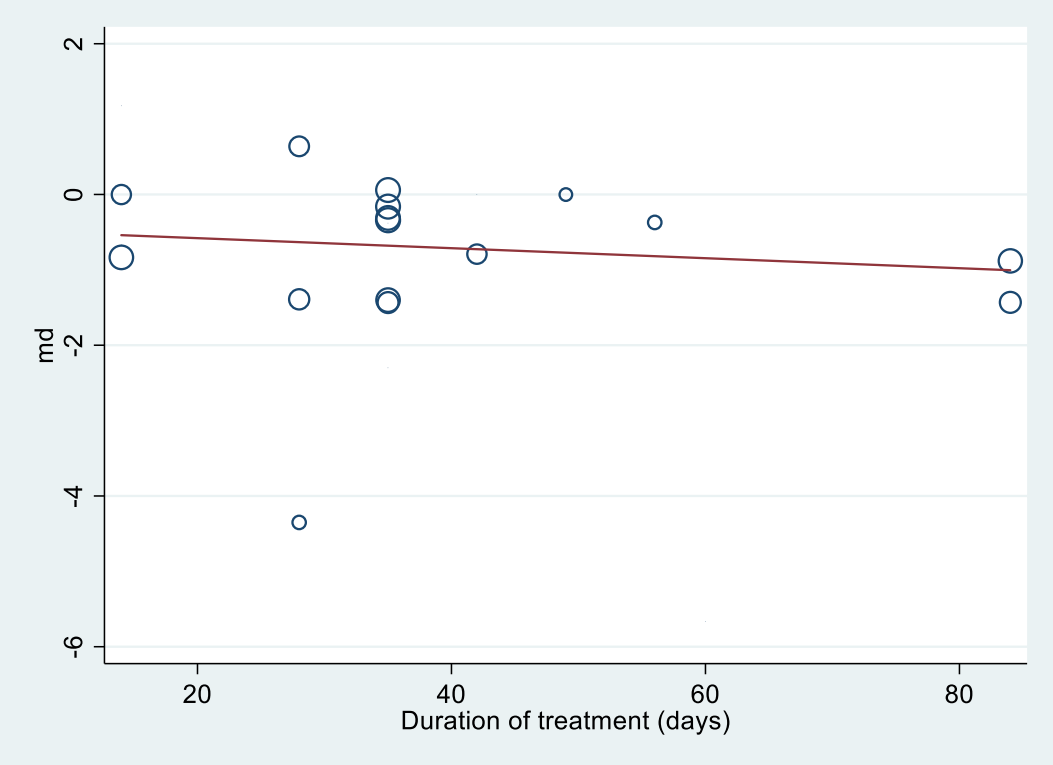
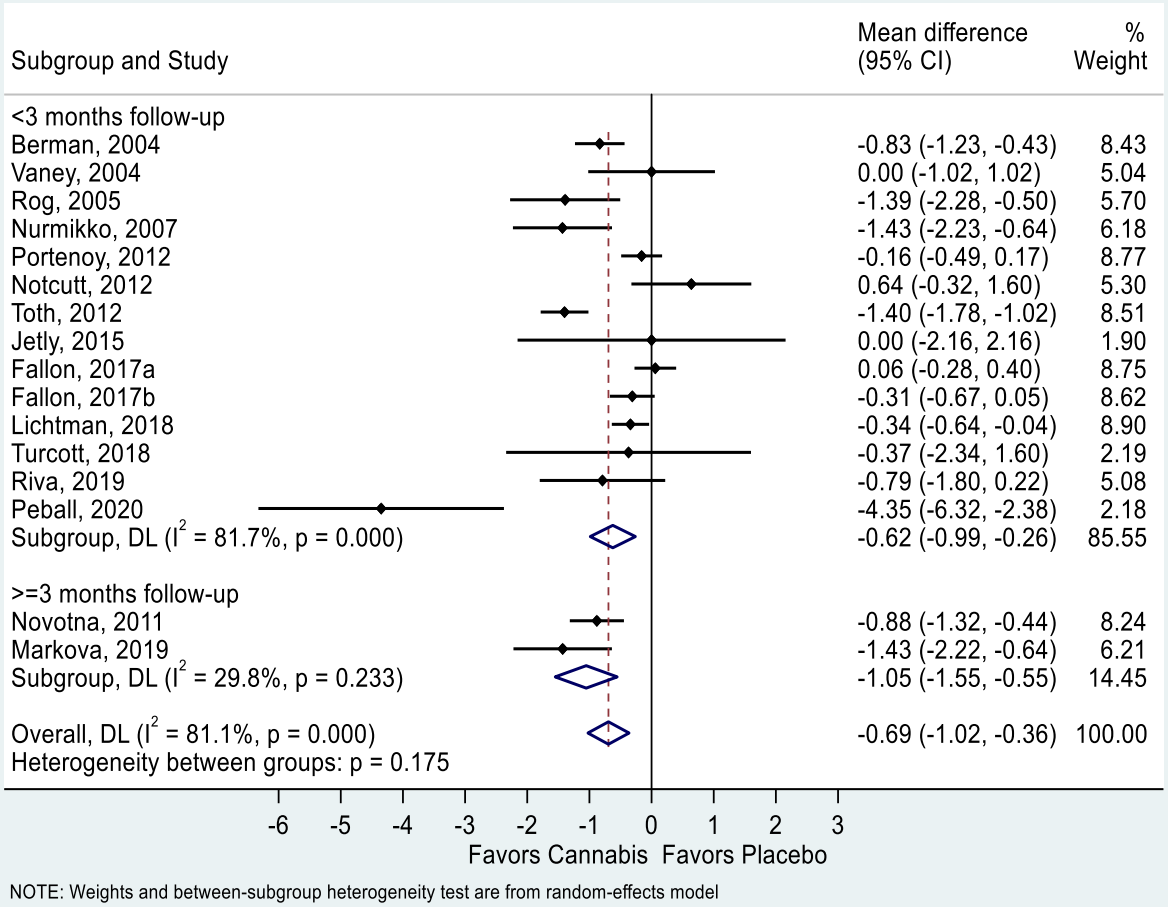


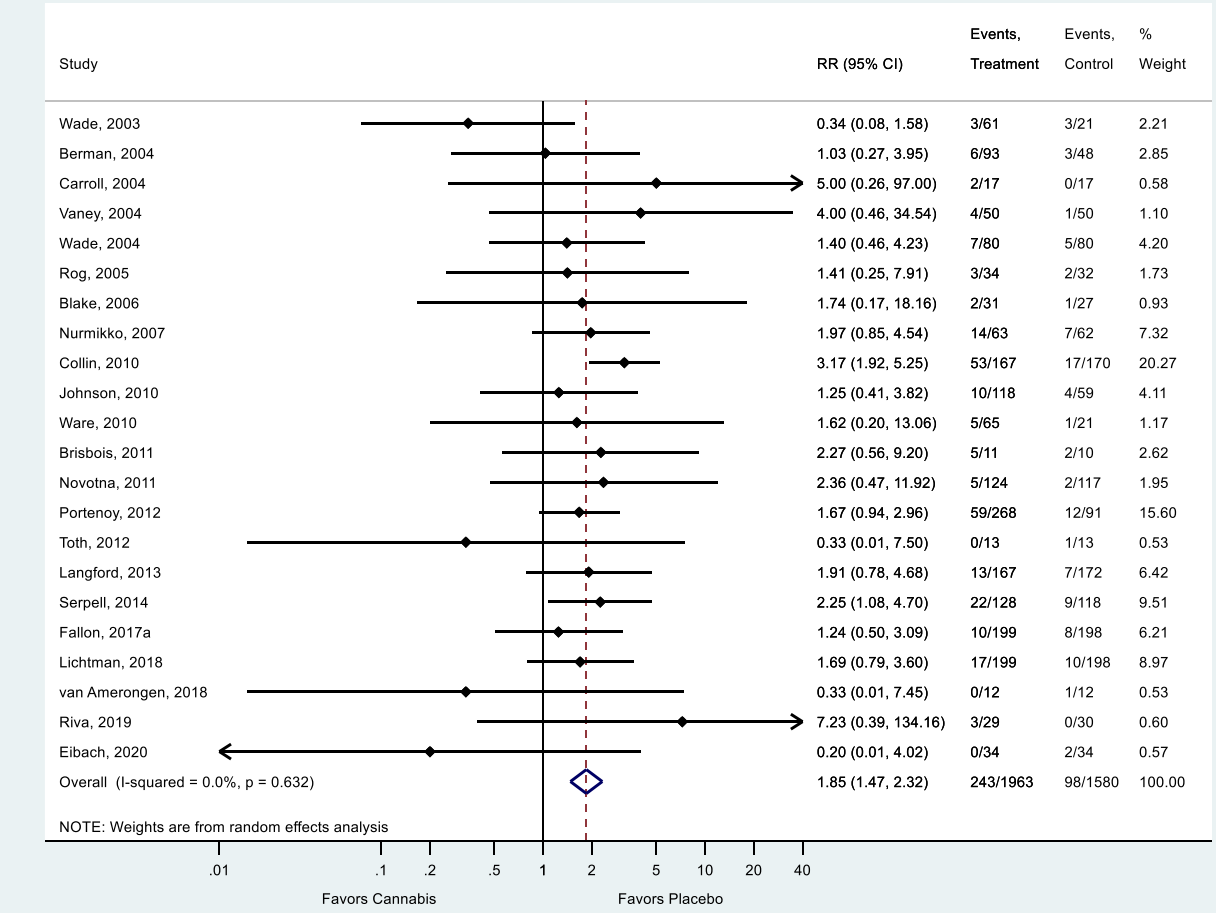
Figure 2.7. Subgroup analysis of shorter vs longer follow-up (interaction p=0.18)



Appendix 2.C. Adverse Events

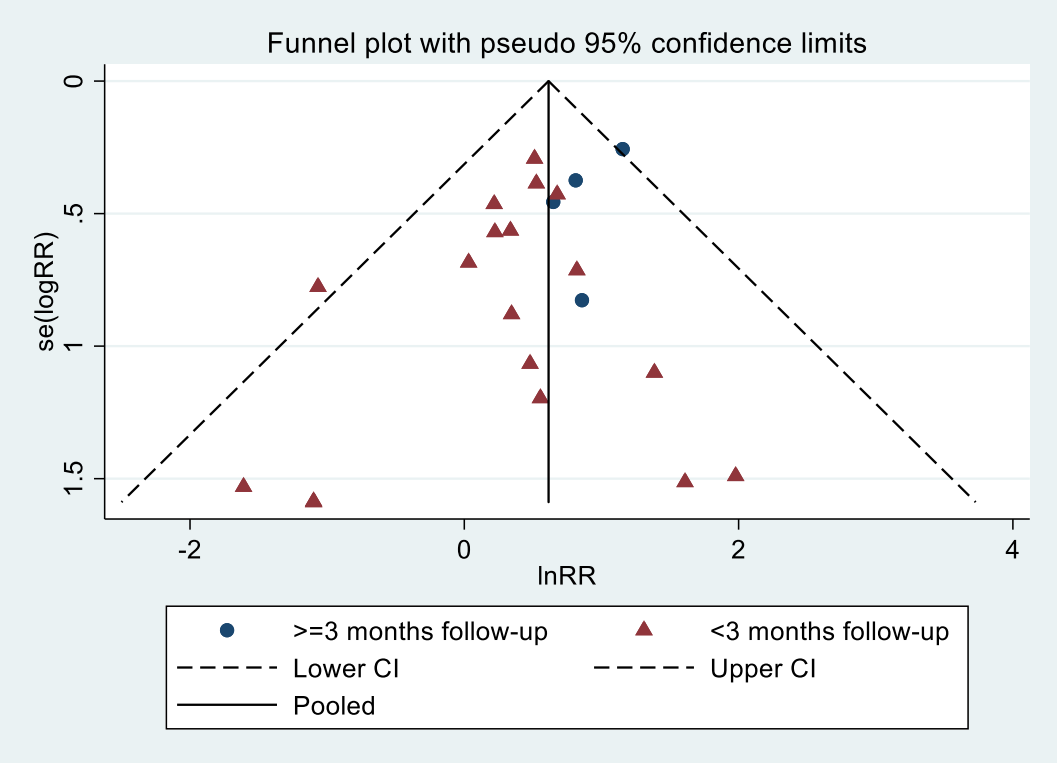
3.Nausea

eFigure 3. Forest plot for nausea for 22 randomized clinical trials of medical cannabis vs. placebo

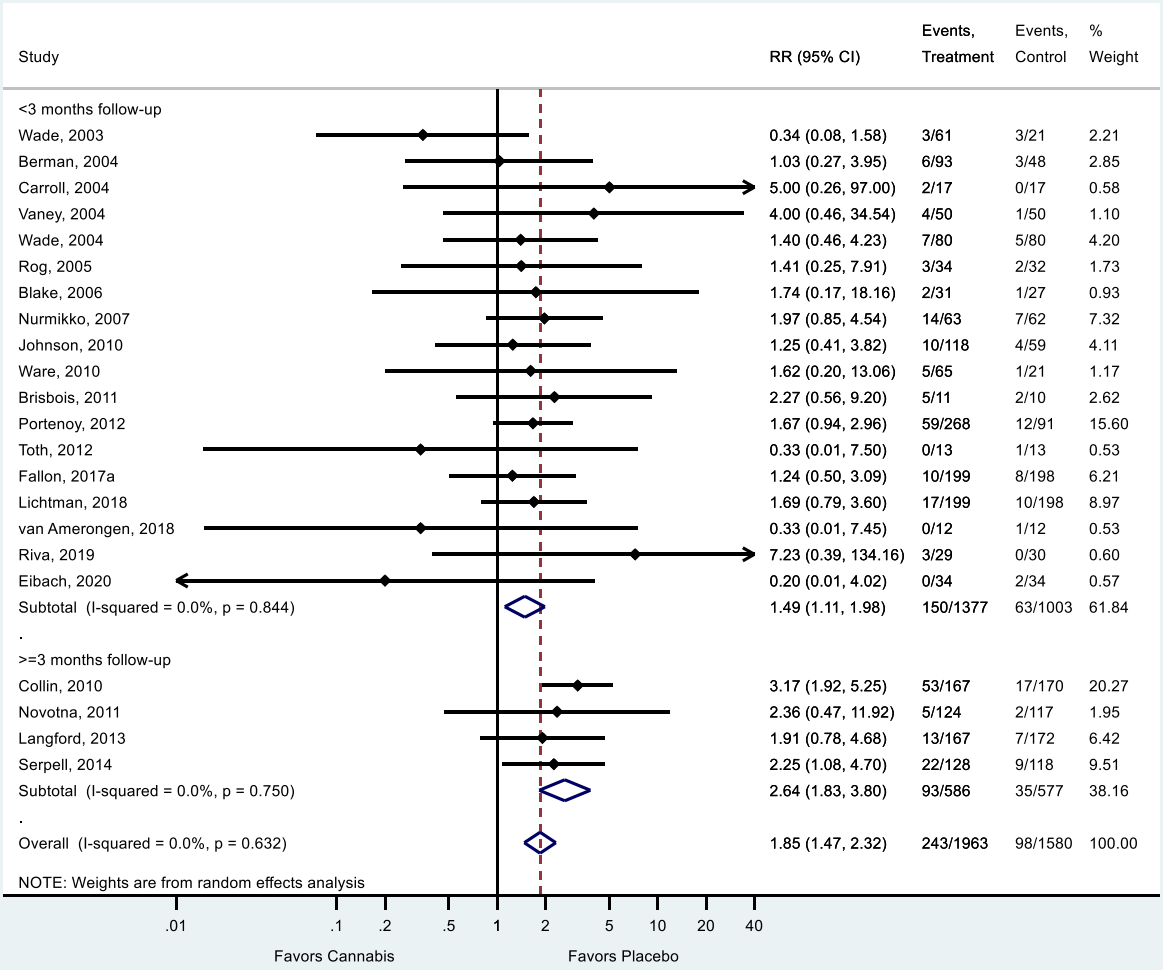


eFigure 3.0. Funnel plot of nausea

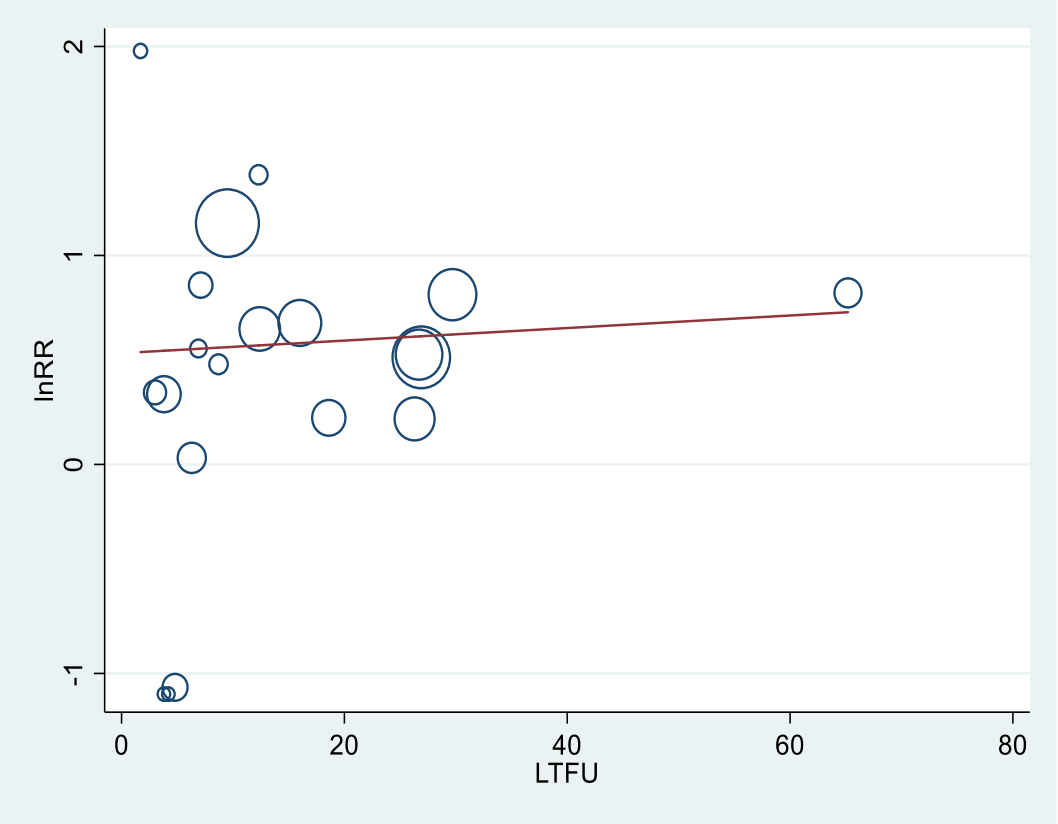
Harbord test p=0.28 for 18 studies with <3 months follow-up



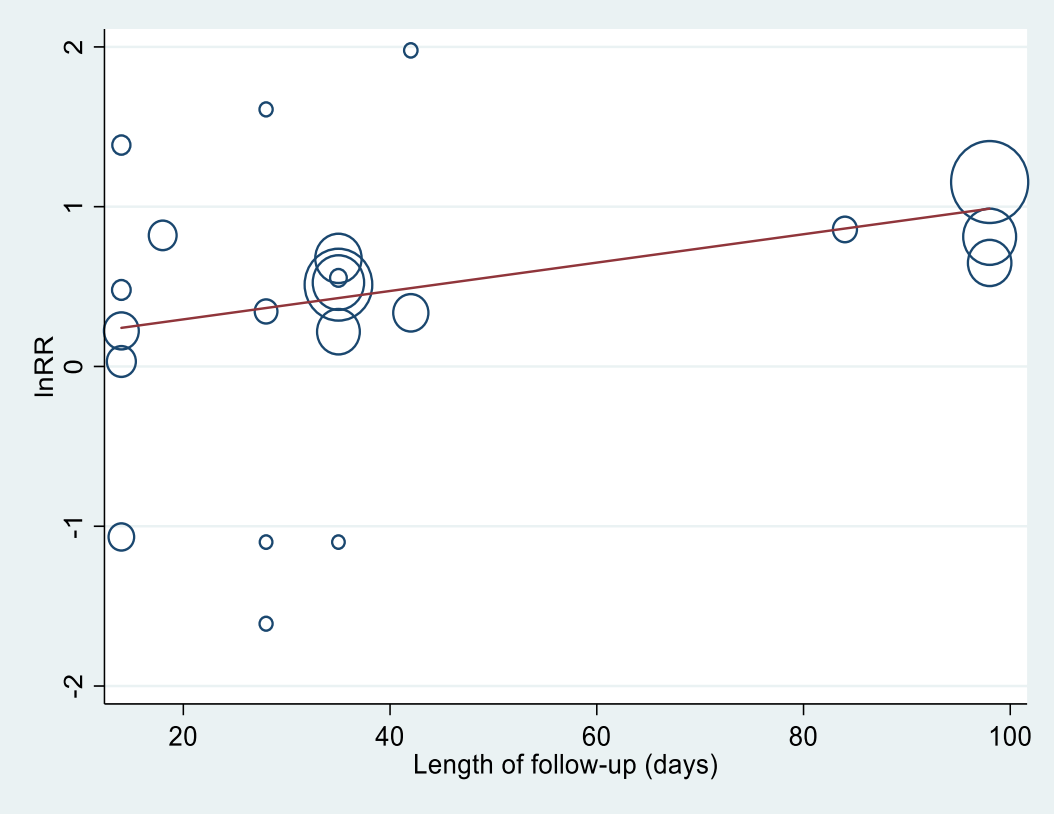
eFigure 3.1. subgroup analysis of nausea for short vs long follow-up (interaction p=0.03)



eFigure 3.2. Meta-regression of loss to follow-up associated with nausea (p=0.80)

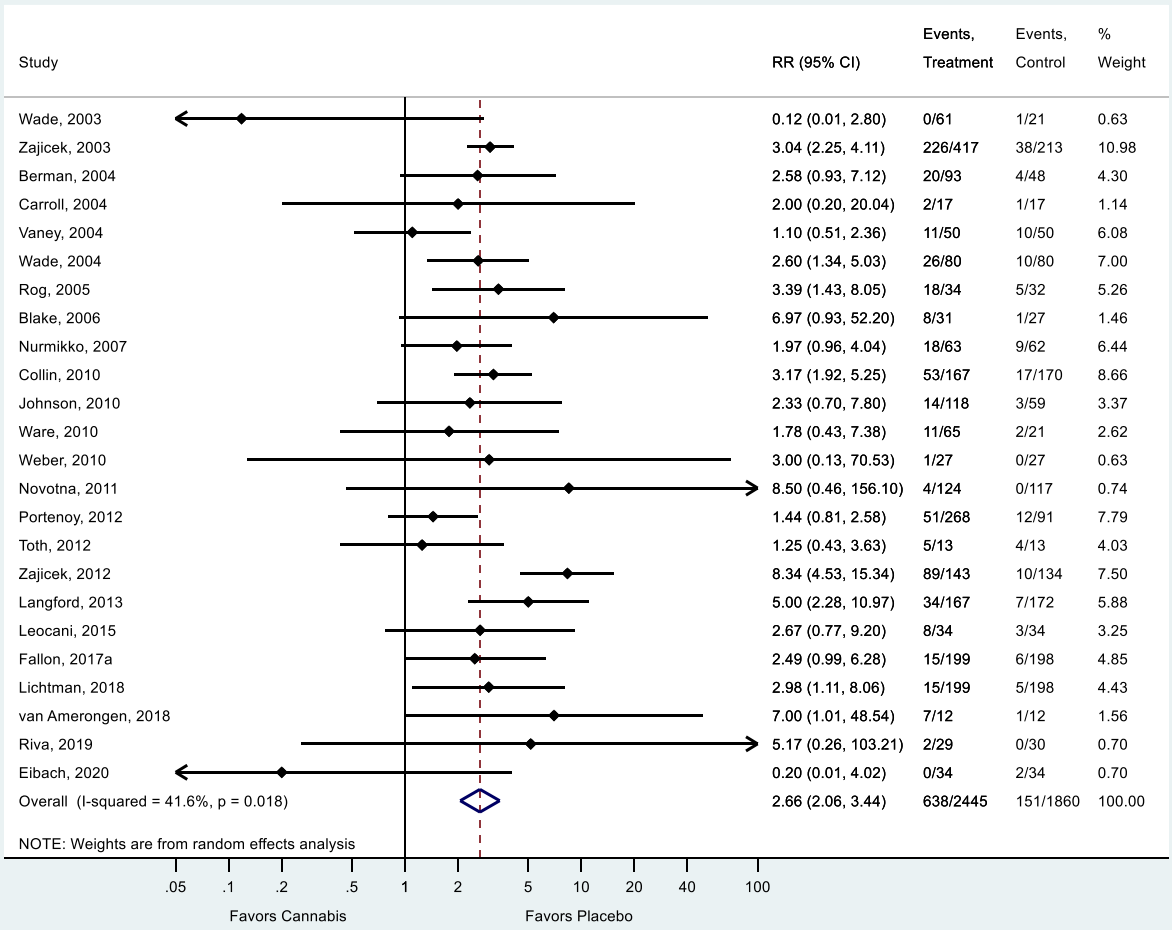


eFigure 3.3. Meta-regression of length of follow-up associated with nausea (p=0.02)



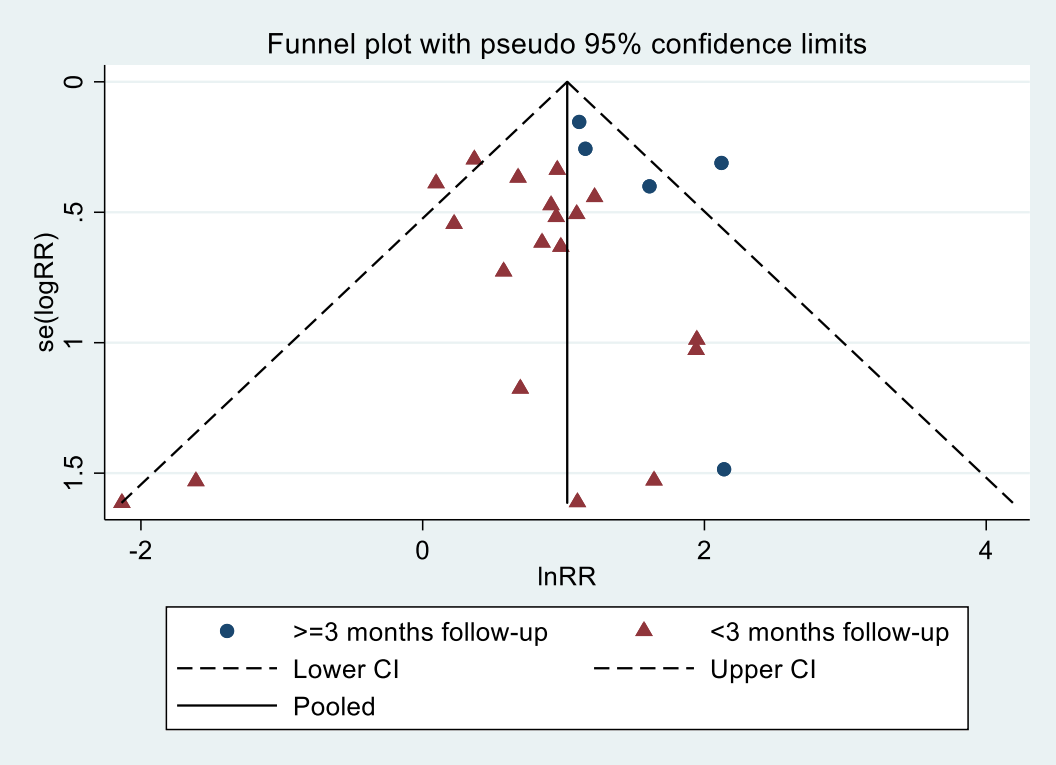
4.Dizziness

eFigure 4. Forest plot for dizziness for 24 randomized clinical trials of medical cannabis vs. placebo



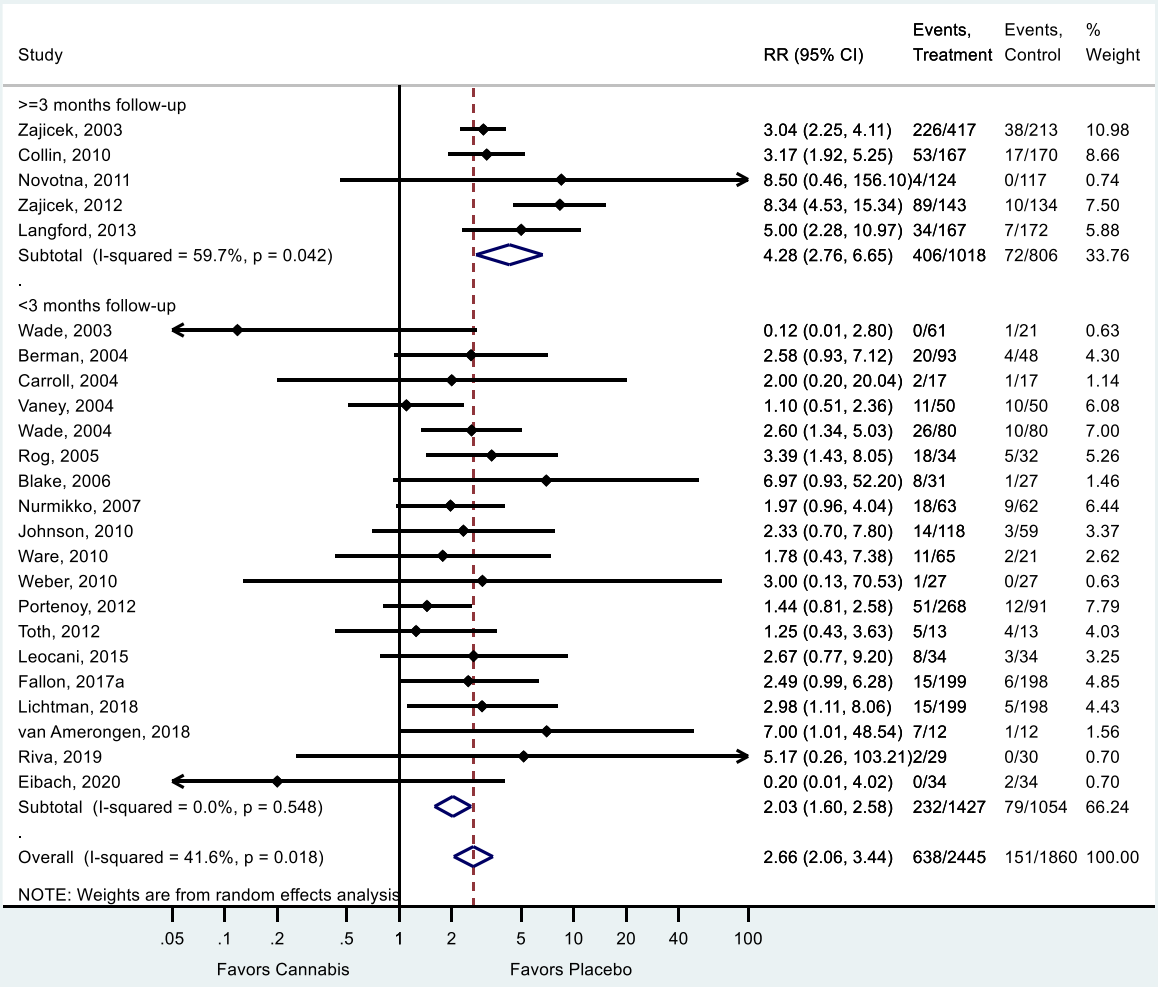
eFigure 4.0. funnel plot of dizziness

Harbord test p=0.72 for 19 studies with <3 months follow-up

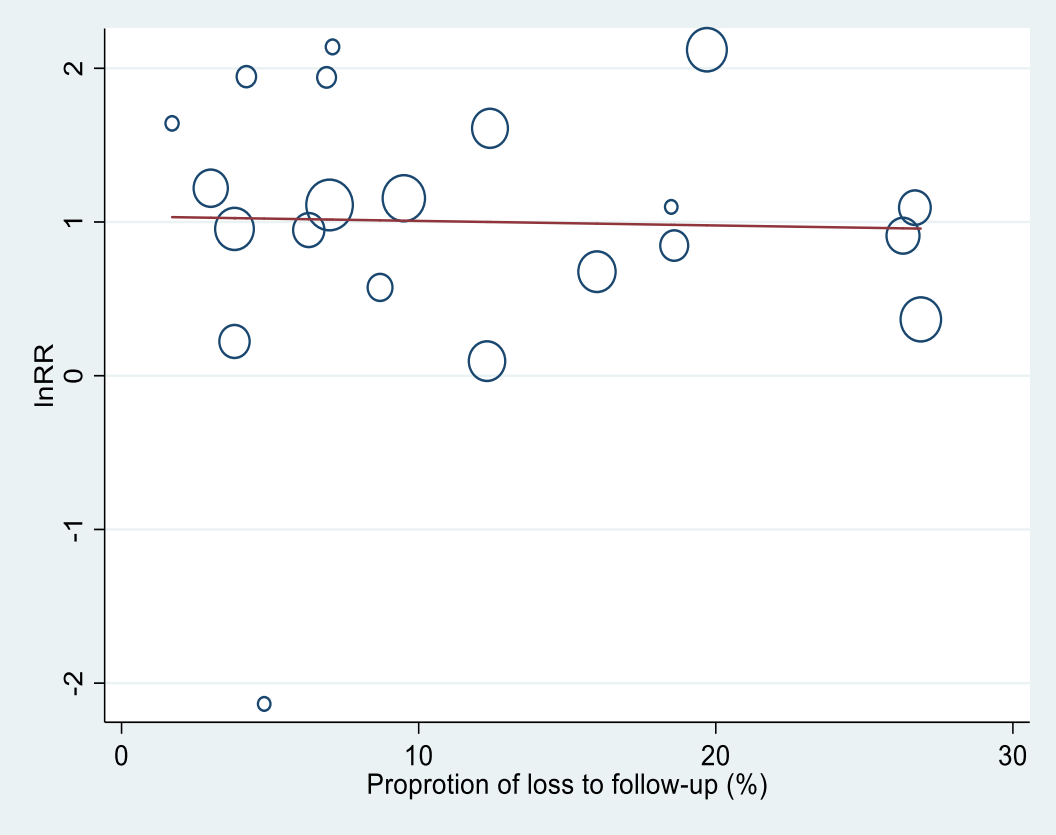


Harbord test p=0.05 for all 24 studies

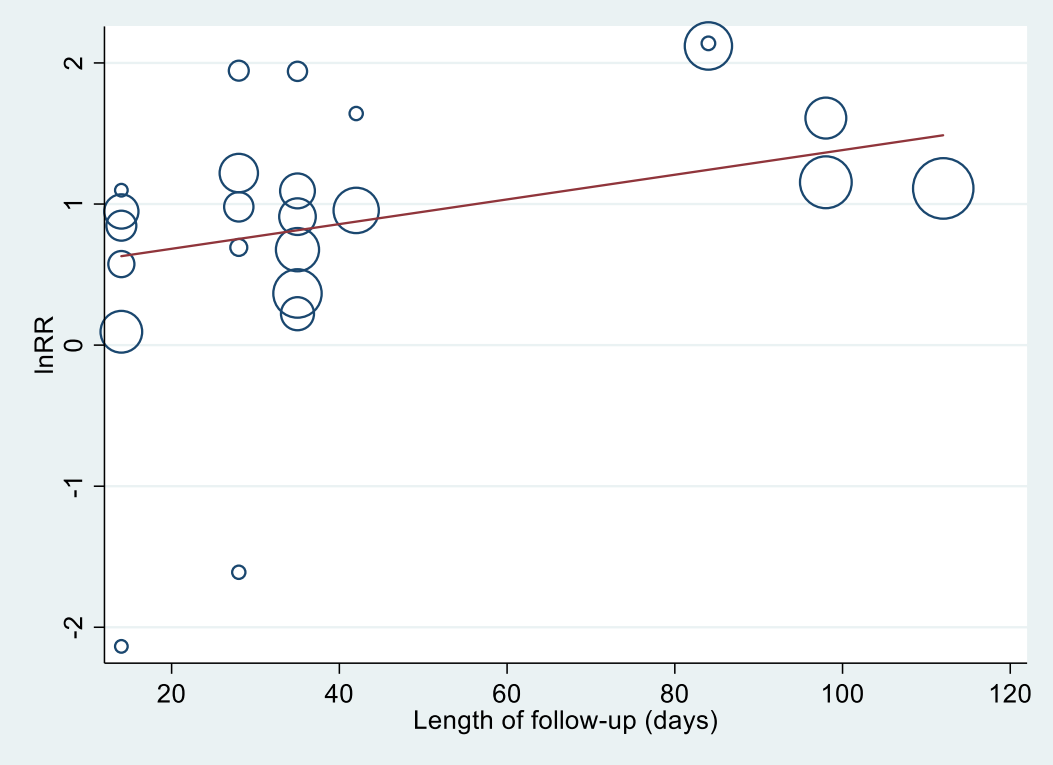
eFigure 4.1. subgroup analysis of shorter vs longer follow-up (interaction p=0.007)



eFigure 4.2. Meta-regression of loss to follow-up and dizziness (p=0.87)

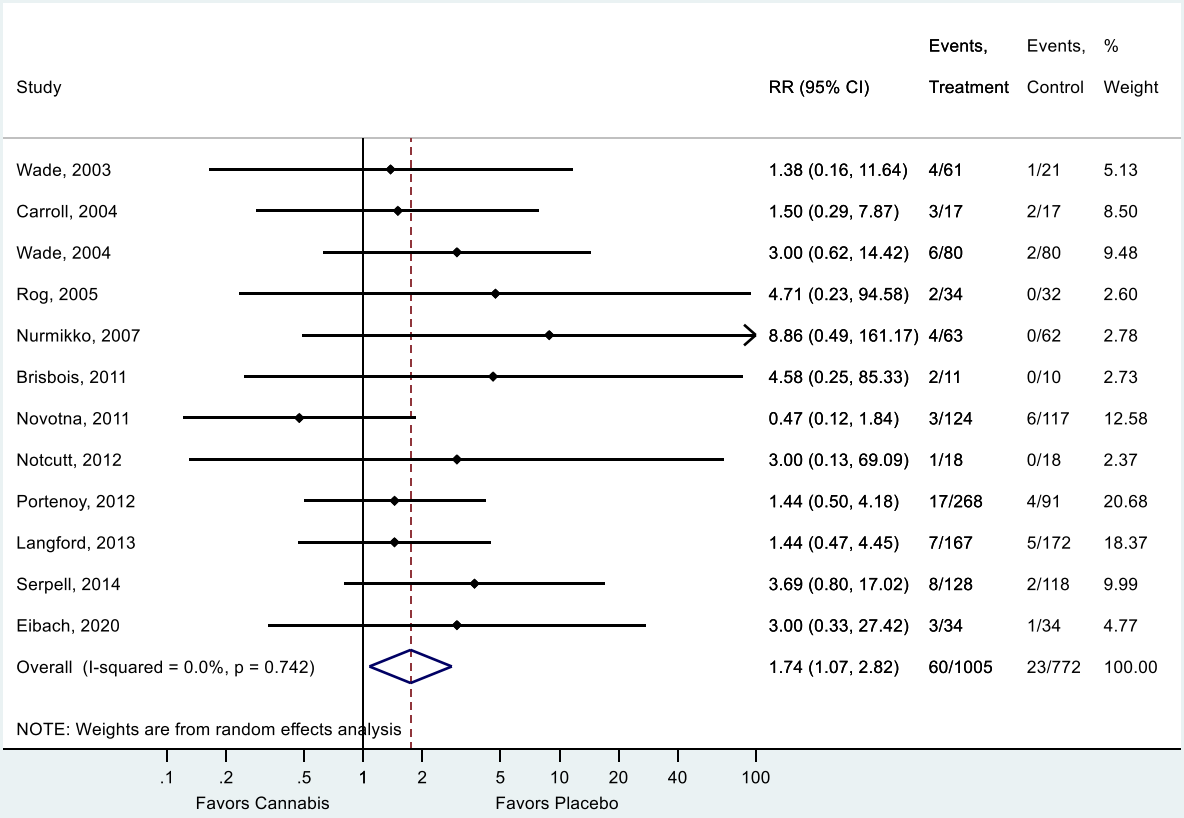


eFigure 4.3. Meta-regression of length of follow-up and dizziness (p=0.02)

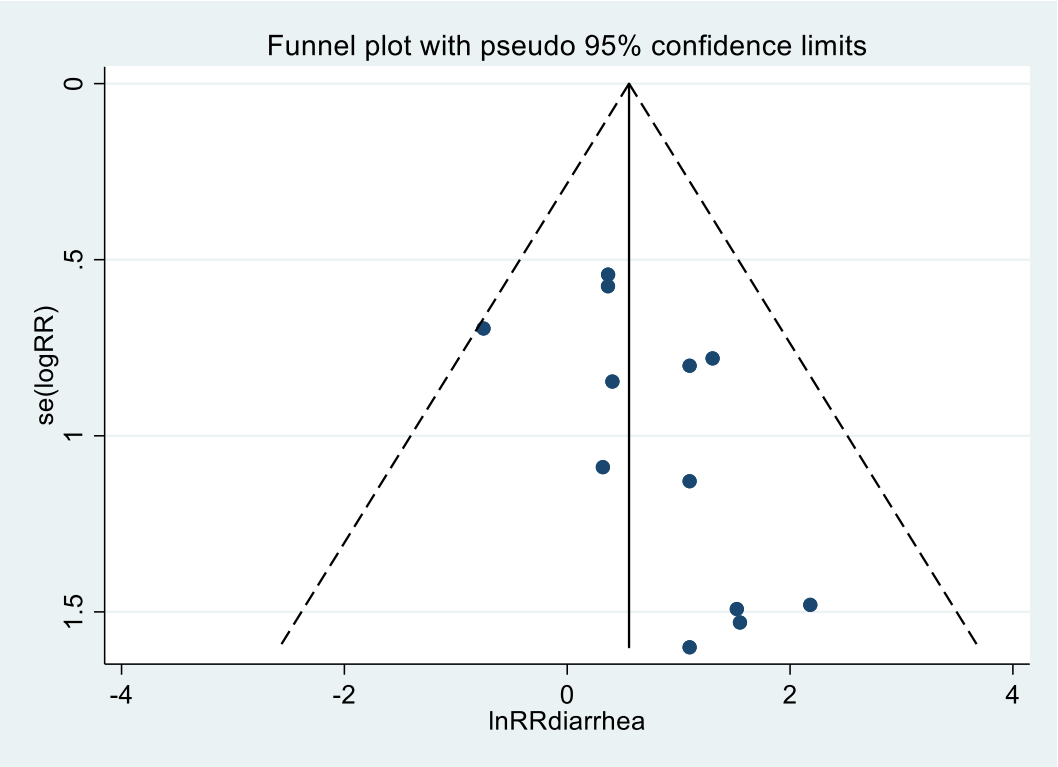


5.Diarrhea

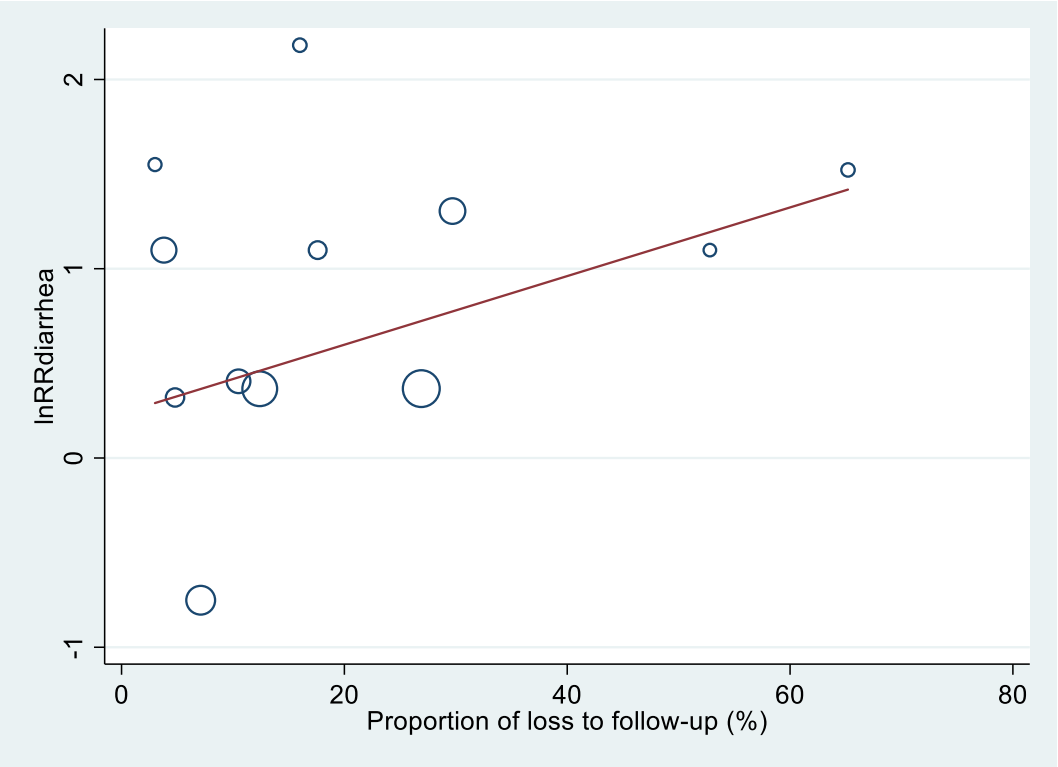
eFigure 5. Forest plot for diarrhea for 12 randomized clinical trials of medical cannabis vs. placebo



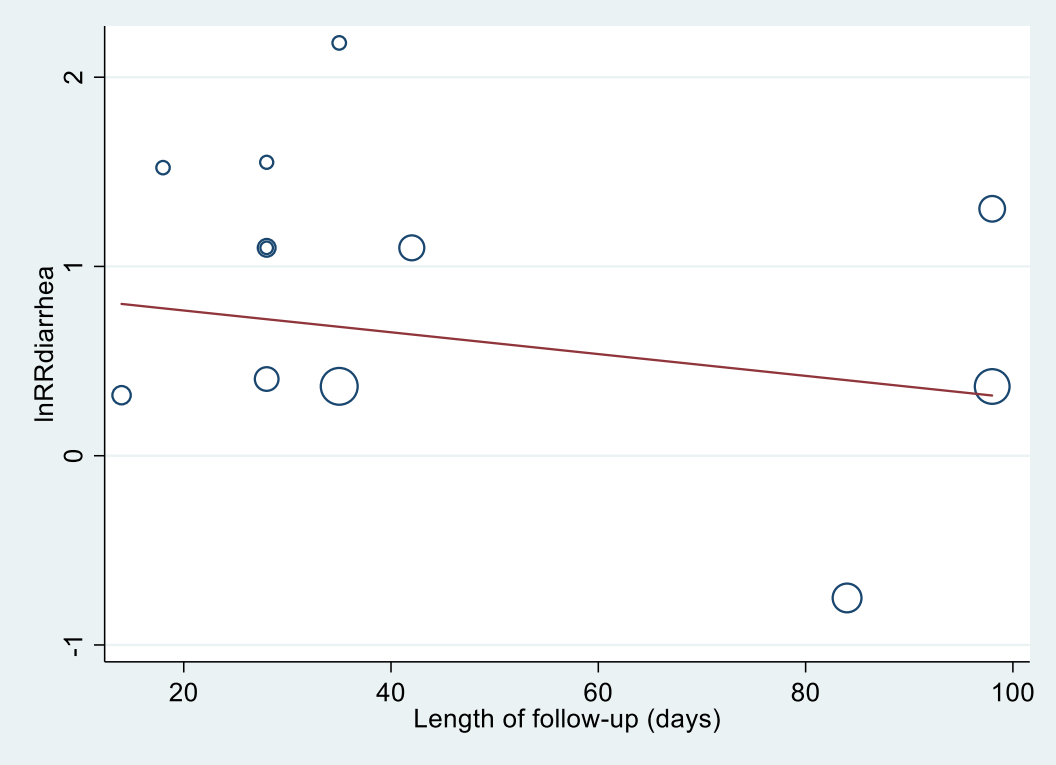
eFigure 5.0. funnel plot of diarrhea (Harbord test p=0.06)



eFigure 5.1. Meta-regression of loss to follow-up and diarrhea (p=0.35)

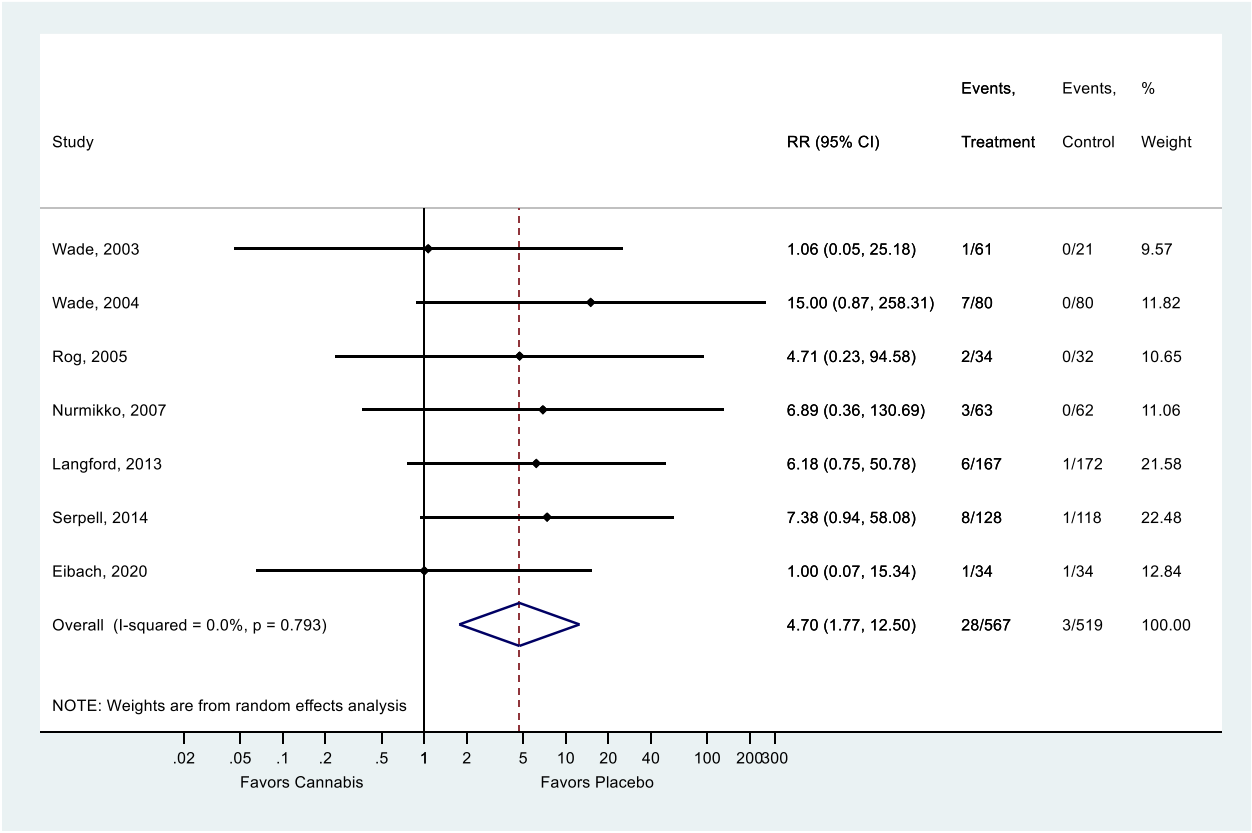


eFigure 5.2. Meta-regression of length of follow-up and diarrhea (p=0.48)

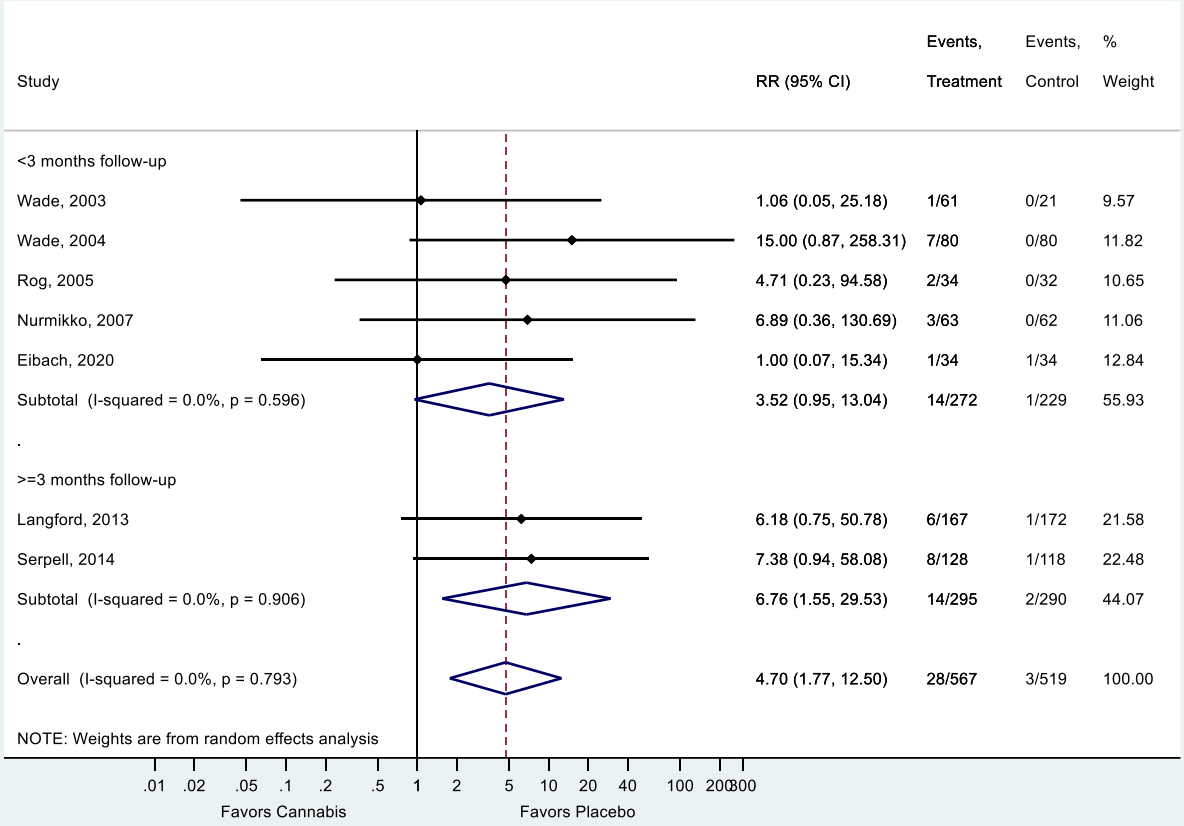


6.Disturbance in attention

eFigure 6. Forest plot for disturbance in attention for 7 randomized clinical trials of medical cannabis vs. placebo

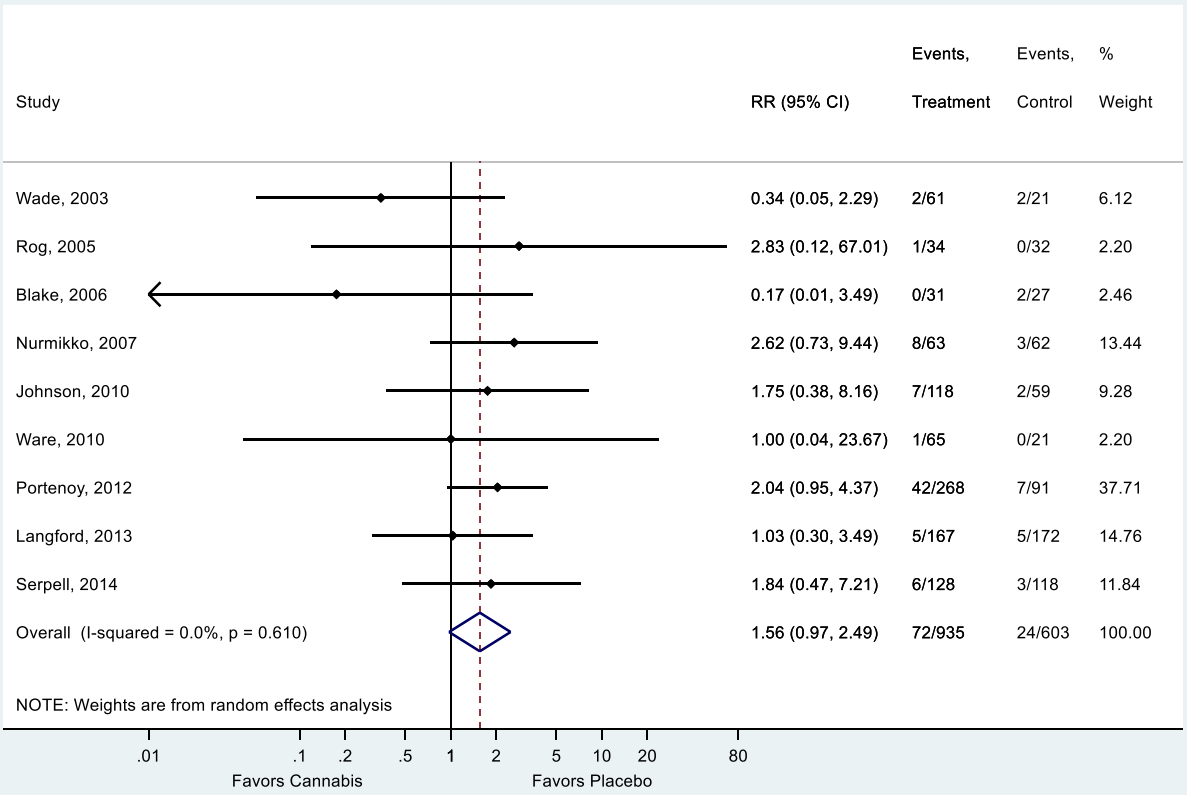


eFigure 6.0. subgroup analysis of Disturbance in attention for short vs long follow-up (interaction p=0.55)

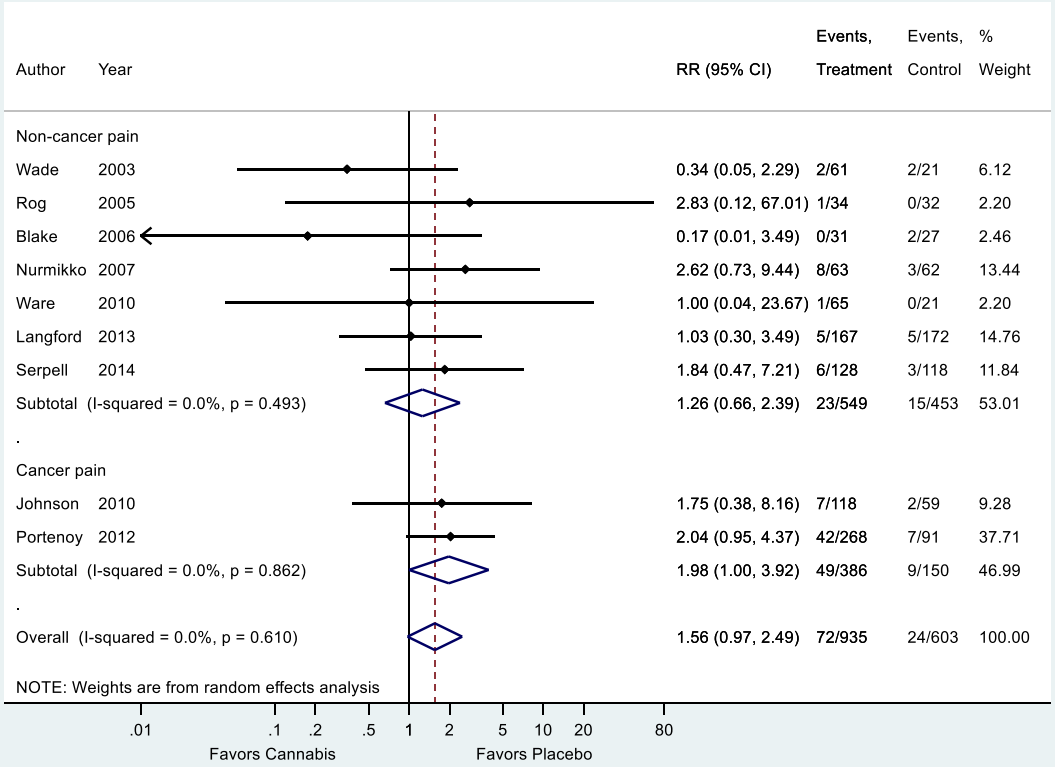


7.Vomiting

eFigure 7. Forest plot for vomiting for 9 randomized clinical trials of medical cannabis vs. placebo

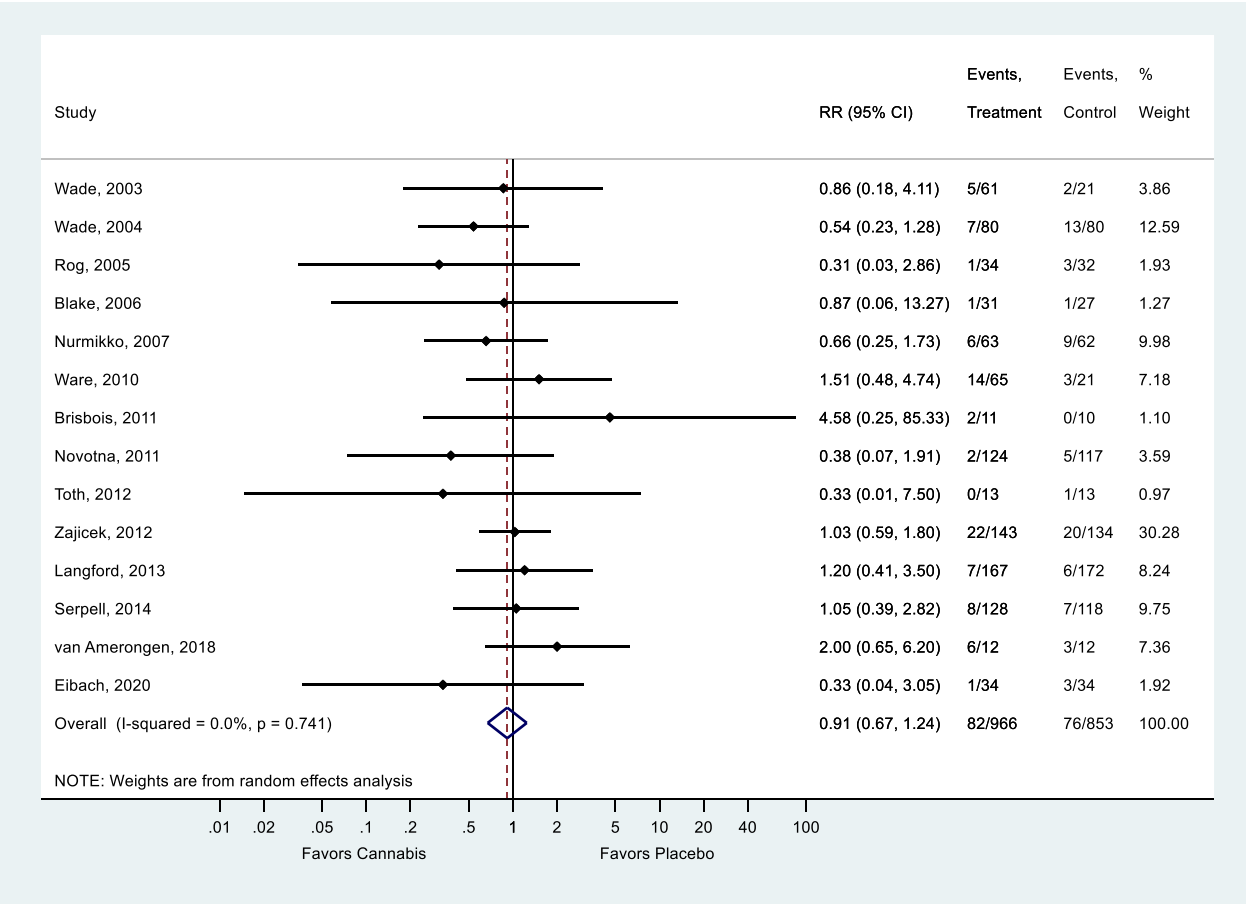


eFigure 7.0. subgroup analysis of vomiting for cancer vs non-cancer (interaction p=0.38)

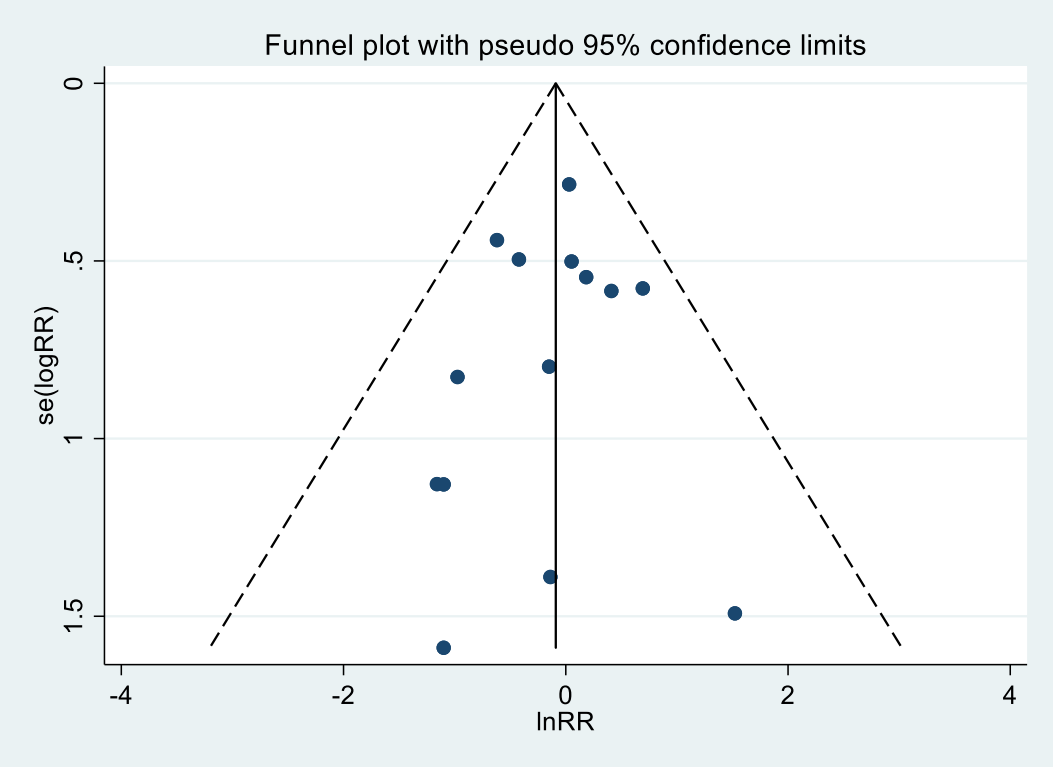


8.Headache

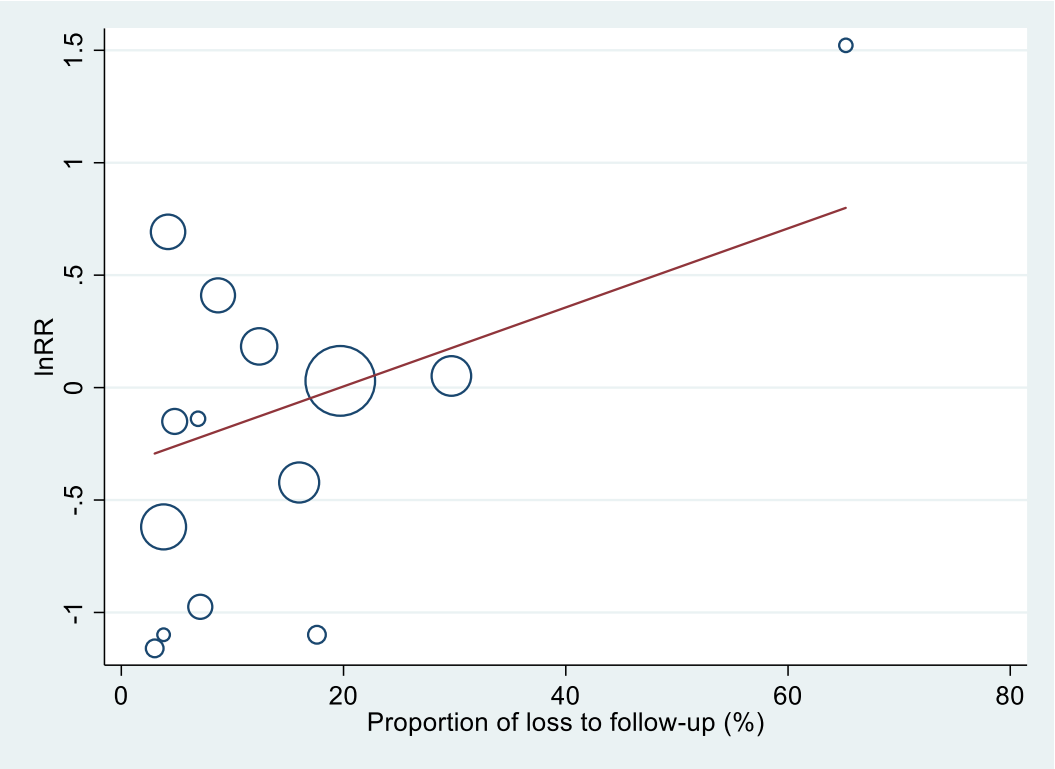
eFigure 8. Forest plot for headache for 14 randomized clinical trials of medical cannabis vs. placebo



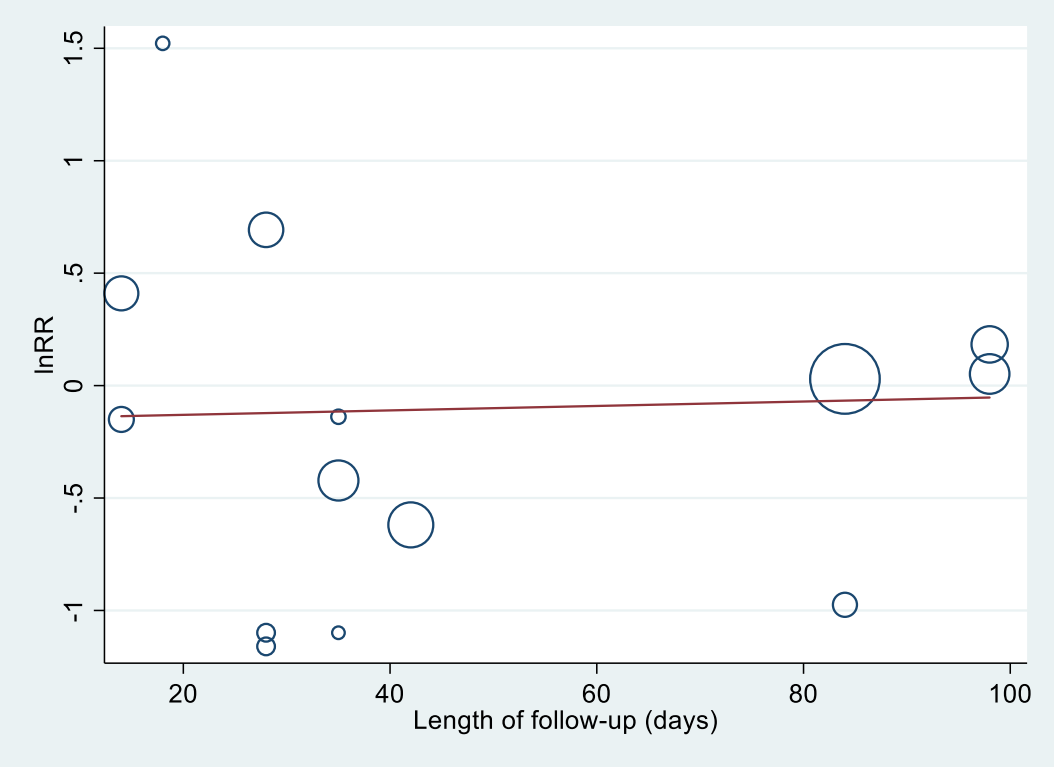
eFigure 8.0. funnel plot of headache (Harbord test p=0.75)



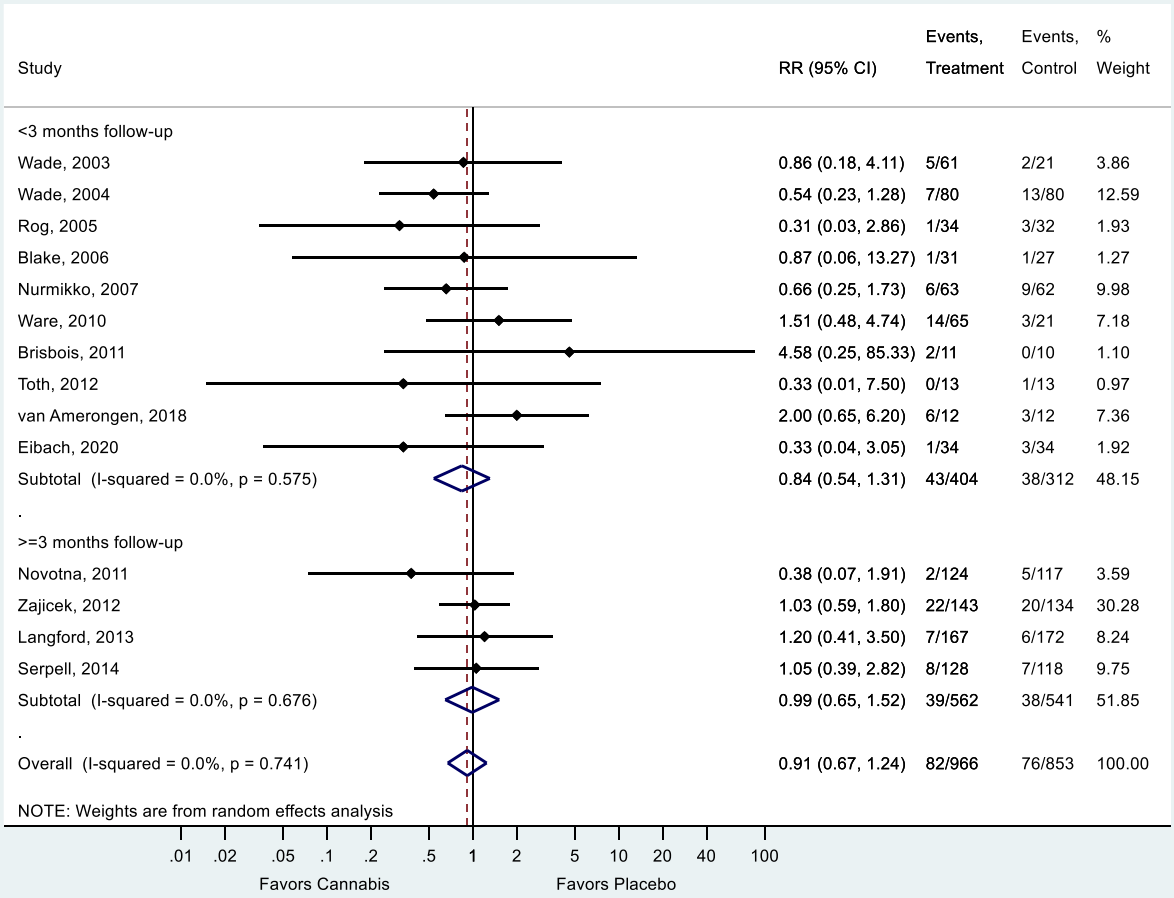
eFigure 8.1. Meta-regression of loss to follow-up and headache (p=0.30)



eFigure 8.2. Meta-regression of length of follow-up and headache (p=0.85)

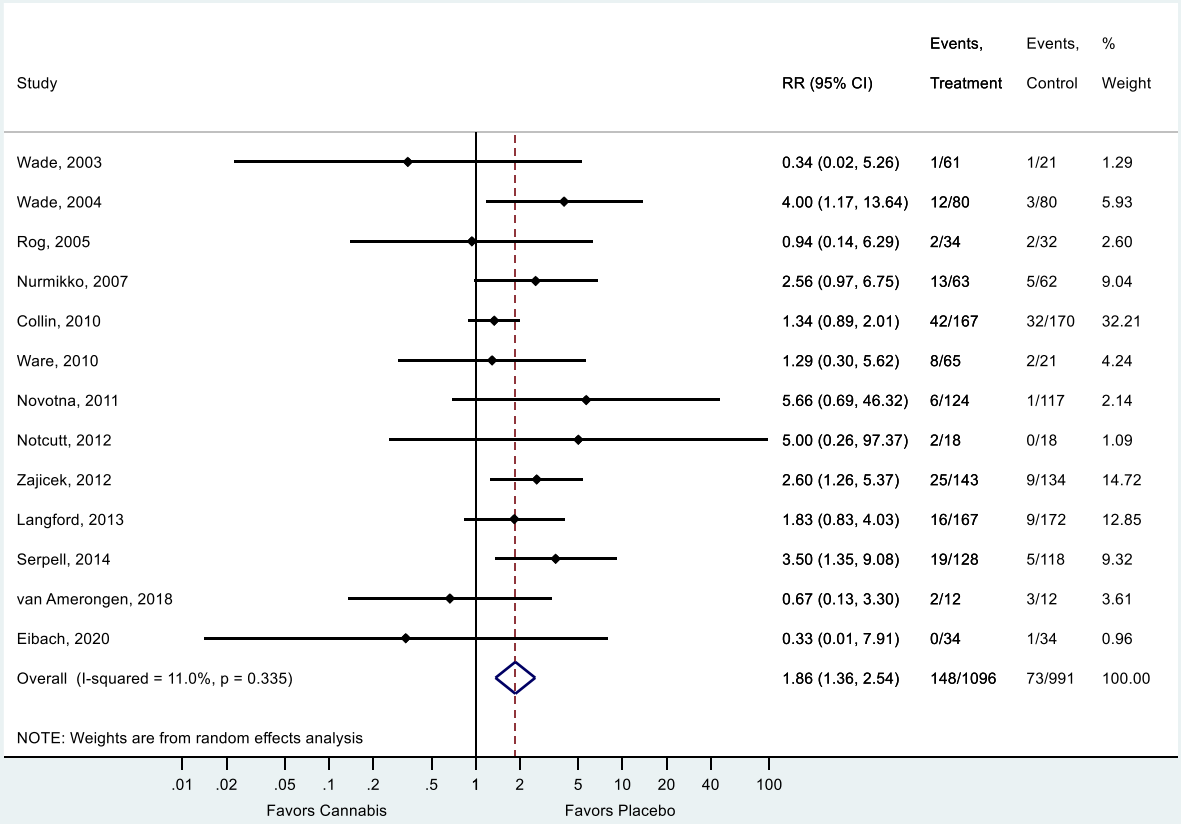


eFigure 8.3 subgroup analysis of headache for short vs long follow-up (interaction p=0.007)

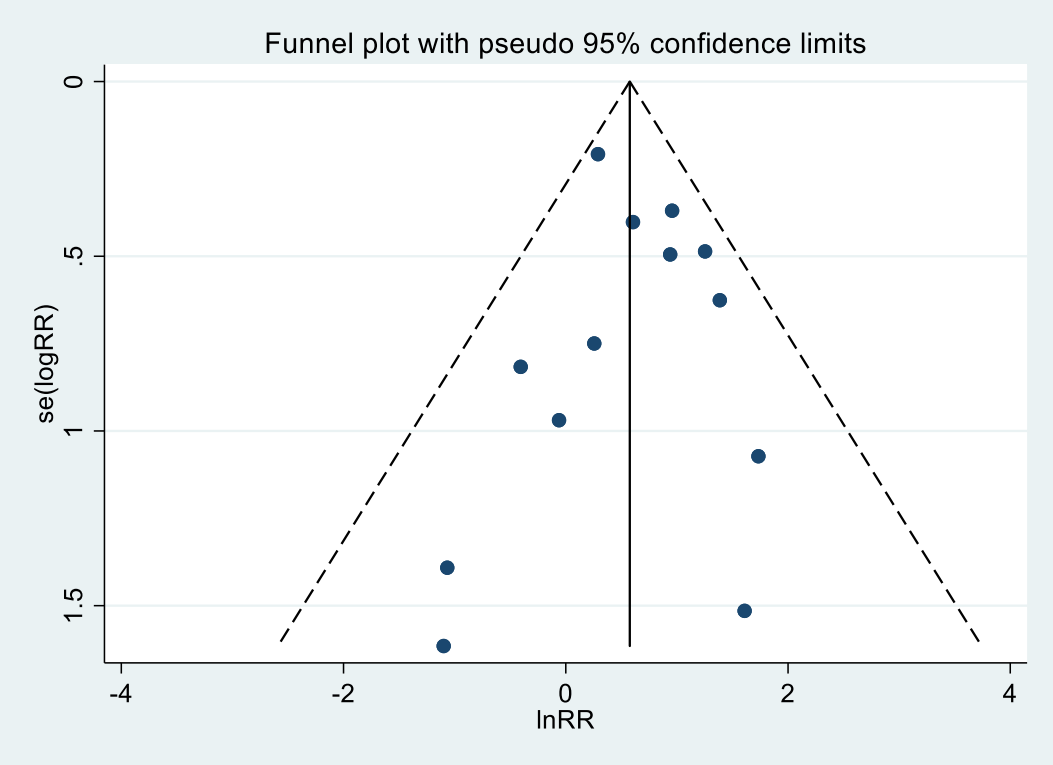


9.Fatigue

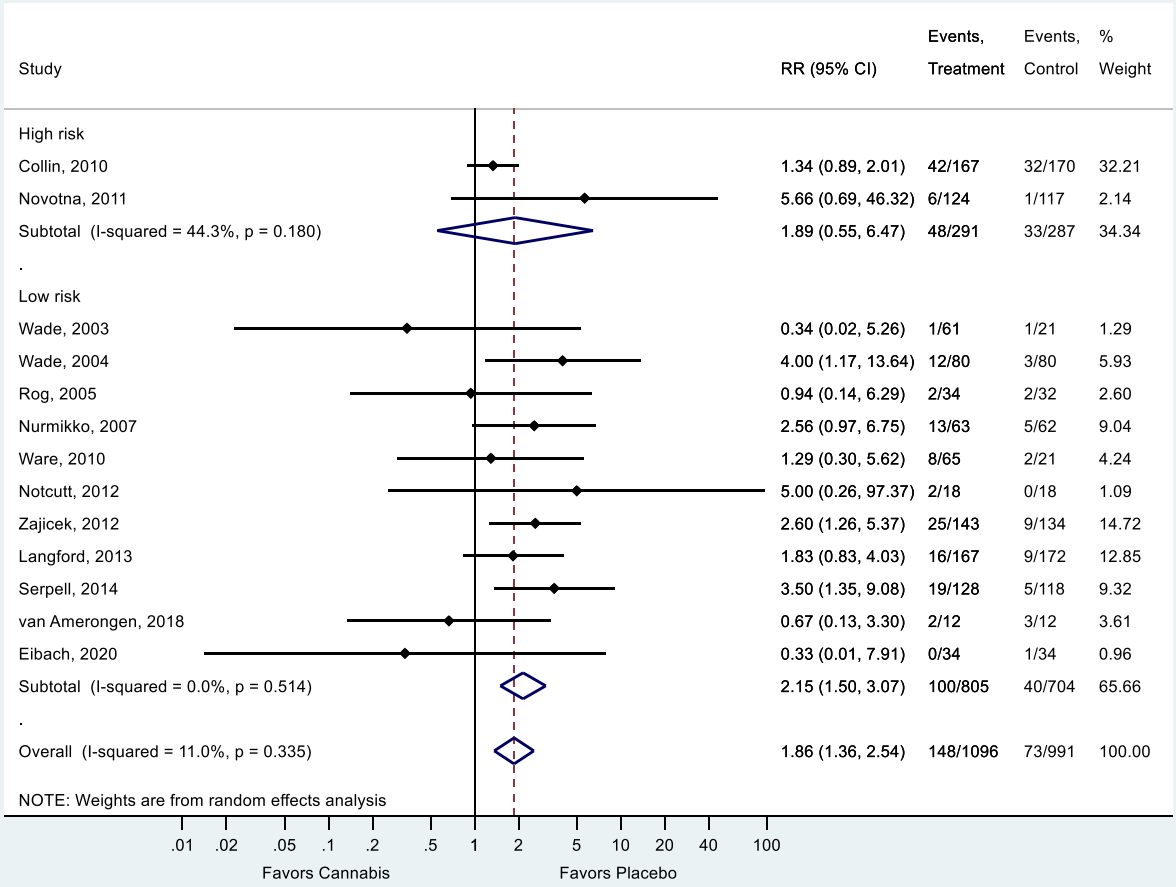
eFigure 9. Forest plot for fatigue for 13 randomized clinical trials of medical cannabis vs. placebo



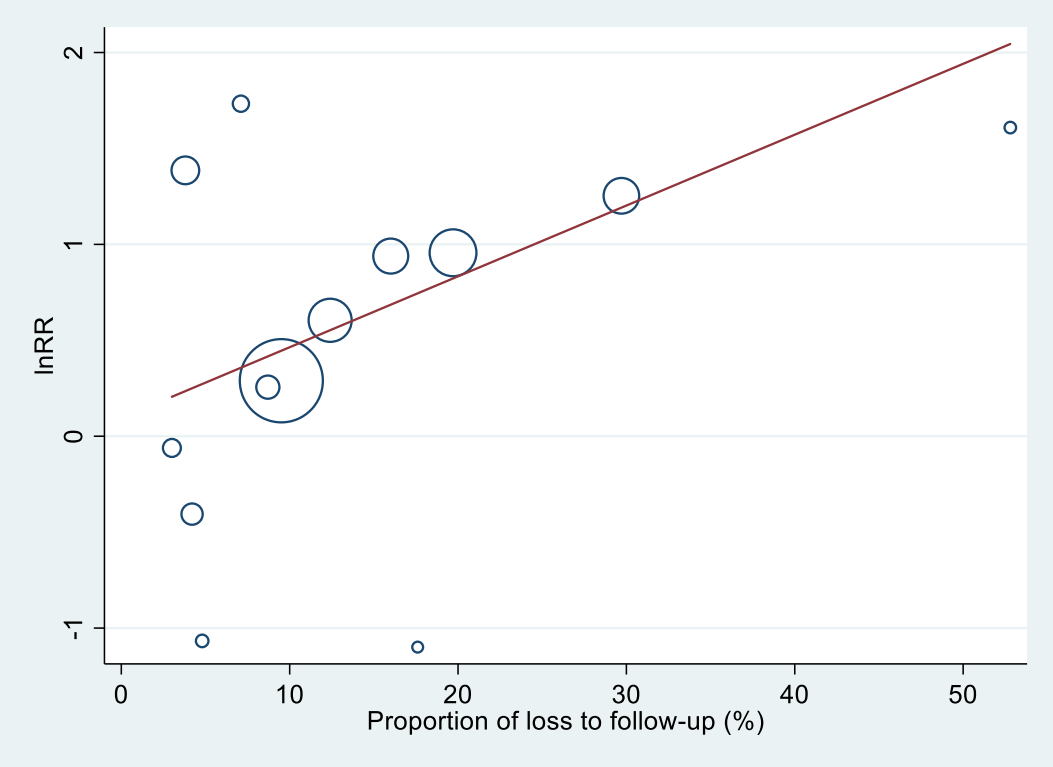
eFigure 9.0 funnel plot of fatigue (Harbord test p=0.51)



eFigure 9.1. subgroup analysis of fatigue for randomization (interaction p=0.15)

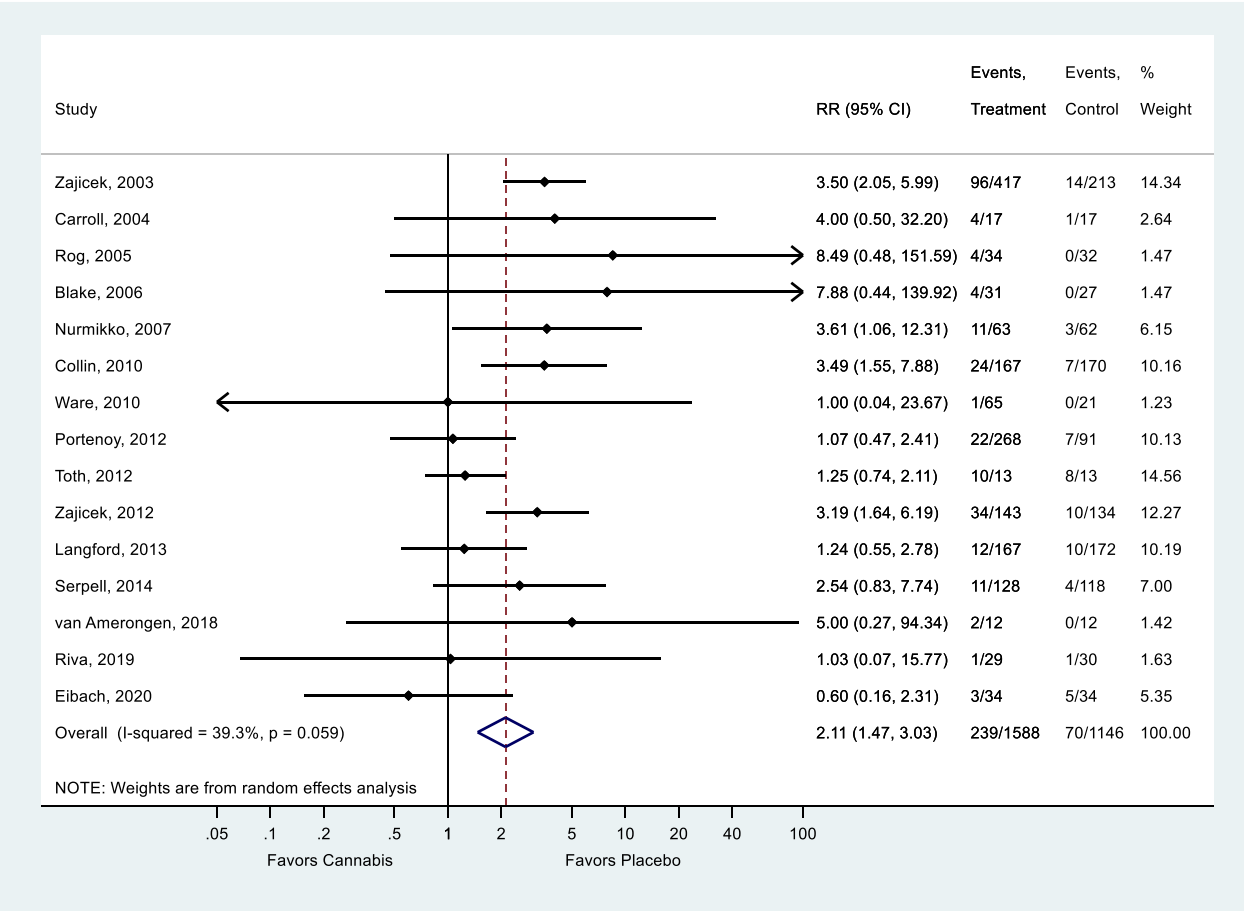


eFigure 9.2. Meta-regression of loss to follow-up and fatigue (p=0.07)



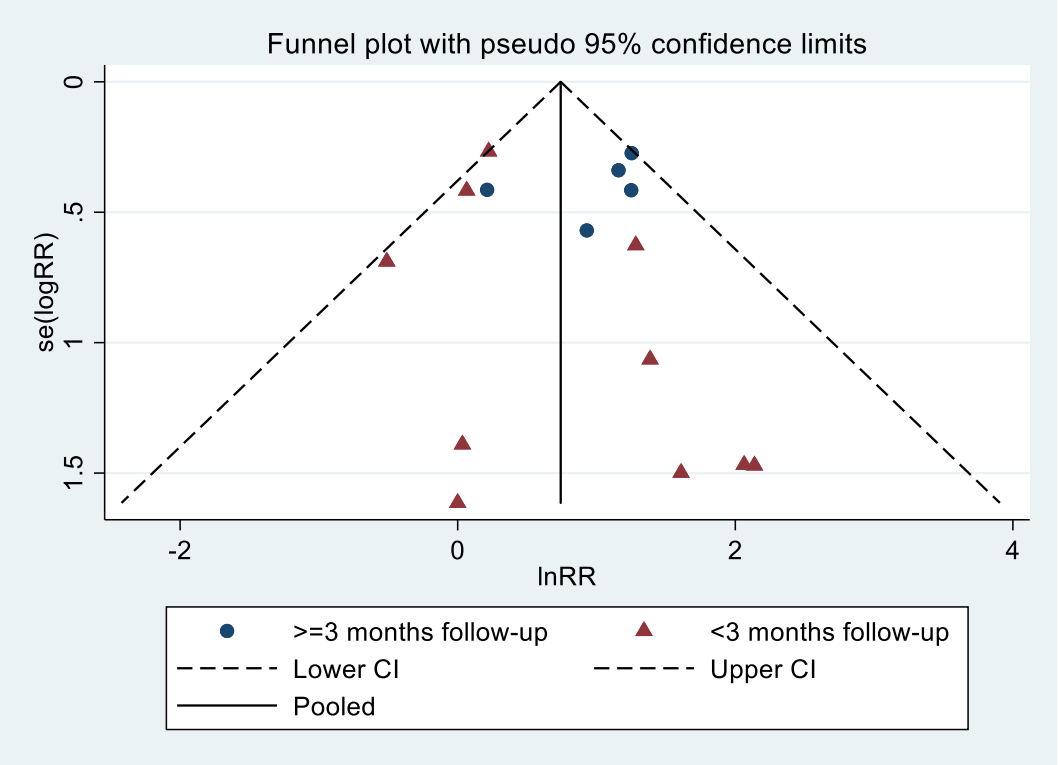
10.Dry mouth

eFigure 10. Forest plot for dry mouth dry mouth for 15 randomized clinical trials of medical cannabis vs. placebo



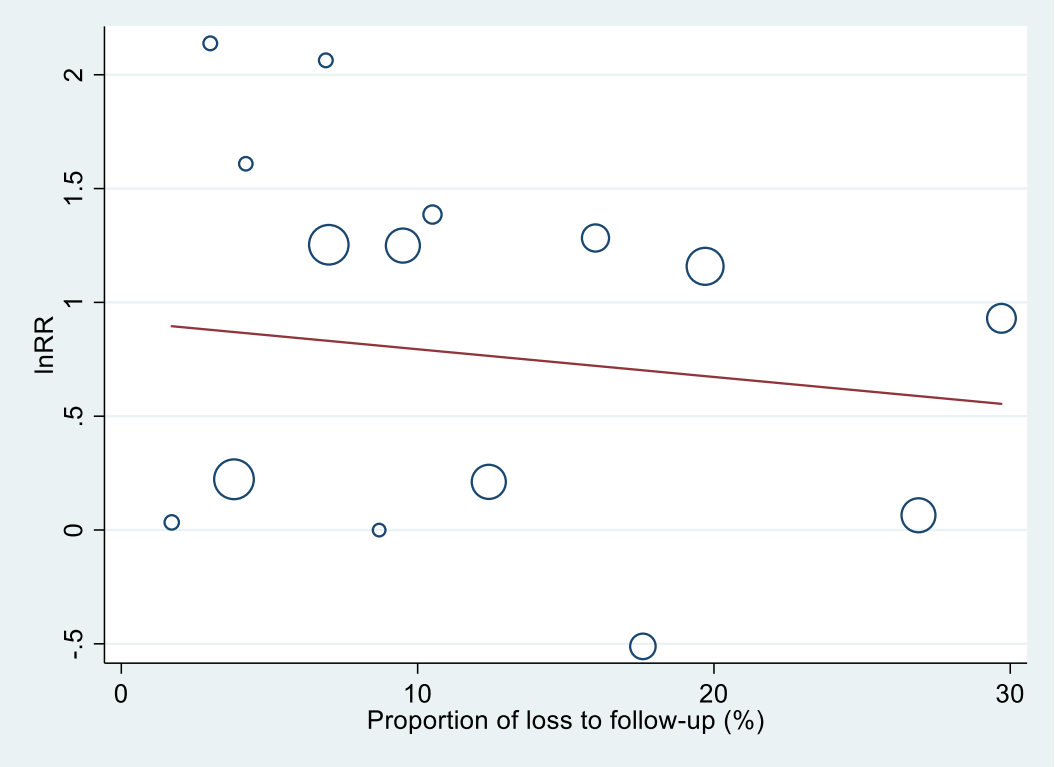
eFigure 10.0 funnel plot of dry mouth (Harbord test p=0.84)

Harbord test p=0.19 for 10 studies with <3 months follow-up

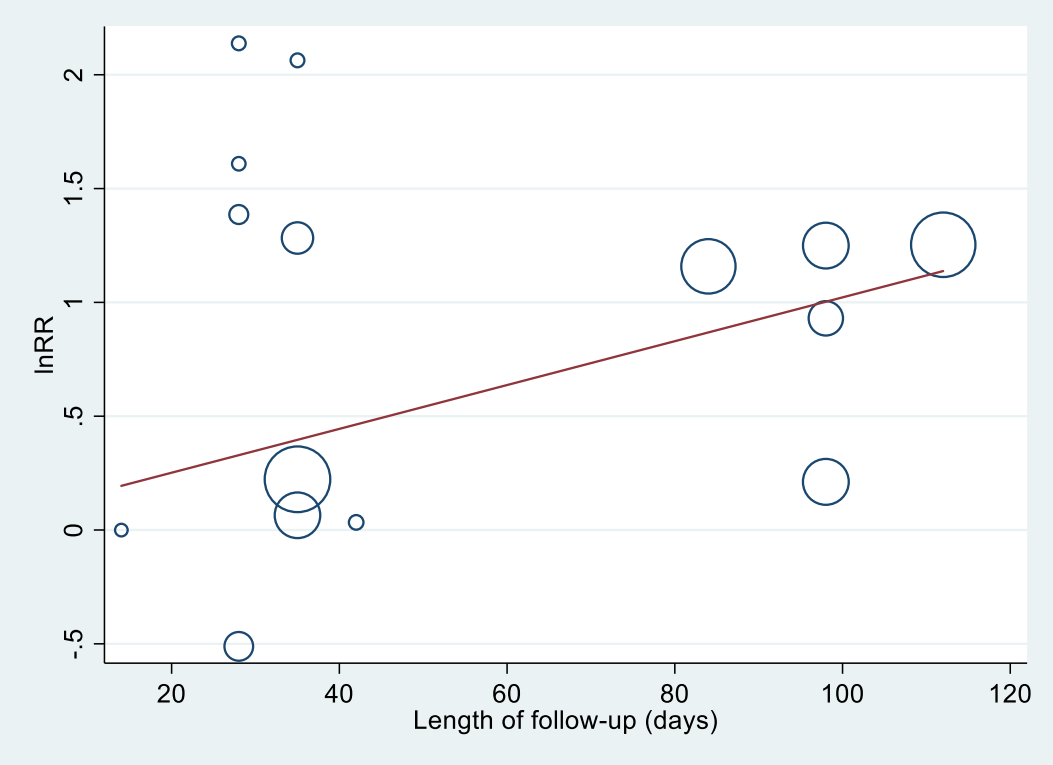


Harbord test p=0.84 for all 15 studies

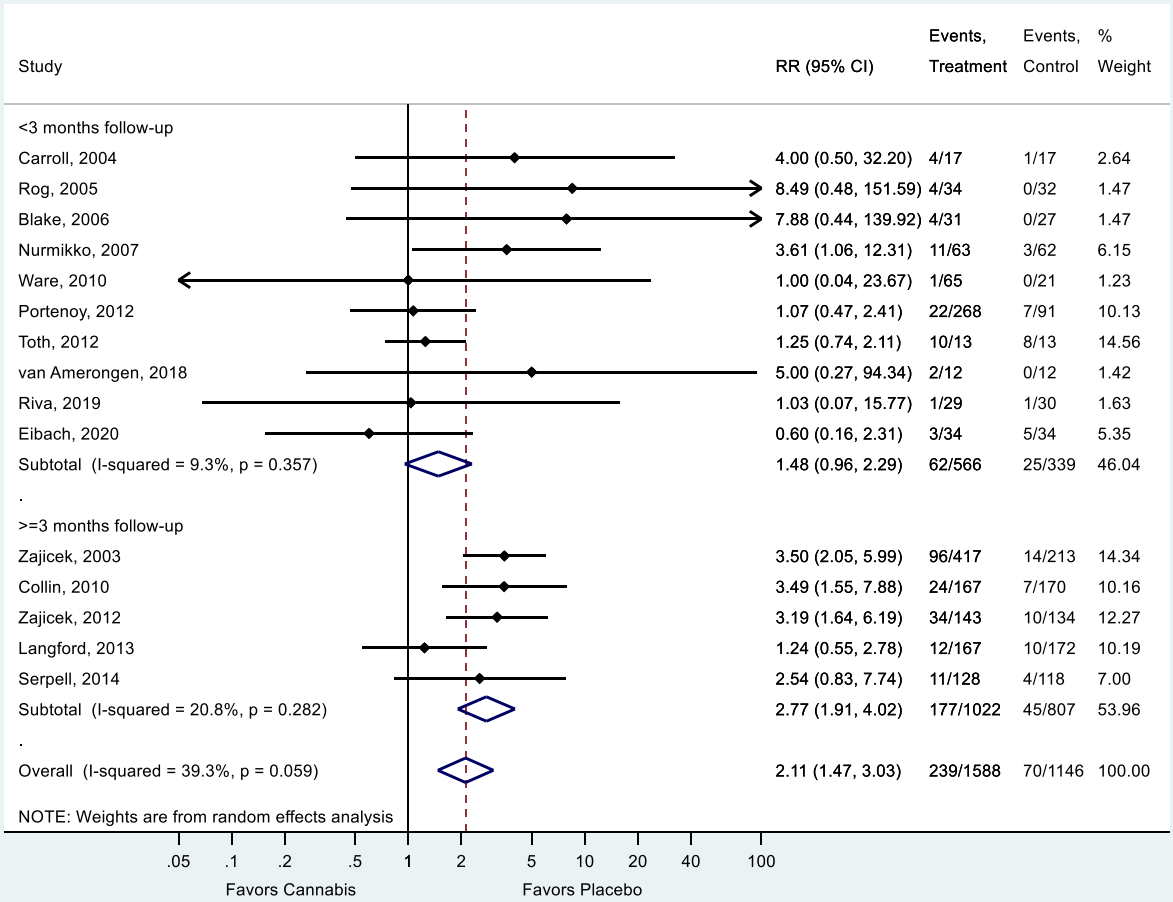
eFigure 10.1. Meta-regression of loss to follow-up and dry mouth (p=0.61)



eFigure 10.2. Meta-regression of length of follow-up and dry mouth (p=0.03)

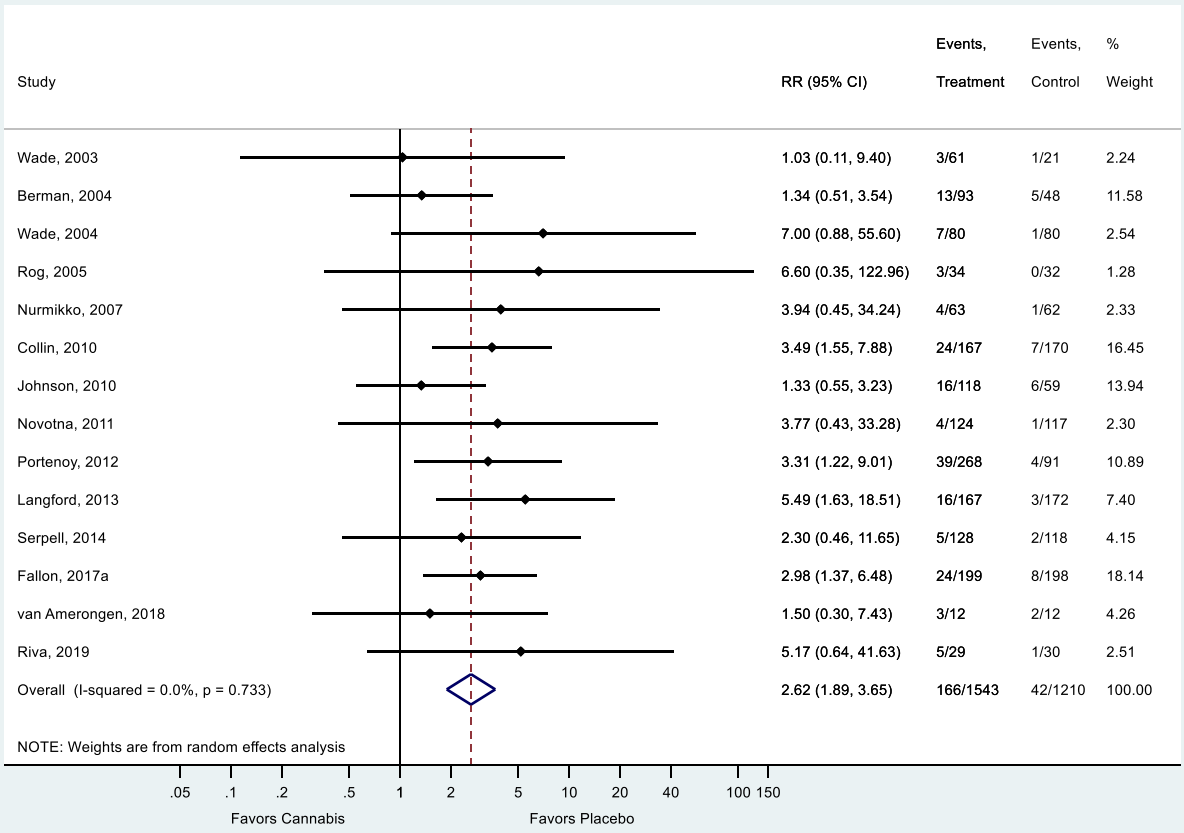


eFigure 10.3. subgroup analysis of dry mouth for short vs long follow-up (interaction p=0.04)

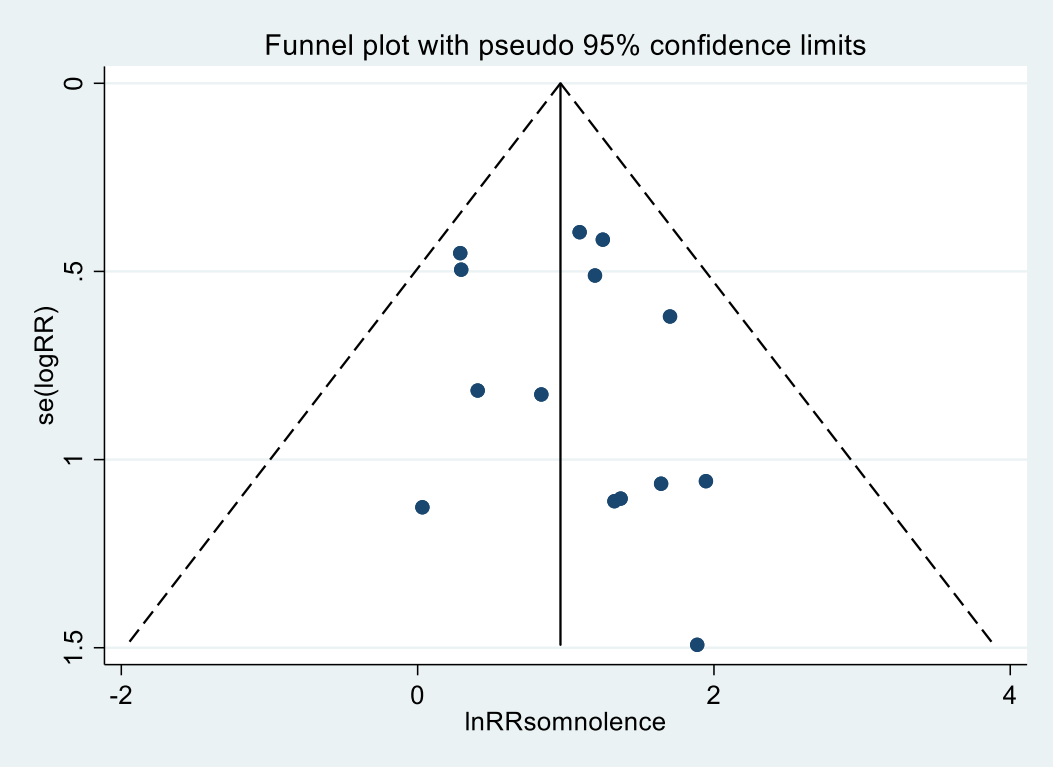


11.Somnolence

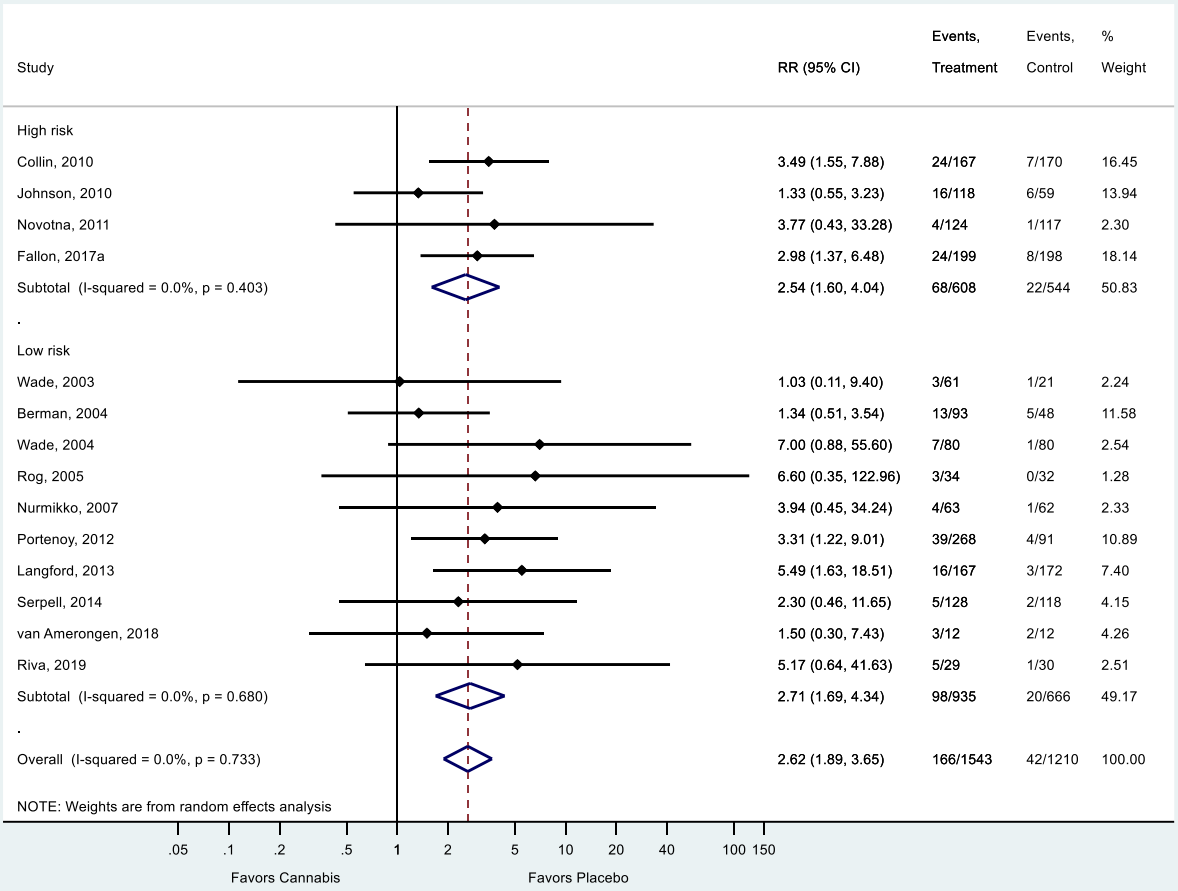
eFigure 11. Forest plot for somnolence for 14 randomized clinical trials of medical cannabis vs. placebo



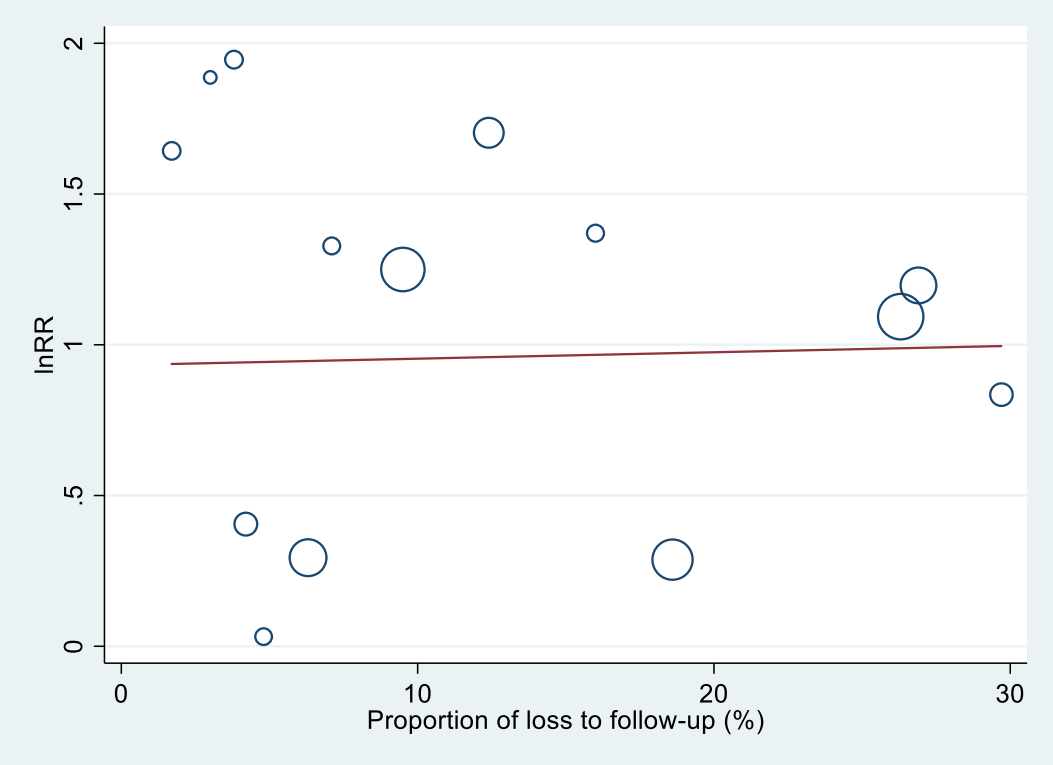
eFigure 11.0. funnel plot of Somnolence (Harbord test p=0.98)



eFigure 11.1. subgroup analysis of Somnolence for randomization (p=0.85)

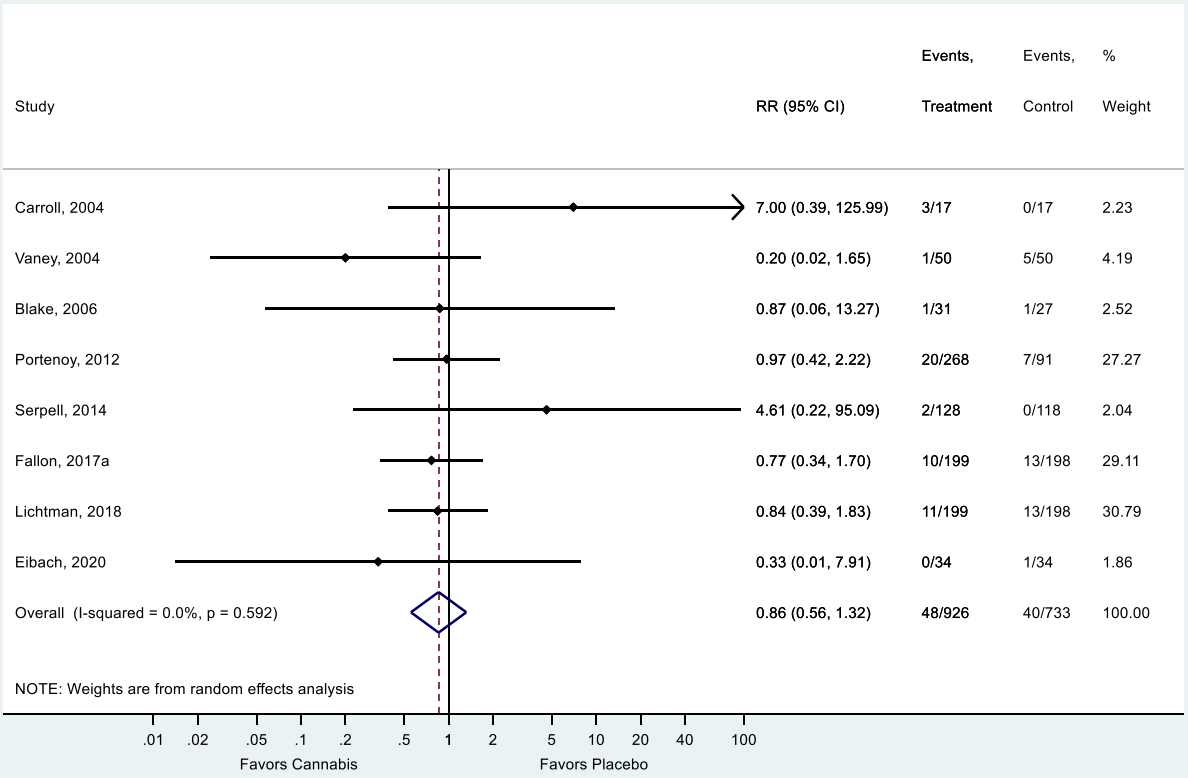


eFigure 11.2. Meta-regression of loss to follow-up and Somnolence (p=0.91)

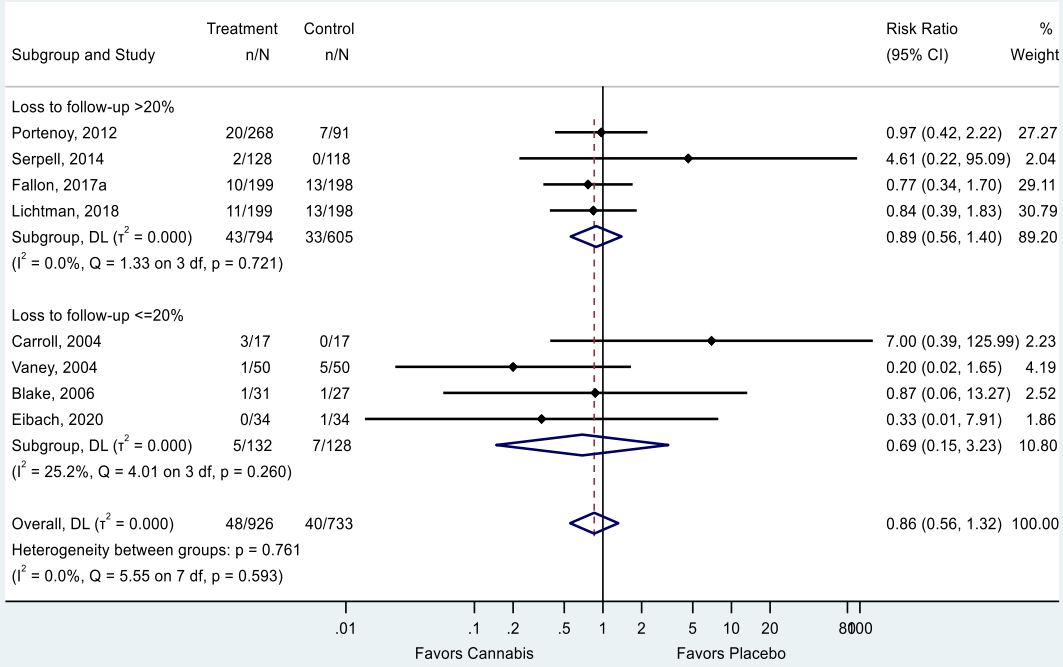


12.Constipation

eFigure 12. Forest plot for constipation for 8 randomized clinical trials of medical cannabis vs. placebo constipation



eFigure 12.0 subgroup analysis of constipation for high vs low risk for missing data (interaction p=0.67)



Appendix 2.D. eTables

eTable 1: The characteristics of the 39 included studies

First Author	Year	Type of Trial	Type of Funding	Total patients randomized	Clinical condition	Age (years)		Female sex	No. of study arms	Cannabinoid or cannabis-based medicine	Control	Route of administration	Maximum dose administered of cannabis intervention?	Sleep Measure	Follow-up/day
						Mean/ median	SD/range	No. (%)							
Jetly	2014	Single Center	Non-Industry funded	10	PTSD	43.6	8.2	0 (0)	2	Nabilone	Placebo	Orally	3 mg	Clinician-Administered PTSD Scale	49
Serpell	2014	Multi-Center	Industry funded	246	Neuropathic Pain	57.6	14.4	85 (66)	2	Sativex	Placebo	Oromucosal Spray	21.6 mg THC and 20mg CBD /3 hours	NRS	98
Collin	2010	Multi-Center	Industry funded	337	Chronic Pain	47.5	9.61	207 (61)	2	Sativex	Placebo	Oromucosal Spray	24 actuations in any 24-hour period	NRS	98
Langford	2013	Multi-Center	Industry funded	339	Neuropathic Pain	48.97	10.47	230 (68)	2	Sativex	Placebo	Oromucosal Spray	12 sprays per 24-h period.	NRS	98
Toth	2012	Single Center	Industry funded	26	Neuropathic Pain	62.2	9.3	12 (46.15)	2	Nabilone	Placebo	Orally	4 mg	Modified brief Pain inventory	35
Novotna	2011	Multi-Center	Industry funded	241	Chronic Pain	48.6	9.33	145 (60)	2	Sativex	Placebo	Oromucosal Spray	maximum of 12 sprays in any 24-h period	NRS	84
Ware	2010	Single Center	Industry funded	32	Chronic Pain	49.5	11.2	26 (81.25)	2	Nabilone	Amitryptiline	Orally	1mg	Insomnia severity index	14
Rog	2005	Single Center	Industry funded	66	Chronic Pain	49.2	8.3	52 (78.78)	2	Sativex	Placebo	Oromucosal Spray	48 sprays in 24 hours	NRS	28
Weber	2010	Single Center	Non-Industry funded	27	Chronic Pain	57	12	7 (25.92)	2	Dronabinol (THC)	Placebo	Orally	10mg	Sleep disorder questionnaire	14

Blake	2006	Multi-Center	Industry funded	58	Chronic Pain	62.8	9.8	46 (79)	2	Sativex	Placebo	Oromucosal Spray	6 actuations	NRS	35
Ware	2010	Single Center	Non-Industry funded	23	Neuropathic Pain	45.4	12.3	12 (52.2)	3	Cannabis flowers	Placebo	Smoking	75mg	Sleep evaluation questionnaire	14
Frank	2008	Multi-Center	Industry funded	96	Neuropathic Pain	50.2	13.63	46 (47.91)	2	Nabilone	Dihydrocodeine	Orally	240 mg	A diary recording the number of hours slept	42
Brisbois	2011	Multi-Center	Non-Industry funded	46	Cancer-related Pain	66.3	9.42	9 (42.86)	2	Dronabinol (THC)	Placebo	Orally	20 mg/day	Side effect survey	18
Zajicek	2003	Multi-Center	Non-Industry funded	630	Chronic Pain	50.54	7.78	413 (65.56)	2	Cannador	Placebo	Orally	25 mg (10 capsules)	NRS	105
Wade	2004	Multi-Center	Partially Industry funded	160	Chronic Pain	50.7	9.33	99 (61.87)	2	Sativex	Placebo	Oromucosal Spray	120mg THC and 120mg CBD per Day	VAS	42
Nurmikko	2007	Multi-Center	Industry funded	125	Neuropathic Pain	53.3	15.47	35 (55.6)	2	Sativex	Placebo	Oromucosal Spray	8 sprays per 3-hour interval; maximum of 48 sprays per 24hrs	NRS	35
Fallon a	2017	Multi-Center	Partially Industry funded	399	Cancer-related Pain	56.8	10.99	196 (49.12)	2	Sativex	Placebo	Oromucosal Spray	Max daily dose of 10 sprays	NRS	35
Fallon b	2017	Multi-Center	Partially Industry funded	206	Cancer-related Pain	61.5	11.33	88 (42.71)	2	Sativex	Placebo	Oromucosal Spray	Max daily dose of 10 sprays	NRS	35
Berman	2004	Single Center	Partially Industry funded	48	Neuropathic Pain	39	Range 23-63	2 (4)	3	Sativex	Placebo	Oromucosal Spray	48 sprays (THC 129.6mg or THC 129.6 mg/CBD 120 mg or placebo) within any 24 h period.	BS-11 scale	14

Vaney	2004	Single Center	Partially Industry funded	57	Chronic Pain	54.9	10	29 (50.87)	2	Cannabis extract	Placebo	Orally	12 active capsules (30mg thc per day)	Diary based-questionnaires	14
Côté	2007	Single Center	Partially Industry funded	56	Cancer-related Pain	64.2	0.66	10 (7.14)	2	Nabilone	Placebo	Orally	2mg (4 pills/day)	Not reported	70
Johnson	2010	Multi-Center	Industry funded	177	Cancer-related Pain	60.2	12.3	82 (46)	3	Sativex	Placebo	Oromucosal Spray	8 sprays in 3 hours, and 48 in 24 hours	NRS	14
Zajicek	2012	Multi-Center	Not Reported	279	Chronic Pain	51.9	7.71	175 (63.17)	2	Cannabis extract	Placebo	Orally	25mg daily	Category rating Scale	84
Portenoy	2012	Multi-Center	Partially Industry funded	360	Cancer-related Pain	58	12.2	174 (48.3)	4	Sativex	Placebo	Oromucosal Spray	4 sprays	NRS	35
Carley	2018	Multic-entre	Non-Industry funded	73	Sleep Apnea	53.6	9	21 (28.76)	3	Dronabinol	Placebo	Orally	2.5mg	Overall apnea–hypopnea index	42
Turcott	2018	single	Partially Industry funded	33	Cancer-related Pain	56.2	11.92	26 (78.78)	2	Nabilone	Placebo	Orally	1mg	Health related quality of life	56
Markova	2019	Multicenter	Industry funded	191	Chronic Pain	51.3	10.2	134 (70.15)	2	Sativex	Placebo	Oromucosal Spray	12 sprays/day	NRS	84
Ameron gen	2017	single	Industry funded	24	Chronic Pain	54.3	8.9	16 (66.7)	2	Namisol	Placebo	Orally	total daily dose of 16 mg	Pittsburgh sleep quality index	28
Notcutt	2012	Multicenter	Industry funded	36	Chronic Pain	57.1	9.95	21 (58.33)	2	Sativex	Placebo	Oromucosal Spray	Not Reported	NRS	28
Riva	2019	Multicenter	Partially Industry funded	60	Neuropathic Pain	57.8	12.24	25 (42.37)	2	Sativex	Plecebo	Oromucosal Spray	Up to a maximum of 12 actuations in 24 h	NRS	28
Gross	1983	Single	Not Reported	11	Anorexia Nervosa	23.6	1.8	11 (100)	2	Delta 9-THC	Diazepam	Orally	30mg	HSCL-90	28

Lichtman	2018	Multicenter	Partially Industry funded	397	Cancer-related Pain	59.9	11.57	183(46.1)	2	Sativex	Placebo	Oromucosal Spray	10 sprays per day	NRS	35
Notcutt	2004	Single	Partially Industry funded	34	Chronic Pain	45.46	11.26	23(67.65)	4	Cannabis Based Medicinal Extracts	Placebo	Oromucosal Spray	NR	Quality of sleep (Good, Fair, Poor)	56
Wade	2003	Single	Industry funded	21	Neuropathic Pain	48	NR	11(52.4)	4	Whole-plant extracts	Placebo	Orally	120 mg / 24 hours	VAS	14
Evangelista	2018	Single	Non-Industry funded	42	Chronic Pain	58.4	14.3	28 (67)	2	Ultra-micronized Palmitoylethanolamide	No treatment	Orally	1200mg/day	PSQI	60
Carroll	2004	Multicenter	Non-Industry funded	19	Parkinson's Disease	67	51-78	7(36.84)	2	Cannador, an ethanolic extract of Cannabis sativa	Placebo	orally	0.25 mg/kg of THC per day	VAS	28
Leocani	2015	Single	Industry funded	43	Multiple sclerosis	48	8	20(46.5)	2	Sativex	Placebo	Oromucosal spray	12 sprays/day	NRS	28
Peball	2020	Single	Partially Industry funded	38	Parkinson's Disease	47	8.12	19(40)	2	Nabilone	Placebo	orally	2 mg daily	Single MDS-UPDRS-I	28
Eibach	2020	Single	Partially Industry funded	34	HIV-Associated Neuropathic Pain	31	8.96	1(3.22)	2	Cannabidivarin (CBDV)	Placebo	orally	400 mg	Insomnia severity	28

PTSD: Post Traumatic Stress Disorder, NRS: Numerical Rating Scale, VAS: Visual Analogue Scale, BS-11: Numerical 11 Point Box categorical rating scale, HSCL-90: The Symptom Checklist-90, PSQI: Pittsburgh Sleep Quality Index, MDS-UPDRS-I: MDS-Unified Parkinson's Disease Rating Scale

eTable 2: Risk of bias assessment of 39 eligible randomized clinical trials

Author	Year	Sequence generation	Allocation concealment	Blinding of participants to the intervention	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of data analysts	Loss to follow-up / missing data (> 20% High RoB)	Report any other sources of bias	Loss to follow-up (%)
Jetly	2015	High risk	High risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk	10
Serpell	2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk	30
Collin	2010	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	10
Langford	2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	12
Toth	2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	4
Novotna	2011	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	7
Ware	2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	9
Rog	2005	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	3
Weber	2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	19
Blake	2006	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	7
Ware	2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	5
Frank	2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk	33
Brisbois	2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk	54
Zajicek	2003	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	3
Wade	2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	4
Nurmikko	2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	16
Fallon a	2017	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk	26
Fallon b	2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	19
Berman	2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	6
Vaney	2004	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	12
Côté	2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	High risk	43
Johnson	2010	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	19

Zajicek	2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	20
Portenoy	2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk	27
Carley	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk	23
Turcott	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	High risk	36
Markova	2019	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	9
Amerongen	2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	4
Notcutt	2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk	53
Gross	1983	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk	27
Lichtman	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	High risk	27
Riva	2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	1.6
Notcutt	2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	29
Wade	2003	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	5
Evangelista	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	0
Carroll	2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	10.52
Leocani	2015	High risk	High risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Low risk	20.93
Peball	2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	0
Eibach	2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	17.64

eTable 3. Detailed description of the results of studies that did not report data suitable for statistical pooling

Autor/Year	Type of outcome measure	Result concordant with the pooled estimate	Detailed description of the study results
Brisbois, 2011	Sleep Quality	Yes	Cancer patients with chemosensory alterations who treated with THC more frequently reported that their quality of sleep was to be 'pleasant'(n=6) compared to placebo group (n=1) on the Side Effect Survey (p=0.046).[35]
Zajicek, 2003	Sleep Quality	Yes	Patients using cannabis extract/THC 153(72%) compared to placebo 59(27%) reported a significant improvement in sleep quality (p=0.02) at week 15 compared to just before the beginning of the study using a 11-point numerical rating scale. [36]
Notcutt, 2004	Sleep Quality	Yes	The results of 34 'N of 1' studies assessing sleep quality based on the percentage of reported 'good' nights showed that the median (IQR) of "good" nights for THC: CBD (55.4%, 78-34,5), THC (42.9% [57.2, 35.7]) and CBD (36.9% [47.9, 28.6]) were all significantly higher than placebo (17.0% [35.7, 3.6]). The respective p-values were as follows: $p < 0.001$, $p < 0.001$ and $p < 0.05$.[54]
Evangelista, 2018	Sleep Quality-Sleep Disturbance	Yes	Patients awaiting carpal tunnel syndrome surgery, suffering from sleep disorders, who were on ultra-micronized palmitoylethanolamide (n=22) reported a highly significant improvement in overall sleep quality (measured with Pittsburgh Sleep Quality Index) and a reduction of sleep disturbances during the pre-surgery periods compared to control group (n=20).[56]

eTable 4: Subgroup analyses of study outcomes for randomized controlled trials of medical cannabis vs. placebo

A: Primary outcomes

Subgroup factor		**Sleep Quality**					**Sleep Disturbance**				
		No. of studies	WMD	95%CI		Interaction test p[a]	No. of studies	WMD	95%CI		Interaction test p
Cannabis components	THC	8	-0.45	-0.82	-0.07	0.79	5	-1.35	-2.13	-0.56	0.05
	CBD	2	-0.40	-1.43	0.63						
	THC/CBD	10	-0.39	-0.67	-0.11		12	-0.52	-0.80	-0.23	
Adequate randomization	Low risk	13	-0.54	-0.8	-0.27	0.08	11	-0.78	-1.22	-0.34	0.48
	High Risk	3	-0.07	-0.38	0.25		5	-0.53	-1.05	-0.02	
Type of Pain	cancer	-	-	-	-	-	5	-0.19	-0.36	-0.03	**0.001[b]**
	non-cancer pain	-	-	-	-		11	-0.99	-1.41	-0.57	
loss to follow-up	(≤20%)	-	-	-	-	-	11	-1.02	-1.41	-0.64	**>0.001[b]**
	(>20%)	-	-	-	-		5	-0.11	-0.35	0.12	
Length of Follow-up	≥ 3 months	4	-0.28	-0.67	0.11	0.45	2	-1.05	-1.55	-0.55	0.18
	≤3 months	12	-0.49	-0.78	-0.19		14	-0.62	-0.99	-0.26	
Allocation concealment	Low	-	-	-	-	-	14	-0.75	-1.10	-0.40	0.14
	High	-	-	-	-		2	0.00	-0.92	0.92	

B: Adverse events

Subgroup factor		dizziness					Somnolence					Nausea				
		No. of studies	WMD	95%CI		Interaction test p[a]	No. of studies	WMD	95%CI		Interaction test p[a]	No. of studies	WMD	95%CI		Interaction test p
Cannabis components	THC	9	2.86	1.35	6.06	0.88	4	1.41	0.64	3.14	0.13	7	1.14	0.55	2.37	0.07
	CBD	2	0.20	0.01	4.02		-	-	-	-		2	0.27	0.04	1.93	
	THC/CBD	18	2.23	1.70	2.92		13	2.91	2.03	4.18		17	2	1.58	2.55	
Adequate randomization	Low risk	19	2.58	1.86	3.58	0.82	10	2.71	1.69	4.34	0.85	18	1.66	1.26	2.18	0.19
	High Risk	5	2.94	1.99	4.35		4	2.54	1.6	4.04		4	2.05	1.17	3.58	
Type of trial	cancer	4	1.93	1.28	2.93	0.36	3	2.36	1.35	4.11	0.60	5	1.58	1.09	2.29	0.30
	non-cancer	20	2.83	2.10	3.80		11	2.84	1.83	4.40		17	2	1.48	2.69	
Length of follow-up	≥3 months	5	4.28	2.76	6.65	**0.007[b]**	4	3.71	2.03	6.75	0.20	4	2.64	1.83	3.8	**0.03[b]**
	<3months	19	2.03	1.60	2.58		10	2.26	1.52	3.35		18	1.49	1.11	1.98	
Allocation concealment	Low risk	22	2.84	2.19	3.67	0.16	-	-	-	-		-	-	-	-	-
	High Risk	2	1.49	0.65	3.41		-	-	-	-		-	-	-	-	

Subgroup factor		Vomiting					Fatigue					Headache				
		No. of studies	WMD	95%CI		Interaction test p[a]	No. of studies	WMD	95%CI		Interaction test p[a]	No. of studies	WMD	95%CI		Interaction test p
Cannabis components	THC	3	1	0.23	4.35	0.76	4	1.71	0.79	3.69	0.76	6	1.22	0.79	1.89	0.23
	CBD	-	-	-	-		2	0.33	0.01	7.91		2	0.50	0.08	3.01	
	THC/CBD	8	1.63	0.99	2.67		9	1.97	1.33	2.9		8	0.70	0.45	1.09	
Adequate	Low risk	-	-	-	-	-	11	2.15	1.50	3.07	0.15	-	-	-	-	-

randomization	High Risk	-	-	-	-		2	1.89	0.55	6.47		-	-	-	-	
Type of trial	cancer	2	1.98	1	3.92	0.38	-	-	-	-		-	-	-	-	-
	non-cancer	7	1.26	0.66	2.39		-	-	-	-		-	-	-	-	
loss to follow-up	(>20%)	2	1.99	1.02	3.87	0.34										-
	(≤20%)	7	1.22	0.63	2.36											

Subgroup factor		**Dry Mouth**					**Diarrhea**					**Constipation**				
		No. of studies	WMD	95%CI		Interaction test p	No. of studies	WMD	95%CI		Interaction test p	No. of studies	WMD	95%CI		Interaction test p
Cannabis components	THC	5	1.94	1.22	3.08	0.40	2	1.42	0.23	8.81	0.87					
	CBD	1	0.6	0.16	2.31		2	2.13	0.35	12.9						
	THC/CBD	10	1.90	1.34	2.69		10	1.65	0.99	2.74						
Adequate randomization	Low risk	-	-	-	-	-	-	-	-	-	-					
	High Risk	-	-	-	-		-	-	-	-						
Type of trial	cancer	-	-	-	-	-	2	1.65	0.61	4.48	0.91	3	0.85	0.54	1.35	0.73
	non-cancer	-	-	-	-		10	1.77	1.02	3.08		5	0.96	0.23	3.97	
loss to follow-up	(>20%)	-	-	-	-	-	-	-	-	-	-	4	0.89	0.56	1.40	0.67
	(≤20%)	-	-	-	-		-	-	-	-		4	0.69	0.15	3.23	
Length of follow-up	≥3 months	5	2.77	1.91	4.02	**0.04**[b]	3	1.31	0.45	3.86	0.33					
	<3months	10	1.48	0.96	2.29		9	2.15	1.15	4.03						

Subgroup factor		**Disturbance in attention**				
		No. of studies	WMD	95%CI		Interaction test p
Cannabis components	THC	-	-	-	-	-
	CBD	-	-	-	-	
	THC/CBD	-	-	-	-	
Adequate randomization	Low risk	-	-	-	-	-
	High Risk	-	-	-	-	
Type of trial	cancer	-	-	-	-	-
	non-cancer	-	-	-	-	
	(>20%)	-	-	-	-	-

loss to follow-up	(≤20%)	-	-	-	-	
Length of follow-up	≥3 months	2	6.76	1.55	29.53-	0.55
	<3months	5	3.52	0.95	13.4	

WMD: Weighted mean difference; 95%CI: 95% confidence interval

[a] p-value from multivariable meta-regression.
[b] there is a significant subgroup effect

eTable 5. Evaluating the credibility of the subgroup effect based on the ICEMAN criteria

Subgroup analysis of sleep disturbance for cancer vs non-cancer pain (interaction p=0.001)			
1: Is the analysis of effect modification based on comparison within rather than between trials?			
[×] Completely between	[ ] Mostly between or unclear	[ ] Mostly within	[ ] Completely within
Comment:			
2: For within-trial comparisons, is the effect modification similar from trial to trial? [×] Not applicable: no or one within-RCT Comparison			
[ ] Definitely not similar	[ ] Probably not similar or Unclear	[ ] Mostly similar	[ ] Definitely similar
Comment:			
3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison			
[ ] Very small	[ ] Rather small or unclear	[×] Rather large	[ ] Large
Comment:			
4: Was the direction of effect modification correctly hypothesized a priori?			
[ ] Definitely no	[] Probably no or unclear	[ ] Probably yes	[×] Definitely yes
Comment:			
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)			
[ ] Chance a very likely	[] Chance a likely explanation or unclear	[ ] Chance may not explain	[×] Chance an unlikely
Comment:			
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?			
[ ] Definitely no	[×] Probably no or unclear	[ ] Probably yes	[ ] Definitely yes
Comment: 6 subgroup analyses performed.			
7: Did the authors use a random effects model?			
[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[×] Definitely yes
Comment:			
8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [ ] not applicable: not continuous			
[ ] Definitely no	[ ] Probably no or unclear	[×] Probably yes	[ ] Definitely yes
Comment:			
9 Optional: Are there any additional considerations that may increase or decrease credibility?			
[ ] yes, probably decrease		[ ] yes, probably increase	
Credibility: Moderate; one response reduced credibility			

eTable 5a. Evaluating the credibility of the subgroup effect based on the ICEMAN criteria

Subgroup analysis of sleep disturbance for loss to follow-up (interaction p<0.001)			
1: Is the analysis of effect modification based on comparison within rather than between trials?			
[×] Completely between	[ ] Mostly between or unclear	[ ] Mostly within	[ ] Completely within
Comment:			
2: For within-trial comparisons, is the effect modification similar from trial to trial? [×] Not applicable: no or one within-RCT Comparison			
[ ] Definitely not similar	[ ] Probably not similar or Unclear	[ ] Mostly similar	[ ] Definitely similar
Comment:			
3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison			
[ ] Very small	[ ] Rather small or unclear	[×] Rather large	[ ] Large
Comment:			
4: Was the direction of effect modification correctly hypothesized a priori?			
[×] Definitely no	[] Probably no or unclear	[ ] Probably yes	[] Definitely yes
Comment:			
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)			
[ ] Chance a very likely	[ ] Chance a likely explanation or unclear	[ ] Chance may not explain	[×] Chance an unlikely
Comment:			
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?			
[ ] Definitely no	[×] Probably no or unclear	[ ] Probably yes	[ ] Definitely yes
Comment: 6 subgroup analyses performed.			
7: Did the authors use a random effects model?			
[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[×] Definitely yes
Comment:			
8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [ ] not applicable: not continuous			
[ ] Definitely no	[ ] Probably no or unclear	[×] Probably yes	[ ] Definitely yes
Comment:			
9 Optional: Are there any additional considerations that may increase or decrease credibility?			
[ ] yes, probably decrease		[ ] yes, probably increase	
Credibility: Low; two responses definitely reduce credibility			

eTable 5b. Evaluating the credibility of the subgroup effect based on the ICEMAN criteria

Subgroup analysis of nausea for short vs long follow-up (interaction p=0.03)			
1: Is the analysis of effect modification based on comparison within rather than between trials?			
[×] Completely between	[ ] Mostly between or unclear	[ ] Mostly within	[ ] Completely within
Comment:			
2: For within-trial comparisons, is the effect modification similar from trial to trial? [×] Not applicable: no or one within-RCT Comparison			
[ ] Definitely not similar	[ ] Probably not similar or Unclear	[ ] Mostly similar	[ ] Definitely similar
Comment:			
3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison			
[ ] Very small	[] Rather small or unclear	[×] Rather large	[] Large
Comment: meta-regression from 20 trials			
4: Was the direction of effect modification correctly hypothesized a priori?			
[] Definitely no	[] Probably no or unclear	[ ] Probably yes	[×] Definitely yes
Comment:			
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)			
[ ] Chance a very likely	[×] Chance a likely explanation or unclear	[ ] Chance may not explain	[ ] Chance an unlikely
Comment:			
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?			
[ ] Definitely no	[×] Probably no or unclear	[ ] Probably yes	[ ] Definitely yes
Comment: 4 subgroup analyses performed.			
7: Did the authors use a random effects model?			
[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[×] Definitely yes
Comment:			
8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [ ] not applicable: not continuous			
[ ] Definitely no	[ ] Probably no or unclear	[] Probably yes	[×] Definitely yes
Comment:			
9 Optional: Are there any additional considerations that may increase or decrease credibility?			
[ ] yes, probably decrease		[ ] yes, probably increase: The effect modification is consistent across related outcomes; and effect modification supported by observational studies.	
Credibility: Moderate; one response definitely reduces credibility			

eTable 5C. Evaluating the credibility of the subgroup effect based on the ICEMAN criteria

Subgroup analysis of dizziness for short vs long follow-up (interaction p=0.007)			
1: Is the analysis of effect modification based on comparison within rather than between trials?			
[×] Completely between	[ ] Mostly between or unclear	[ ] Mostly within	[ ] Completely within
Comment:			
2: For within-trial comparisons, is the effect modification similar from trial to trial? [×] Not applicable: no or one within-RCT Comparison			
[ ] Definitely not similar	[ ] Probably not similar or Unclear	[ ] Mostly similar	[ ] Definitely similar
Comment:			
3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison			
[ ] Very small	[ ] Rather small or unclear	[] Rather large	[×] Large
Comment: meta-regression from 21 trials			
4: Was the direction of effect modification correctly hypothesized a priori?			
[] Definitely no	[] Probably no or unclear	[] Probably yes	[×] Definitely yes
Comment:			
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)			
[ ] Chance a very likely	[×] Chance a likely explanation or unclear	[] Chance may not explain	[ ] Chance an unlikely
Comment:			
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?			
[ ] Definitely no	[×] Probably no or unclear	[ ] Probably yes	[ ] Definitely yes
Comment: 4 subgroup analyses performed.			
7: Did the authors use a random effects model?			
[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[×] Definitely yes
Comment:			
8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [ ] not applicable: not continuous			
[ ] Definitely no	[ ] Probably no or unclear	[] Probably yes	[×] Definitely yes
Comment:			
9 Optional: Are there any additional considerations that may increase or decrease credibility?			
[ ] yes, probably decrease		[×] yes, probably increase: The effect modification is consistent across related outcomes; and effect modification supported by observational studies.	
Credibility: Moderate; one response definitely reduced credibility			

eTable 6C. Evaluating the credibility of the subgroup effect based on the ICEMAN criteria

Subgroup analysis of dry mouth for short vs long follow-up (interaction p=0.04)			
1: Is the analysis of effect modification based on comparison within rather than between trials?			
[×] Completely between	[ ] Mostly between or unclear	[ ] Mostly within	[ ] Completely within
Comment:			
2: For within-trial comparisons, is the effect modification similar from trial to trial? [×] Not applicable: no or one within-RCT Comparison			
[ ] Definitely not similar	[ ] Probably not similar or Unclear	[ ] Mostly similar	[ ] Definitely similar
Comment:			
3: For between-trial comparisons, is the number of trials large? [ ] Not applicable: no between RCT comparison			
[ ] Very small	[] Rather small or unclear	[×] Rather large	[] Large
Comment: meta-regression from 15 trials			
4: Was the direction of effect modification correctly hypothesized a priori?			
[] Definitely no	[] Probably no or unclear	[ ] Probably yes	[×] Definitely yes
Comment:			
5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)			
[] Chance a very likely	[×] Chance a likely explanation or unclear	[ ] Chance may not explain	[ ] Chance an unlikely
Comment:			
6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?			
[ ] Definitely no	[×] Probably no or unclear	[ ] Probably yes	[ ] Definitely yes
Comment: 4 subgroup analyses performed.			
7: Did the authors use a random effects model?			
[ ] Definitely no	[ ] Probably no or unclear	[ ] Probably yes	[×] Definitely yes
Comment:			
8: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [ ] not applicable: not continuous			
[ ] Definitely no	[ ] Probably no or unclear	[] Probably yes	[×] Definitely yes
Comment:			
9 Optional: Are there any additional considerations that may increase or decrease credibility?			
[ ] yes, probably decrease		[ ] yes, probably increase: The effect modification is consistent across related outcomes; and effect modification supported by observational studies.	
Credibility: Moderate; one response definitely reduced credibility			

eTable 6: GRADE Evidence Profile of Medical Cannabis and Cannabinoids vs Placebo Predominantly for Patients with Chronic pain Included in Randomized Clinical Trials

Outcome Measure	No. of Trials- patients	Follow-up range (week)	Risk of Bias [a]	*Inconsistency* [b]	Indirectness [c]	*Imprecision* [d]	*P* Value for Publication Bias	Risk Difference for Achieving the MID (95% CI) %	WMD-RR (95% CI)	Quality of Evidence
Headache	1819 (14 RCTs)	2-14	not serious [e]	not serious I-squared=0%	not serious	serious [f]	Undetected 0.75	-1(-3,2)	RR 0.91 lower (0.67 lower to 1.24 higher)	Moderate
Fatigue	2087 (13 RCTs)	2-16	not serious [e]	not serious I-squared=11%	not serious	not serious	Undetected 0.51	6 (3, 11)	RR 1.86 higher (1.36 higher to 2.54 higher)	High`
Dry mouth (RCTs ≥3 months follow-up)	1829 (5 RCTs)	12-16	not serious [e]	not serious I-squared=20.8%	not serious	not serious	Uncertain: only five trials	10(5-17)	RR 2.77 higher (1.91 higher to 4.02 higher)	High
Dry Mouth (RCTs <3 months follow-up)	905 (10 RCTs)	2-6	not serious [e]	not serious I-squared=9.3%	not serious	serious [f]	Undetected 0.19	4(0-10)	RR 1.48 higher (0.96 lower to 2.29 higher)	Moderate

Somnolence	2753 (14 RCTs)	2-14	not serious [e]	not serious I-squared=0 %	not serious	not serious	Undetected 0.19	6 (3, 9)	RR 2.62 higher (1.89 higher to 3.65 higher)	High
Constipation	1659 (8 RCTs)	2-14	serious [g]	not serious I-squared=0%	not serious	serious [f]	Uncertain: only eight trials	-1(-2,2)	RR 0.86 lower (0.56 lower to 1.32 higher)	Low

a. A modified Cochrane risk of bias instrument was used for assessing risk of bias.
b. An I^2 value between 75% and 100% may demonstrate considerable heterogeneity.
c. If the intervention, patients, or outcomes are different from the review question.
d. A symmetric funnel plot and the Egger's test were used to assess publication bias when there were at least 5 studies available. No publication bias was detected in any included studies.
e. We did not rate down for risk of bias as subgroup analysis showed no significant difference in low vs. high risk of bias on a component-by-component basis or the relative contribution of trials at high risk of bias to pooled estimate was lower than 15% (eTable 7 in Appendix 2.D).
f. Confidence intervals include benefit and harm.
g. One study was not adequately randomized (Fallon a, 2017) and the relative contribution of trials at high risk of bias to pooled estimate was greater than 29.11%.

eTable 7. The relative contribution of trials at high risk of bias to pooled estimates for which subgroups effects could not be explored

Outcome	Studies at high RoB without subgroup analysis	Weight in pooled analysis	eFigure
Sleep Quality	1 study (Leocani, 2015) has no adequate allocation concealment	1.97%	eFig 1.0 in Appendix 2.B
Sleep Disturbance	CNCP: 2 studies, 10.57% 1 study has no adequate allocation concealment (Vaney, 2004) 5.04% 1 study with >20% LTFU (Notcutt 2012) 5.30%; Cancer: 4 studies with >20% LTFU, 28.61%; meta regression for LTFU p<0.001	CNCP: 2 studies, 10.34% Cancer: 4 studies, 28.61%	eFig 2.5 in Appendix 2.B
Nausea	1 study has no adequate allocation concealment (Vaney, 2004)	1.10%	eFig 3 in Appendix 2.C
Dizziness	None	NA	eFig 4.1 in Appendix 2.C
Diarrhea	1 study has no adequate randomization (Novotna, 2011)	12.58%	eFig 5 in Appendix 2.C
Disturbance in attention	1 study (Serpell, 2014) with LTFU>20%	22.48%	eFig 6 in Appendix 2.C
Vomiting	1 study has no adequate randomization (Johnson,2010)	9.28%	eFig 7 in Appendix 2.C
Headache	1 study has no adequate randomization (Novotna, 2011)	3.59%	eFig 8 in Appendix 2.C
Fatigue	None	NA	eFig 9.1 in Appendix 2.C
Dry Mouth	1 study has no adequate randomization (Collin, 2010)	10.16%	eFig 10 in Appendix 2.C
Somnolence	None	NA	eFig 11.1 in Appendix 2.C
Constipation	1 study has no adequate randomization (Fallon a, 2017)	29.11%	eFig 12.0 in Appendix 2.C

Appendix 3. Interview Guide

Semi-Structured Interview

Attitudes towards chronic pain: General

1.Tell me about yourself.

Probes: your age, background, chronic pain history, etc.

2. Could you describe your experience with chronic pain?

3. You have been prescribed medical marijuana to treat your chronic pain. Can you tell me how medical marijuana came to be prescribed to help you with the pain?

Attitudes towards medical cannabis

Three basic clusters:

(1) ***Medical cannabis as an alternative to other medications***

1. Had you tried other treatments before marijuana? If so, what treatments or drugs did you have before marijuana?
2. Are you currently receiving other treatments along with marijuana? If so, what treatments or drugs do you have?
3. How do you find marijuana compared to other treatment options?
4. Can you please explain how much you are satisfied with the benefits of marijuana?

If not satisfied: do you plan to continue exploring other options?

5. Do you find marijuana effective enough on its own, or is it part of a treatment approach?

Probes: can you explain more. How useful or useless do you think it is in reducing your pain? I am wondering what you think are the advantages or disadvantages of using medical marijuana? Are you concerned with any side effects of marijuana?

(2) ***The impact of medical cannabis use on other medication use and patients' life***

6. Can you tell me what happened for using other pain medications when you started using medical marijuana? Have use of your other medications changed – increased or decreased since you began using medical marijuana?

   If so, can you provide details?

7. Can you tell me how marijuana has had effects on your life?

Probes: your quality of life, sleep, your personal or marital life, your relationships to others (colleagues, friends, family, wife, partner, etc.).

(3) ***The possible barriers, challenges, and concerns regarding medical cannabis use***

8. Can you please explain if you have ever run into any challenges using medical marijuana?

   Probes: tell me more…. what was that like? What happened then?

   Barriers, concerns, challenges, stigmatization; ask if they know others who that has happened to?

9. Can you tell me about how people view your medical marijuana use? I am interested in how you think other people view your use of medical marijuana.
10. Do you ever tell anyone about it? What would make you share that information / or not share it? What kinds of responses have you had when someone learned you use marijuana for chronic pain? (Explore specific instances that are shared)

Probes: family, friends, colleagues; how this different view if any affects your medical marijuana usage?

If the answer is yes to question 10, ask the questions below. If not, skip to wrapping up section.

11. Could you describe your experience about the growing of these views over the time of using marijuana?

Probes: did you become less or more sensitive to these views over time?

12. How have these people's views affected your medical marijuana use?
13. Do you have any thoughts/suggestions about how barriers to use medical marijuana can be overcome?

    Probes: any other suggestions, comments?

Wrapping up

We are approaching the end of the interview. The purpose of this study was to learn from you about attitudes and usage of the medical marijuana for chronic pain.

Is there anything else you would like to say or add about using medical marijuana?

Thank you so much for participating in this interview.

Appendix 4.

Figure 4.1. Flow Diagram

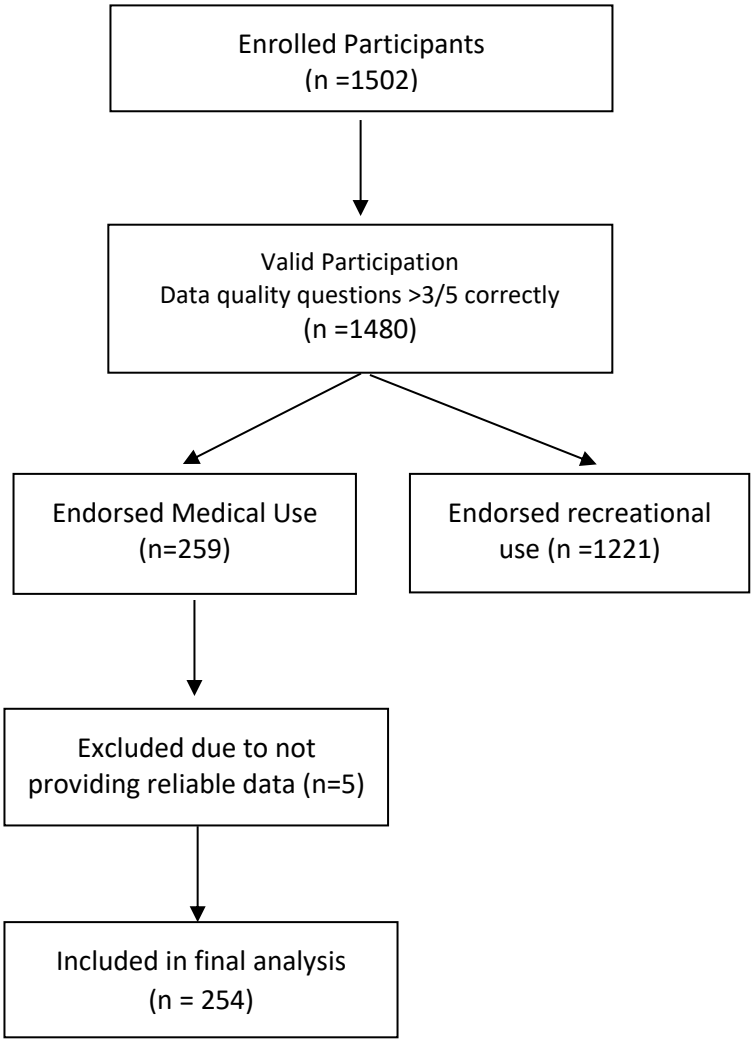


Figure 4.2. Substitution of cannabis for prescribed medication, alcohol and other drugs 6-month before legalization of recreational cannabis

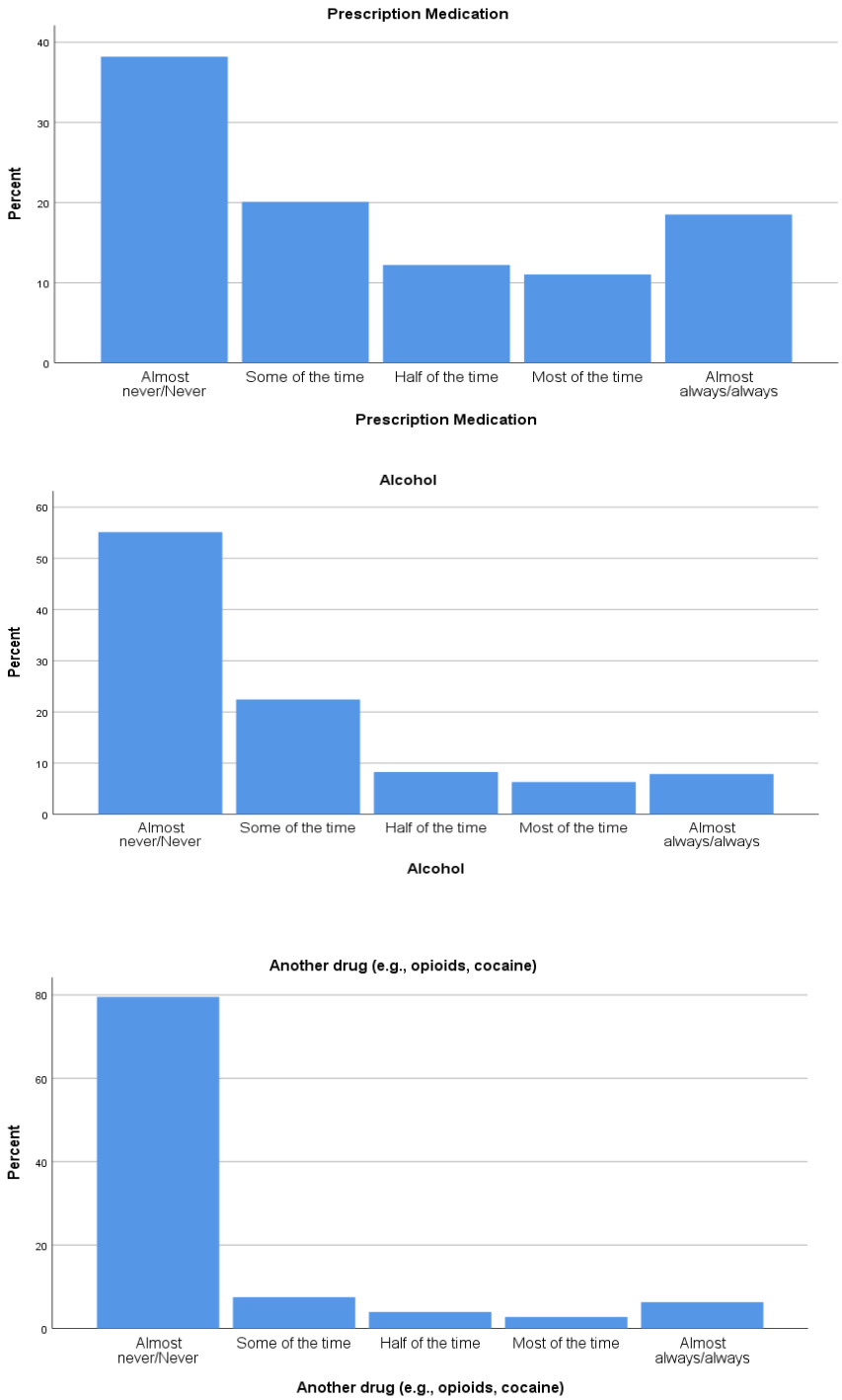


Figure 4.3. Substitution of cannabis for prescribed medication and alcohol 6-months after legalization of recreational cannabis