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Effects of Exposure to Second and Third-Hand Marijuana Smoke: A Systematic Review

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	nor the long-term health effects of passive exposure. Interpretation: Passive exposure leads to cannabinoid metabolites in bodily fluids and individuals experience psychoactive effects after exposure to secondhand smoke. Alignment of tobacco and marijuana smoking bylaws may result in the most effective public policies. More research to understand the impact of third-hand exposure and the long-term health outcomes of passive exposure is required.

Effects of Exposure to Second and Third-Hand Marijuana Smoke: A Systematic Review

Running Title: Passive Exposure to Marijuana Smoke

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ABSTRACT

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Interpretation: Passive exposure leads to cannabinoid metabolites in bodily fluids and individuals experience psychoactive effects after exposure to secondhand smoke. Alignment of tobacco and marijuana smoking bylaws may result in the most effective public policies. More research to understand the impact of third-hand exposure and the long-term health outcomes of passive exposure is required.

Keywords: cannabis, marijuana smoking, passive smoking, tobacco smoke pollution, hand smoke

BACKGROUND

Marijuana is the most frequently used illicit drug in the United States. [1] A 2014 nationally representative U.S. study found that 7.2% of individuals had used marijuana in the past 12 months.[2] There are a variety of modes to smoke marijuana, including: in a joint, in a blunt (rolled in tobacco-leaf paper from a cigar), using a pipe, and using a water pipe or bong. Each of these modes carries with it its own health concerns. Among users, the most frequent methods of consumption were by combusting marijuana (76.3%), followed by edibles or drinks (16.1%), and vaporizing (7.6%).[2]

Harms of direct marijuana use from the literature include a higher risk of developing mental illness, being involved in a motor vehicle accident, and negative effects on brain development in adolescents.[3] However, the effects of passive exposure to *marijuana* smoke remain largely unknown. Effects of passive exposure to *tobacco* smoke, including both second- and third-hand smoke, have been reported.[4-8] Exposure to secondhand smoke, which is "smoke exhaled by a smoker or is emitted from the burning cigarette that is then inhaled by an individual in close proximity",[9] from tobacco is known to cause fetal anomalies, reproductive complications, respiratory disease, cancers and cardiovascular disease.[4-6,10] The potential effects of third-hand smoke, which is "residual tobacco smoke pollution that occurs after smoking"[9] are now also being reported.[11-14] These effects include DNA damage from exposure to non-gaseous particles that react with nitrous acid in the environment.[15] While investigation into the health harms from passive exposure to marijuana smoke is limited, there is preliminary evidence from an animal model that shows endothelial function is impaired post-exposure.[16]

Where marijuana remains an illegal substance, it is difficult to impose regulations or health warnings to try to limit both direct and passive exposure to humans; causing concern for public health. In the last 5 years recreational marijuana has been legalized in six jurisdictions: Uruguay, Alaska, Colorado, Oregon, Washington and Washington D.C. On November 8, 2016, five additional U.S. States voted on proposals to legalize marijuana; the proposals passed in Nevada, California, Maine, Massachusetts, and failed in Arizona. Canada plans to legalize marijuana in 2018 and it is likely that more U.S. States and jurisdictions will legalize marijuana in the coming years. With this changing landscape in mind, there is a need to better understand the public and

individual health risks associated with passive marijuana smoke exposure. The objective of this work is to synthesize the available evidence on the immediate, short-term and long-term effects of exposure to second and third-hand marijuana smoke. This information will be important to support evidence-informed policy, the public health risks associated with marijuana and to support individual patient-care provider conversations to reduce harm.

METHODS

Data Sources

A systematic review on the effects of exposure to second- and third-hand marijuana smoke was conducted. Six databases (MEDLINE, the Cochrane Database of Systematic Reviews, EMBASE, PsychINFO, CINAHL, and the HTA database) were searched from their inception until June 10, 2016. A library and information specialist developed the search strategies. The search was conducted using all MESH terms referring to marijuana (e.g. ganga, bhang, hashish, pot, shatter, weed) and MESH terms referring to potential outcomes from passive exposure to marijuana smoke (e.g. adverse reaction, cancer, positive drug test, urine level test, dependence). The full MEDLINE search strategy is available in the online appendix. The PRISMA guidelines and reporting standards were followed throughout data acquisition and reporting.

Study Selection

Abstract review was conducted independently by two reviewers. Inclusion criteria were: reported in English or French; human, in vivo, or in vitro studies with more than one case; reported original, quantitative data; and reported any outcome (e.g. blood or urine analysis, tetrahydrocannabinol (THC) levels in the air). Abstracts were excluded if they failed to meet all the inclusion criteria thus all case reports, commentaries, editorials, or letters were excluded. Studies included by either reviewer proceeded to full text review, which was also conducted by two independent reviewers. Any disagreements between reviewers were resolved through discussion of the full text. If required, a third reviewer was consulted. After full text review, the included studies were hand-searched for other relevant studies.

Data Extraction

Data extraction was completed by two reviewers in 2016, and included details on the design of the intervention, number of experimental trials, length of exposure, participant recruitment methods, number of participants, inclusion criteria, and characteristics (e.g. demographics). Three outcomes were extracted: 1) concentrations of THC and THC metabolites in blood, oral fluid, and/or urine samples from both active and passive marijuana smokers; 2) air concentrations of THC depending on environmental factors; and, 3) subjective self-reported effects of secondhand smoke exposure.

Quality Assessment

For human studies, the quality of the included studies was assessed in duplicate using the Downs and Black Checklist.[17] There are five constructs of the Checklist: reporting, external validity, internal validity - bias, internal validity - confounding, and power.[17] The 27-item checklist provides studies with a score of either one or zero for each criterion, with a higher score indicating higher quality.[17] The maximum score using this checklist is 28.[17] No quality assessment tool was applied to in vitro studies.

Analysis

Records were categorized as studies that measured the chemical components of marijuana smoke or those that investigated the immediate effects on individuals passively exposed to smoke. Based on outcomes reported, the studies that investigated the immediate effects of exposure were further categorized into three sub-categories: cannabinoids (e.g. THC) and metabolites in bodily fluids, effects of ventilation on passive smoke effects, and psychoactive effects of passive exposure. The findings within each category were synthesized qualitatively. Synthesis involved reporting those aspects of the findings that were similar or, if there were discrepancies between studies, reporting the differences in study design, methods, or execution that could account for the differences.

RESULTS

One thousand four hundred and fifty-nine unique abstracts were identified. Of those, 56 proceeded to full text review, 18 of which were included in the final data set (Figure 1). The 18 records reported findings from 11 unique studies. Seven records reported from seven unique

studies,[18-24] and eleven records reported data from four studies.[25-35] Two of the records reported the same data from the same study in separate publications.[28,29] Details of each included study are included in eTable 1.

Three studies assessed the in vitro effects of smoke exposure on non-human cells [33-35] and fifteen studies were experimental studies on the immediate effects of smoke exposure on humans in a controlled environment.[18-32] The fifteen experimental studies all followed a similar protocol where passive non-smokers sat in proximity to individuals who were actively smoking. Physiological or psychological outcomes were measured after a period of exposure.[18,19,21-32] None of the included studies investigated third-hand marijuana smoke.

All included studies assessed short-term effects of passive exposure; none assessed long-term health effects. Meta-analysis was not possible due to heterogeneous outcomes and reporting, and therefore, the included studies have been narratively synthesized.

Using the Downs and Black quality assessment tool, all of the included studies were of low to moderate quality. The average score for quality assessment was 17.8, with a range of 13[24]- 22 [25,26,29,30] out of a possible score of 27. The studies with the highest quality scores were experimental designs with multiple trials completed.[25,26,29,30]

Immediate Clinical Outcomes from Passive Marijuana Smoke Exposure

Cannabinoids and cannabinoid metabolites in bodily fluids

Five reports from 3 studies assessed THC concentrations in oral fluid samples.[23,25,30-32] Eight reports from 6 studies assessed THC metabolite concentrations in blood,[18,20,21,24,25,28-30] and thirteen reports from 9 studies assessed THC metabolite concentrations in urine samples.[18-22,24,26-32] No direct relationship between the percent THC content in the smoked marijuana and THC metabolites in the urine was observed (Figure 2).[24,25,31]For example, four hours after exposure to marijuana with 1.5% THC, one of five passively exposed tested over the 20 ng/mL threshold for urine testing, while four hours after exposure to marijuana with 11.3% THC all exposed participants tested over 15 ng/mL, with a maximum 28.3 ng/mL concentration cannabinoid metabolites in the urine.[18,26]

Blood concentrations of THC were measured in eight reports from six studies.[18,20,21,24,25,28-30] Those passively exposed had lower blood concentrations of THC than active smokers;[18,24,25,30] however, there were detectable amounts of THC in the passive smoker's blood samples.[20,21,28,29] In one study, that used multiple trials to test marijuana of different percent THC content (5.3% and 11.3%), there were no significant differences in the blood concentrations of THC and THC metabolites between trial groups.[25]

Oral fluid concentrations of THC were reported in four reports from three studies.[23,25,31,32] All studies found THC in the oral fluid of individuals who had been passively exposed to marijuana smoke.[23,31,32]

Two studies conducted multiple trials in ventilated and unventilated environments.[25-27,30] The ventilation was manipulated through opening a door,[27] or by altering the air circulation rate of the ventilation-exhaust system in the room.[25,26,30] The results of these studies demonstrated that both urine THC metabolite concentrations and blood THC levels were higher in passive smokers in an unventilated environment when compared to a ventilated environment.[25-27,30] Other factors that mediated the effects of passive exposure included: air volume, number of passive inhalers, THC content, number of marijuana cigarettes lit, and number of active smokers.[25,26]

Psychoactive effects

Two studies reported the psychoactive effects reported by passive smokers; one study used a validated measure (the Drug Effect Questionnaire) [19] while the other study used a self-reported feeling of "high".[19,25] Passive smokers exposed to marijuana with higher THC content reported stronger drug effects (Figure 2).[19,25] The same trend was reported in active smokers; those who smoked marijuana with higher THC content reported feeling stronger drug effects.[19,25] These data indicate that passive and active smokers follow a similar pattern of intoxication; however, passive smokers consistently report weaker drug effects than active smokers.[25]

Other effects

In one study, passively exposed individuals reported discomfort and eye irritation due to smoke in the room.[26] During the experiment, all participants expressed discomfort.[26] As a result, active smokers ceased smoking when they would have continued.[26]

In-Vitro Outcomes of Exposure to Passive Marijuana Smoke

One study investigated the chemical composition, genotoxicity, and/or cytotoxicity of passive marijuana smoke compared to tobacco smoke in vitro.[33-35] The findings in these reports demonstrate that marijuana smoke is chemically similar to tobacco smoke, although with different quantitative makeup of chemical components.[33-35] For example, marijuana smoke had more ammonia, hydrogen cyanide, and select aromatic amines than comparative tobacco smoke, although these compounds were detected in both kinds of smoke.[35] Furthermore, a study by the same author found that marijuana smoke is more cytotoxic than tobacco smoke due to the significant difference in the levels of hydrogen cyanide and other chemicals when compared to tobacco smoke.[34]

Two reports from this study evaluated how concentrations of chemicals found in secondhand marijuana smoke, such as hydrogen cyanide and ammonia, interfere with cellular processes and compared the effects to those of tobacco smoke.[33,34] One study found that marijuana smoke is more cytotoxic and mutagenic than tobacco smoke.[33] The other study reported that secondhand marijuana smoke is more disruptive to the steroid biosynthesis, apoptosis, and inflammation pathways than secondhand tobacco smoke.[34]

DISCUSSION

Passive exposure to marijuana smoke can lead to cannabinoid metabolites in bodily fluids sufficient for positive results on urine, blood, and oral fluid testing and can lead to experiences of the psychoactive effects of marijuana among those passively exposed. There is evidence of a weak dose-response relationship between THC content of cannabis and effects on those passively exposed. There is evidence that the relationship that is mediated by environmental factors including whether the air space is ventilated, volume of air, number of marijuana cigarettes lit at one time, potency of the marijuana and number of smokers.

The simulated environments within some of the included studies may not represent "real world" scenarios. Some studies placed subjects in simulated environments where subjects were exposed to smoke in closed rooms with controlled ventilation systems. In the context of legalization, individuals may be passively exposed to secondhand marijuana smoke outside in parks or in passing on the sidewalk. This type of exposure may not result in cannabinoid metabolites in bodily fluids as the exposure may be of shorter time duration and less intense than in unventilated areas. However, exposure in closed spaces such as in cafés, bars, and clubs may occur depending on the regulations prohibiting smoking in indoor spaces. In addition, exposure in unventilated spaces, such as in a vehicle or a small room in a private home, is still likely to occur. Thus, the observed relationship between passive exposure and cannabinoid metabolites in bodily fluids is likely to be generalizable to real-world contexts. Particularly in the presence of children, the elderly, and those with respiratory illness, marijuana use in enclosed spaces should be limited, ideally through public health measures and legislation in those jurisdictions where marijuana is legalized.

In addition to protecting children, the elderly, and those with respiratory illness, in some domains mirroring public health legislation to protect workers and the general public from secondhand tobacco exposure will be appropriate. For example, bylaws forbidding smoking in indoor spaces such as bars, nightclubs and in shared outdoor spaces such as beaches or parks should be considered. As U.S. States develop their public policies to regulate marijuana consumption, tobacco frameworks may be useful to inform control regulation. Alignment of tobacco and marijuana smoking bylaws, with a coherent policy approach to exposures to smoke of any kind may result in the most effective public policies.

Evidence suggests that the chemical composition of secondhand marijuana smoke is similar to secondhand tobacco smoke although differences in the concentrations of the components vary.[33,34] However, no studies report the long-term health effects of passive exposure to marijuana smoke. Even in the absence of studies that report the long-term health effects of passive exposure, clinicians should assess the risk of passive exposure in their patients and advise marijuana users to limit their use to open outdoor spaces where regulations permit, similar to tobacco use.

Using levels of cannabinoid or THC metabolites found in blood or urine samples to determine marijuana use or intoxication is challenging. There is no universal threshold that can differentiate between those who have actively smoked marijuana and are intoxicated, those who have actively smoked marijuana in the past, and those who have been passively exposed. In many jurisdictions that have adopted thresholds for THC for drivers, 5.0 ng/ML for blood and 10 ng/ml are common thresholds to indicate intoxication. [36] These levels are present in those passively exposed 4-8 hours after passive exposure within the studies included in this review. This raises questions about whether there should be tolerance for individuals who produce positive urine tests and claim that it was due to passive it exposure.[37]

As more jurisdictions legalize marijuana for recreational use individuals may feel that use in common public areas or around children is acceptable and subsequently, harms associated with secondhand exposure may also increase. In the current state of the literature on passive exposure to marijuana, it is difficult for clinicians to prepare to engage in thorough assessments of marijuana exposure with patients, as they would with tobacco and for policymakers to make evidence-based decisions. Future research to inform the development of effective communication tools, prevention strategies, and policies to minimize harms to individual users and society is required.

Our systematic review did not identify any studies reporting the effects of passive exposure on long-term outcomes nor the effects of thirdhand smoke. In addition, none of the included studies investigate long-term exposure. Participants were not followed beyond the experiment, and it is not known how repeated exposure or one-time exposure to marijuana smoke may impact one's health. Given the known harms associated with active marijuana use such as mental illnesses, brain developmental changes, respiratory illnesses, and poor prenatal outcomes, the impact of passive exposure on long-term outcomes requires further study. These important areas will remain controversial. However, in the absence of evidence, based on the learnings from tobacco, a focus on harm reduction and limiting passive exposure may be prudent.

Limitation

One limit of the search strategy is that non-English and non-French studies were excluded, and the included studies were conducted primarily in Anglophone countries. Furthermore, the included records are limited in transferability due to small sample sizes and the homogeneity of the population studied. The body of literature assessing passive marijuana exposure employs an experimental study design that may not be generalizable more broadly. However, it is likely that under some regulatory conditions people will be passively exposed in similar ways to those of the trials enhancing the generalizability to the "real world".[37] Additionally, the study designs of included studies do not investigate effects in individuals who have been repeatedly exposed to passive marijuana smoke; all study participants were exposed for short periods of time. Exposure would likely be longer if individuals had been visiting with a friend of family where marijuana smoke was present.

CONCLUSIONS

Individuals retain THC metabolites in their bodies and report the experience of psychoactive effects after exposure to secondhand smoke. On a cellular level, marijuana smoke has similar chemical components to tobacco smoke, though they are present in different amounts. While these studies provide support for the biological plausibility for the relationship between secondhand marijuana exposure and negative health outcomes, there is a gap in the literature on the health outcomes from secondhand marijuana smoke exposure. If second hand exposure has similar health risks as direct marijuana use, it may be associated with conditions such as respiratory and cardiac diseases, as well as mental illness.[3,38] However, high-quality research on the long and short term health outcomes secondhand marijuana smoke are still required to confirm these possible risks. Given the current state of knowledge, coherent policy approaches to exposures to smoke of any kind may result in the most effective harm reduction policy.

REFERENCES

1. Hedden SL. *Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health.* 2015.
2. Schauer GL, King BA, Bunnell RE, Promoff G, McAfee TA. Toking, vaping, and eating for health or fun: Marijuana use patterns in adults, US, 2014. *American journal of preventive medicine.* 2016;50(1):1-8.
3. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med.* 2014;370(23):2219-2227.
4. National Cancer Institute, California Environmental Protection Agency. *Health effects of exposure to environmental tobacco smoke: the report of the California Environmental Protection Agency.* [Bethesda, Md.]: U.S. Dept. of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute; 1999.
5. Jinot J, Bayard S. Respiratory health effects of exposure to environmental tobacco smoke. *Reviews on environmental health.* 1996;11(3):89-100.
6. Simpson WJ. A preliminary report on cigarette smoking and the incidence of prematurity. *American journal of obstetrics and gynecology.* 1957;73(4):808-815.
7. Aligne CA, Stoddard JJ. Tobacco and children: an economic evaluation of the medical effects of parental smoking. *Archives of pediatrics & adolescent medicine.* 1997;151(7):648-653.
8. Courage CM, Tamburlini G, von Ehrenstein OS. *Environmental tobacco smoke.* Geneva, Switzerland: World Health Organization;2002.
9. Merriam-Webster.com. "secondhand smoke". 2016. Accessed September 15, 2016, 2016.
10. Hecht SS. Carcinogen derived biomarkers: applications in studies of human exposure to secondhand tobacco smoke. *Tob Control.* 2004;13(suppl 1):i48-i56.
11. Ferrante G, Simoni M, Cibella F, et al. Third-hand smoke exposure and health hazards in children. *Monaldi Arch Chest Dis.* 2015;79(1).
12. Becquemin M, Bertholon J, Bentayeb M, et al. Third-hand smoking: indoor measurements of concentration and sizes of cigarette smoke particles after resuspension. *Tob control.* 2010;19(4):347-348.
13. Rabin RC. A New Cigarette Hazard:'Third-Hand Smoke.'. *Retrieved January.* 2009;26:2012.
14. Deming D. The impact of second-hand tobacco smoke exposure on pregnancy outcomes, infant health, and the threat of third-hand smoke exposure to our environment and to our children. *Przeglad Lekarski.* 2012;69(10):717-720.
15. Acuff L, Fristoe K, Hamblen J, Smith M, Chen J. Third-hand smoke: old smoke, new concerns. *J Community Health.* 2016;41(3):680-687.
16. Wang X, Derakhshandeh R, Liu J, et al. One minute of marijuana secondhand smoke exposure substantially impairs vascular endothelial function. *Journal of the American Heart Association.* 2016;5(8):e003858.
17. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384.
18. Morland J, Bugge A, Steen A, et al. Cannabinoids in blood and urine after passive inhalation of cannabis smoke. *J Forensic Sci.* 1985;30(4):997-1002.
19. Zeidenberg. Marijuana intoxication by passive inhalation: Documentation by detection of urinary metabolites. *Am J Psychiatry.* 1977;134(1):76-77.
20. Röhrich J, Schimmel I, Zörntlein S, et al. Concentrations of Δ9-tetrahydrocannabinol and 11-nor-9-carboxytetrahydrocannabinol in blood and urine after passive exposure to cannabis smoke in a coffee shop. *J Anal Toxicol.* 2010;34(4):196-203.
21. Perez□Reyes M, Di Guiseppi S, Mason AP, Davis KH. Passive inhalation of marihuana smoke and urinary excretion of cannabinoids. *Clin Pharmacol Ther.* 1983;34(1):36-41.

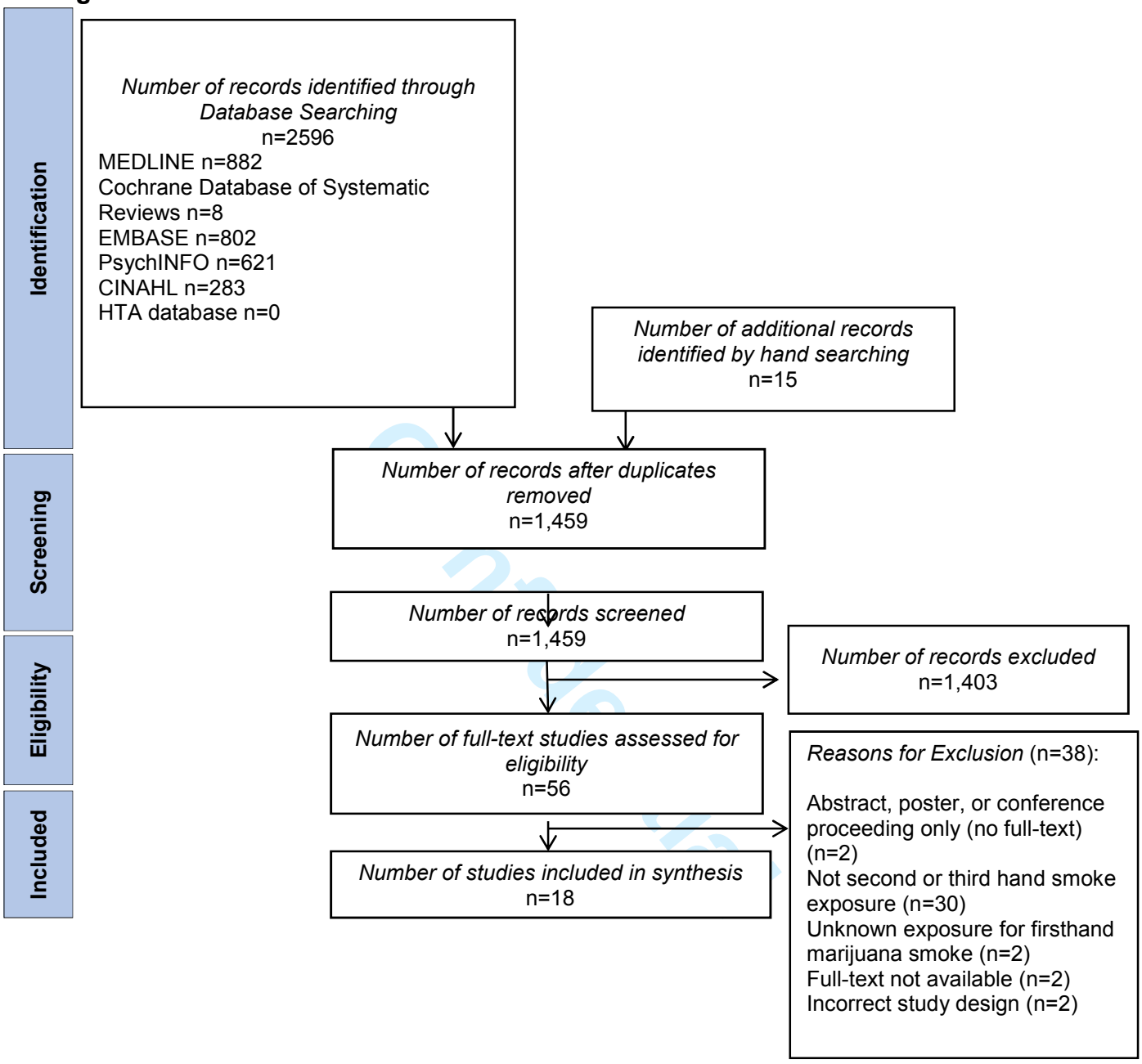
22. Mule S, Lomax P, Gross S. Active and Realistic Passive Marijuana Exposure Tested by Three Immunoassays and GCIMS in Urine. *J Anal Toxicol.* 1988;12(3):113-116.
23. Moore C, Coulter C, Uges D, et al. Cannabinoids in oral fluid following passive exposure to marijuana smoke. *Forensic science international.* 2011;212(1-3):227-230.
24. Law B, Mason PA, Moffat AC, King LJ, Marks V. Passive inhalation of cannabis smoke. *J Pharm Pharmacol.* 1984;36:578-581.
25. Cone EJ, Bigelow GE, Herrmann ES, et al. Nonsmoker Exposure to Secondhand Cannabis Smoke. III. Oral Fluid and Blood Drug Concentrations and Corresponding Subjective Effects. *J Anal Toxicol.* 2015;39(7):497-509.
26. Cone EJ, Bigelow GE, Herrmann ES, et al. Non-smoker exposure to secondhand cannabis smoke. I. Urine screening and confirmation results. *J Anal Toxicol.* 2015;39(1):1-12.
27. Cone EJ, Johnson RE, Darwin WD, et al. Passive inhalation of marijuana smoke: urinalysis and room air levels of delta-9-tetrahydrocannabinol. *J Anal Toxicol.* 1987;11(3):89-96.
28. Cone EJ, Roache JD, Johnson RE. Effects of Passive Exposure to Marijuana Smoke. Paper presented at: The Committee on Problems of Drug Dependence1986.
29. Cone EJ, Roache JD, Johnson RE. Effects of passive exposure to marijuana smoke. *NIDA Research Monograph Series.* 1986(76):150-156.
30. Herrmann ES, Cone EJ, Mitchell JM, et al. Non-smoker exposure to secondhand cannabis smoke II: Effect of room ventilation on the physiological, subjective, and behavioral/cognitive effects. *Drug Alcohol Depend.* 2015;151:194-202.
31. Niedbala RS, Kardos KW, Fritch DF, et al. Passive cannabis smoke exposure and oral fluid testing II. Two studies of extreme cannabis smoke exposure in a motor vehicle. *J Anal Toxicol.* 2005;29:607-615.
32. Niedbala RS, Kardos KW, Salamone S, Fritch DF, Bronsgeest M, Cone EJ. Passive cannabis smoke exposure and oral fluid testing. *J Anal Toxicol.* 2004;28:546-552.
33. Maertens RM, White PA, Rickert W, et al. The genotoxicity of mainstream and sidestream marijuana and tobacco smoke condensates. *Chem Res Toxicol.* 2009;22(8):1406-1414.
34. Maertens RM, White PA, Williams A, Yauk CL. A global toxicogenomic analysis investigating the mechanistic differences between tobacco and marijuana smoke condensates in vitro. *Toxicology.* 2013;308:60-73.
35. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol.* 2007;21(2):494-502.
36. Wong K, Brady JE, Li G. Establishing legal limits for driving under the influence of marijuana. *Injury Epidemiology.* 2014;1(1):26.
37. Hayden JW. Passive inhalation of marijuana smoke: A critical review. *J Subst Abuse.* 1991;3:85-90.
38. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet.* 2009;374(9698):1383-1391.

Figure Titles:

Figure 1. PRISMA Flow Chart of Identified Citations

Figure 2. Urine levels of THC metabolites and subjective effects in individuals passively exposed to marijuana smoke by percent THC content in an unventilated environment, four to eight hours' post-exposure. When more than 1 study reported a urine THC or psychological effect, estimates from each study are reported.

Figure 1. PRISMA Flow Chart of Identified Citations



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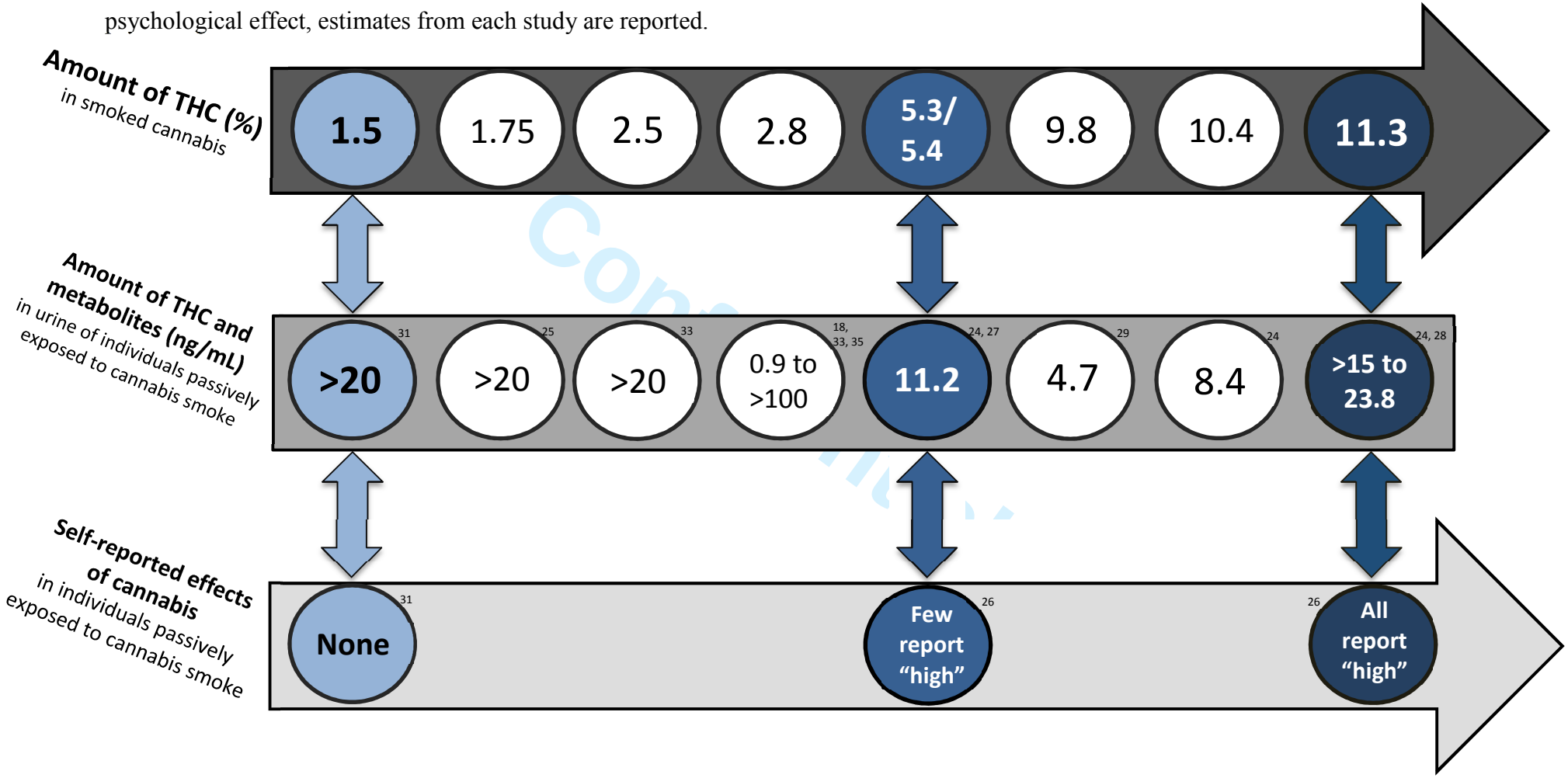

APPENDIX

Passive Marijuana Smoke and Health Impacts and Harms

Search Strategy

MEDLINE (882 abstracts)

1. Cannabis/ae, de, pd, po, to [Adverse Effects, Drug Effects, Pharmacology, Poisoning, Toxicity]

2. exp Marijuana Abuse/

3. 1 or 2

4. Tobacco Smoke Pollution/

5. exp Environmental Exposure/

6. (exposure or exposed or involuntary or passive or second hand or secondhand or thirdhand or third hand).tw,kw.

7. 4 or 5 or 6

8. 3 and 7

9. ((bhang or bhangs or bhangstar or cannabutter or cannabis* or doobie* or ganga or gangas or ganja or ganjas or grass or hash* or hashish* or hemp or hemps or honeycomb or mary jane* or marihuana* or marijuana* or moon rock or pot or reefer* or roach* or shatter or weed) adj3 (exposure or exposed or involuntary or passive or second hand or secondhand or thirdhand or third hand)).tw.

10. (addicted or addiction or adverse event* or adverse reaction* or behavioral or behavioural or birth defect* or blood pressure or cancer* or cogniti* or death* or dependenc* or developmental or (drug* adj3 interact*) or effect or effects or fetal or faetal or harm or harms or impact or impacts or impair* or lung or lungs or morbidit* or mortalit* or negative drug test* or oral fluid test* or outcome or outcomes or poison* or positive drug test* or psycho* or pulmonary or respiratory or risks or safety or (saliva adj3 (level* or test*)) or (urine adj3 (level* or test*)) or toxic*).tw.

11. 9 and 10

12. 8 or 11

13. limit 12 to (english or french)

14. limit 13 to (case reports or comment or editorial or letter)

15. 13 not 14

16. limit 15 to "review"

17. 15 not 16

18. limit 17 to (meta analysis or systematic reviews)

19. ((systematic or critical or scoping) adj3 (overview* or review* or synthesis)).tw.

20. 15 and 19

21. 17 or 18 or 20

eTable 1: Characteristics of Included Studies

Author, Year of Publication, Country	Intervention	Patient Selection	Number of Included Participants	Patient Characteristics	Reported Outcomes	Quality Assessment
Cone, 2015, United States	*Intervention*: Drug-free non-smokers were exposed to marijuana smoke from individuals smoking marijuana in a controlled environment laboratory over three sessions. The potency and ventilation of the environment was changed between each of the sessions. *Multiple trials:* (1) 5.3% THC in unventilated environment, (2) 11.3% THC in unventilated environment, (3) 11.3% THC in ventilated environment	*Participant Selection:* Participants recruited through newspaper ads, flyers posted on a university campus and around the community, and by word-of-mouth *Inclusion Criteria for smokers:* self-reported use of cannabis at least two times per week during the past 90 days and did not test positive for any other illicit substances *Inclusion Criteria for non-smokers:* Healthy individuals who self-reported lifetime cannabis use but had not used cannabis or any other illicit drugs in the past 6 months.	*Smokers:*6	NR	Oral fluid, whole blood, self-report of drug effects (Drug Effects Questionnaire – visual analogue scale)	22
			Non-smokers: 6	NR		
Cone, 2015, United States	*Intervention*: Drug-free non-smokers were exposed to marijuana smoke from individuals smoking marijuana in a controlled environment laboratory over three sessions. The potency and ventilation of the environment was changed between each of the sessions. *Multiple trials:* (1) 5.3% THC in unventilated environment, (2) 11.3% THC in unventilated environment, (3) 11.3% THC in ventilated environment	*Participant Selection:* Participants recruited through newspaper ads, flyers posted on a university campus and around the community, and by word-of-mouth *Inclusion Criteria for smokers:* self-reported use of cannabis at least two times per week during the past 90 days and did not test positive for any other illicit substances *Inclusion Criteria for non-smokers:* Healthy individuals who self-reported lifetime cannabis use but had not used cannabis or any other illicit drugs in the past 6 months.	*Smokers:*8	3 females, 5 males with an average age of 29 (SD 6) years, and an average BMI of 25.6 kg/m^2	Total cannabis use (weight), Urine analysis	22
			Non-smokers: 18	9 females, 9 males with an average age of 28 (SD 7) years, and an average BMI of 24.7 kg/m^2		
Cone, 1987, United States	*Intervention*: Individuals with drug-free urine samples were exposed to the smoke of marijuana cigarettes with 2.8% THC under double-blind conditions *Multiple trials*: 5 trials, 3 with 4 cigarettes (one ventilated, one not) and 2 with 16 cigarettes (all unventilated)	*Participant selection*: NR *Inclusion criteria for smokers*: NA *Inclusion criteria for non-smokers*: Healthy, drug-free subjects with history of marijuana use with 14 consecutive days of cannabinoid-free urine tests; two cannabis-naïve subjects who were members of the research team	*Smokers: 0*	NR	Room-air concentrations of THC, Urine analysis	20
			Non-smokers:7	All males, average age 36 years, average weight of 74.7 kg		
Cone, 1986, United States	*Intervention*: Individuals with drug-free urine samples were exposed to the smoke of marijuana cigarettes with 2.8% THC under double-blind conditions *Multiple trials*: 3 trials, one with 4 cigarettes and two with 16 cigarettes, one with five previous cannabis users and one with two cannabis-naïve subjects	*Participant selection*: NR *Inclusion criteria for smokers*: NA *Inclusion criteria for non-smokers*: Healthy, drug-free subjects with history of marijuana use with 14 consecutive days of cannabinoid-free urine tests; two cannabis-naïve subjects	*Smokers:* 0	NR	Urine analysis (EMIT 20, 100), whole blood analysis, pulse, blood pressure, Measured by subscales of the	22
			*Non-smokers:*7	All males, average age 36 years, average weight of 74.7 kg		

					Addiction Research Center Inventory, a single-dose questionnaire, and a visual analog scale	
Cone, 1986, United States	*Intervention*: Individuals with drug-free urine samples were exposed to the smoke of marijuana cigarettes with 2.8% THC under double-blind conditions *Multiple trials*: 3 trials, one with 4 cigarettes and two with 16 cigarettes, one with five previous cannabis users and one with two cannabis-naïve subjects	*Participant selection*: NR *Inclusion criteria for smokers*: NA *Inclusion criteria for non-smokers*: Healthy, drug-free subjects with history of marijuana use with 14 consecutive days of cannabinoid-free urine tests; two cannabis-naïve subjects	*Smokers: 0* *Non-smokers:7*	NR All males, average age 36 years, average weight of 74.7 kg	Urine analysis (EMIT 20, EMIT 100), whole blood analysis, Subscales of the Addiction Research Center Inventory: single-dose questionnaire, visual analog scale, circular lights task, digit-symbol substitution task	19
Herrmann, 2015, United States	*Intervention*: Drug-free non-smokers were exposed to marijuana smoke from individuals smoking marijuana in a controlled environment laboratory over three sessions. Unlimited marijuana was provided to smokers. *Multiple trials:* (1) 11.3% THC in unventilated environment, (2) 11.3% THC in ventilated environment (11 air-exchanges per hr)	*Participant Selection:* Participants were recruited from Baltimore, MD using media advertising and word-of-mouth *Inclusion Criteria for smokers:* 18-45 years old, use cannabis at least two times per week during the past 90 days, provide urine sample that is THC positive and negative for other drugs, negative breath alcohol reading at screening and day of session, BMI 19-34kg/m^2, not pregnant or nursing *Inclusion Criteria for non-smokers:* 18-45 years old, cannabis use at least once but not during the past 6 months, provided urine sample negative for all drugs, negative breath alcohol reading at screening and session, BMI 19-34kg/m^2, not pregnant or nursing	*Smokers: 7* *Non-smokers: 12*	4 males, 3 females with an average age of 29.4 (SD 5.8) and an average BMI of 25.6 kg/m^2 3 males, 3 females with an average age of 28.7 and an average BMI of 25.3 kg/m^2	Total weight of cannabis smoked. blood, urine, heart rate, blood pressure, Drug Effect Questionnaire, Divided attention task (DAS), digit symbol substitution task (DSST), paced auditory serial addition task (PASAT)	22
Law, 1984, United Kingdom	*Intervention*: Nonsmokers were exposed to marijuana smoke (9.8% THC) in a small, unventilated room *Multiple trials*: No *Timeline of exposure*: Smokers consumed their cannabis cigarette (which took 10 to 34 minutes), and then the nonsmoking participants remained in the room for three hrs	*Participant selection*: NR *Inclusion criteria for smokers*: NR *Inclusion criteria for non-smokers*: NR	*Smokers: 6* *Non-smokers:4*	*NR* *NR*	Gas-chromatography determined environmental exposure, Urine analysis, whole blood analysis (using radioimmunoassay)	13
Maertens, 2009, Canada	*Intervention*: Tobacco and marijuana cigarettes were combusted and sidestream and mainstream smoke was passed through a filter and the condensates were tested for genotoxicity (Salmonella mutagenicity) and cytotoxicity (THC not reported) *Multiple trials*: Two trials – one at 'standard' smoking	*NA*	*NA*	NA	Cytotoxicity, mutagenicity, concentration of bi-nucleoid cells	18

	conditions and the other at 'extreme' smoking conditions					
Maertens, 2013, Canada	*Intervention*: Tobacco and marijuana cigarettes were combusted and mainstream smoke was passed through a filter and the smoke condensates were collected (THC not reported) *Multiple trials*: One trial was conducted with tobacco and the other with marijuana	*NA*	*NA*	*NA*	Cytotoxicity, RNA extractions, microarray hybridization	17
Moir, 2007, Canada	*Intervention*: Combustion of cannabis cigarettes in a controlled environment and systematic comparison of the contents of both mainstream and side stream marijuana and tobacco smoke *Multiple trials*: No	*NA*	*NA*	*NA*	Quantify content of mainstream and side stream marijuana and tobacco smoke	16
Moore, 2011, United States	*Intervention*: Passive exposure to marijuana in a Dutch "coffee shop" *Multiple trials*: 2 trials in 2 different coffee shops, with varying numbers of active smokers (varying % THC)	*Participant selection*: Volunteers, selection strategy not reported *Inclusion criteria for smokers*: Any active smoker in the coffee shop during the 3-hr exposure timeline *Inclusion criteria for non-smokers*: Healthy non-marijuana smokers	*Smokers:* 16 in Trial 1, 6 in Trial 2	NR	Air cannabinoid content (Quantisal collection device), Oral fluid (Quantisal collection device)	19
			Non-smokers:10	5 males, average age 22.8 years, weight 84 kg, height 1.9 m, BMI 233; 5 females, average age 23.8 years, weight 62.4 kg, height 1.71 m, BMI 21.2		
Morland, 1985, Norway	*Intervention*: Subjects were exposed to marijuana and hashish smoke in a small, unventilated car *Multiple trials*: First trail with hashish (1.5% THC), second trial with marijuana (1.5% THC)	*Participant selection*: Volunteers, selection strategy not reported *Inclusion criteria for smokers*: Not reported *Inclusion criteria for non-smokers*: Healthy, cannabis naïve individuals	*Smokers: 5*	NR	Blood cannabinoid levels (RIA), urine analysis (EMIT)	16
			Non-smokers:10	7 males, 3 females "… of normal weight in relation to their height, age, and sex."		
Mule, 1988, United States	*Intervention*: In the first part of this experiment, smokers were asked to smoke cannabis as they usually do and observed. In the second part, non-smokers were exposed to four cannabis cigarettes (27 mg THC) in an unventilated room *Multiple trials*: No	*Participant selection*: Not reported *Inclusion criteria for smokers*: Occasional (1 cig/week) or moderate (1-3 cigs/week) smokers, *Inclusion criteria for non-smokers*: Not reported	*Smokers: 8*	All male, 5'9"-6'1" tall, weighed between 154-175 lbs, and were 21-27 years old	Urine analysis (EMIT)	18
			Non-smokers:3	*NR*		
Niedbala, 2005, United States	*Intervention*: Participants were placed in severe secondhand smoke conditions in an unventilated van for 1 hr *Multiple trials*: Two trials, each with four smokers and four passive inhalers. Trial 1 5.4% THC, and Trial 2 10.4% THC.	*Participant selection*: Volunteers, does not state recruitment strategy *Inclusion criteria for smokers*: Healthy, Caucasian males who reported infrequent cannabis use in the past *Inclusion criteria for non-smokers*: Healthy, Caucasian males who tested as cannabis-free prior to the study based on oral fluid, urine tests, and	*Smokers: 8*	18 to 24 years of age for both groups	Intercept collector pads, Oral fluid, urine analysis	16
			Non-smokers:8	34 to 50 years old for the first group, and 25 to 50 years old for		

		self-report data		the second group		
Niedbala, 2004, United States	*Intervention*: Participants sat in a sealed room, smokers consumed one cannabis cigarette each with an approximate THC level of 1.75% *Multiple trials*: No	*Participant selection*: Volunteers, does not state recruitment strategy *Inclusion criteria for smokers*: Healthy, caucasian males who reported prior infrequent use of cannabis *Inclusion criteria for non-smokers*: Healthy, caucasian males who tested as cannabis-free prior to the start of the study	*Smokers: 5* *Non-smokers: 4*	21 to 25 years old 37 to 49 years old	Air sample, Oral fluid analysis, urine analysis	15
Perez-Reyes, 1983, United States	*Intervention*: Four subjects smoked cannabis cigarettes in the presence of two non-smokers in both a room (Trials 1 & 3) and a car (Trial 2), biological samples were taken and compared between smoking and non-smoking groups. *Multiple trials*: Three; Trial 1 with two cigarettes with 2.5 and 2.8% THC, Trial 2 with two cigarettes with 2.8% THC, and Trial 3 with four cigarettes with 2.8% THC	*Participant selection*: Not reported *Inclusion criteria for smokers*: Experienced marijuana users *Inclusion criteria for non-smokers*: Marijuana-naïve subjects	*Smokers: 6* *Non-smokers: 6*	Three males, three females; "…healthy and of normal weight and height in relation to their age and sex." Three males, three females; "…healthy and of normal weight and height in relation to their age and sex."	THC presence in air, Urine analysis (EMIT), blood samples	16
Rohrich, 2010, Germany	*Intervention*: Individuals were exposed to marijuana smoke in a Dutch "coffee shop with ventilation (% THC not available) *Multiple trials*: No	*Participant selection*: NR *Inclusion criteria for smokers*: Active smoker in the coffee shop at the time *Inclusion criteria for non-smokers*: No history of cannabis use, and no contact with cannabis in the month proceeding the experiment	*Smokers:* 8 to 25 at one time *Non-smokers:* 8	*NR* 4 male, 4 female	Blood testing (Inspec), urine analysis (GC-MS)	15
Zeidenberg, 1977, United States	*Intervention*: A number of heavy marijuana smokers consumed cannabis around a placebo smoker in a locked ward (THC level not reported) *Multiple trials*: No	*Participant selection*: NR *Inclusion criteria for smokers*: NR *Inclusion criteria for non-smokers*: NR	*Smokers:* 5 *Non-smokers:* 1	NR *NR*	Urine analysis, Subjective reporting, physical exam	14

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

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