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Article *in* European Neuropsychopharmacology · March 2020

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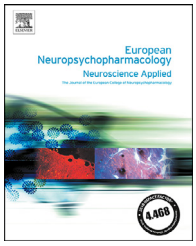

REVIEW

The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms

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Received 24 April 2019; accepted 17 February 2020
Available online xxx

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https://doi.org/10.1016/j.euroneuro.2020.02.003

Please cite this article as: E. Campeny, H. López-Pelayo and D. Nutt et al., The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.02.003

KEYWORDS
Cannabis;
Harms;
Risks;
Mental health;
Organic;
injury

Abstract
Cannabis is the third most used psychoactive substance worldwide. The legal status of cannabis is changing in many Western countries, while we have very limited knowledge of the public health impact of cannabis-related harms. There is a need for a summary of the evidence of harms and risks attributed to cannabis use, in order to inform the definition of cannabis risky use. We have conducted a systematic review of systematic reviews, aiming to define cannabis-related harms. We included systematic reviews published until July 2018 from six different databases and following the PRISMA guidelines. To assess study quality we applied the AMSTAR 2 tool. A total of 44 systematic reviews, including 1,053 different studies, were eligible for inclusion. Harm was categorized in three dimensions: mental health, somatic harm and physical injury (including mortality). Evidence shows a clear association between cannabis use and psychosis, affective disorders, anxiety, sleep disorders, cognitive failures, respiratory adverse events, cancer, cardiovascular outcomes, and gastrointestinal disorders. Moreover, cannabis use is a risk factor for motor vehicle collision, suicidal behavior and partner and child violence. Cannabis use is a risk factor for several medical conditions and negative social consequences. There is still little data on the dose-dependency of these effects; evidence that is essential in order to define, from a public health perspective, what can be considered risky use of cannabis. This definition should be based on quantitative and qualitative criteria that informs and permits the evaluation of current approaches to a regulated cannabis market.

1. Introduction

Cannabis is the third most prevalent psychoactive substance worldwide, only after alcohol and tobacco. The annual global estimated prevalence of cannabis use, during the last 12 months, is about 3.9%, meaning that a total of approximately 192 million people aged between 15 and 64 years have used cannabis in 2016 (United Nations Office on Drugs and Crime, 2018).

Cannabis legislative frameworks are evolving worldwide. As of November 2017, medical use, and consequently, production and sale of cannabis is allowed in Australia, Canada, Chile, Colombia, Germany, Israel, Jamaica, The Netherlands, Peru, and in 29 US states (Abuhasira et al, 2018). The recreational use of cannabis has been approved in eight states of the USA, plus the District of Columbia, Uruguay and Canada, which means that new frameworks for controlling the production, distribution and sale of cannabis have been put in place (Government of Canada, 2018). In countries like Spain, Belgium and The Netherlands, cannabis has an ambiguous legal situation and laws concerning production, distribution and sale are not settled yet (United Nations Office on Drugs and Crime, 2018).

These legal changes reflect in part a social perception of decreased risks associated to cannabis (United Nations Office of Drugs and Crime, 2017). In Western countries, and regardless of its legal situation, risk perception of cannabis use is closer to that of alcohol and tobacco than to illicit drugs such as cocaine or heroin. This could contribute to higher cannabis use prevalence (Parker and Anthony, 2018) and in fact, the prevalence of cannabis use in these countries is much closer to alcohol and tobacco than to illegal drugs (United Nations Office on Drugs and Crime, 2018).

Such high prevalence and low social risk perception point to the need to develop secondary prevention strategies aiming at the early identification of risky cannabis users (Casajuana et al., 2016). However, an appropriate identification of 'risky use' is still needed, since the literature on the harms associated to cannabis use is scarce and often inconclusive, not discriminating for instance between different types of marijuana (mixed delta-9THC/cannabidiol, mixtures from "skunk"). Narrative and systematic reviews have been conducted on several dimensions of cannabis related harm (Hall, 2015; "WHO | Cannabis," 2010). More specifically, the American Academies of Science report summarizes the evidence regarding multiple health effects of cannabis and cannabinoid use (National Academies of Sciences, Engineering, 2017). Nevertheless, a global view from a public health perspective is still lacking (Fischer et al/, n.d.).

Hence, the aim of this work is to systematically review all systematic reviews on cannabis related harms, as a first step in the assessment of global risks associated to cannabis use, which in the end should inform the definition of cannabis risky use.

2. Experimental procedures

This systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). This protocol provides a checklist for reporting systematic reviews (Table 1). The study protocol was registered with PROSPERO (registration number: CRD42018089130).

2.1. Search strategy

An electronic search was made in Science Direct (1823 - July 2018), Medline (1950 - July 2018), EBM Reviews-Cochrane Database of Systematic Reviews (2005 - July 2018), EBM Reviews - ACP Journal Club (1991 - July 2018), and EBM Reviews-Cochrane Central Register of Controlled Trials (1991 - July 2018). The search was split into six core concepts, for an explanatory purpose: a) social: social, economy, absenteeism, learning; b) organic: disease, disturbances, "organic pathology"; c) mental health: "psychiatric disorder", "mental health"; d) injury: injury, violence, traffic;

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Table 1 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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
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.	4
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.	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
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).	4
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.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
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.	-
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	-
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.	-
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).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
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.	5-11
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.	5-11
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).	-
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.	-
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-

(*continued on next page*)

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Table 1 (*continued*)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
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).	12-15
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.	15
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.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

e) mortality: mortality, hospitalization, morbidity; f) somatic: chronic, pathology*, "health impact*", infect*, cancer, circulat*, respirat*, pulm*, gastro*, bronch*, pregnan*, prenatal, HIV, skin. A combination of the following key words was used with every core concept: cannabis, marihuana, delta 9-tetrahydrocannabinol, risk, harm, consequences, "systematic review" and meta-analysis.

A secondary search was performed, by reviewing reference lists in order to find additional relevant studies.

2.2. Selection criteria

Full systematic reviews and meta-analyses of studies examining harms, risks and consequences of cannabis use up to July 2018, were eligible for inclusion. Exclusion criteria were: Animal studies, laboratory and neuroimaging studies, synthetic cannabinoid studies, studies based on proving the beneficial effects of cannabinoids, studies based on proving the efficacy of treatments and interventions, studies based on proving the efficacy of cannabis use identification. No languages restrictions were applied.

2.3. Data extraction and quality assessments

EC and HL-P searched the articles and independently screened titles and abstracts of retrieved studies for eligibility. Both reviewers met afterward to discuss inclusion/exclusion of the articles; any disagreement was discussed together with two senior researchers (MB and AG). From the selected systematic reviews and meta-analysis the following information was extracted: authors, year of publication, aims, number of papers, number of subjects included, type of studies, age range, gender, pattern of cannabis use, outcomes and limitations.

To assess study quality, two researchers applied the AMSTAR 2 tool "assessment of multiple systematic reviews", for randomized and non-randomized systematic reviews of healthcare interventions (Shea et al., 2017). In case of doubts or discrepancy in any item, an agreement between both researchers was achieved.

All reported results are statistically significant unless otherwise specified.

3. Results

We found 6,725 unique entries of systematic reviews and meta-analyses. Finally, 44 publications were included (Fig. 1). The results of the quality assessment indicated an AMSTAR 2 average of 60.1% affirmative punctuation.

The six dimensions previously included for the search strategy resulted in three domains: 1) mental health (Table 2); 2) somatic (Table 3); 3) injury and mortality (Table 4). Main results are synthesized in Table 5.

3.1. Mental health harms

Nineteen systematic reviews were included, with an average quality of 65.1% (AMSTAR 2). Reviews included the following outcomes: psychosis, affective disorders, anxiety disorders, pathological gambling, personality disorders and cannabis dependence.

3.1.1. Psychosis (number of systematic reviews and meta-analyses: 10)

Multiple studies have revealed a clear relationship between cannabis consumption and psychotic symptoms. The risk for developing schizophrenia (OR 3.9 CI95% 2.84-5.34) and other psychotic disorders (OR 5.07 CI95% 3.62-7.09) is higher among heavy cannabis users, compared to non-users (Marconi et al., 2016a). Psychotic symptoms are attributed to cannabis use in different forms: using cannabis at least five times per month (OR 2.2 CI95% 1.5-3.3), up to fifty times per month (OR 3.1 CI95% 1.7-5.5), using cannabis before 15 years old (OR=4.5, CI 95% 1.1-18.2), and heavy cannabis use (OR 3.59 CI95% 2.42-5.32) (Le Bec et al., 2009; Marconi et al., 2016a). The risk of psychotic disorders is increased by gene-environment interaction (e.g. with variants of COMT 158Val and DRD2 rs1076560 T) (Misiak et al., 2017). Evidence is still unclear concerning lifetime cannabis use (vs.

Table 2 Mental health harms.

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Twomey, C. D. (2017)	Anxiety	Association of cannabis use with the development of elevated anxiety symptoms in the general population	10 longitudinal studies	75%	58538 (general population) Up to 12 years old	Use vs. Non-use (7/10) Regular use vs. non regular use (1/10) Daily /weekly/ occasional use vs. no use (1/10) Maturing-out/late-onset/chronic users vs. non-users or low-users (1/10)	Cannabis use associated with anxiety, small OR of 1.15 (95% CI 1.03-1.29) and minimal heterogeneity (I2= 23%). High-quality studies (k=5) decreased the OR to a non-significant level of 1,04 (95% CI 0.97-1.19; I2 = 0%)., as did adjusting for publication bias displayed in the funnel plot (OR=1,08; 95% CI 0.94-1.23). Studies operationalizing the exposure as cannabis use/non use (k=7) rather than frequency of cannabis use yielded a non-significant OR of 1,09 (95% CI 0.97-1.24; I2=18%). Studies measuring the outcome of anxiety using diagnosis (k=6) yielded a non-significant OR of 1,08 (95% CI 0.96-1.21; I2=0%).
Large, M. et al. (2011)	Psychosis	To establish the extent to which use of cannabis, alcohol, and other psychoactive substances affects the age onset of psychosis.	89 papers/83 cohort studies	75%	**41**/131 samples of the mean age at onset of psychosis in substance-using and non-substance-using individuals with psychotic disorder. Comprised to **8167** substance-using patients and non-substance using.	Cannabis-using Non cannabis-using	The age at onset of psychosis was 2.70 earlier among samples of cannabis users (CI 95%; −0.526 to −0.301).

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Table 2 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Moore, T., et al. (2007)	Psychosis and affective disorders	The relation between cannabis use and subsequent psychotic or affective mental health outcomes.	35 longitudinal studies: 11 psychosis 24 affective outcomes	78.1%	-	Cannabis use	There is an increased risk of any psychotic outcomes in individuals who had ever used cannabis (pooled adjusted OR= 1.41 95% CI 1.20-2.84). Consistent with a dose-response effect, with greater risk in people who used cannabis most frequently (2.09, 1.54 to 2.84). Cannabis frequent use and depression: 95% CI, OR 1.49 (1.15-1.94). For suicidal ideation according to cannabis exposure: 4.55 (1.37 to 15.11). Anxiety outcomes according to cannabis exposure: 1.40 (0.96 to 2.04).
Kraan, T., et al. (2016)	Psychosis	Association between cannabis use and transition to psychosis in ultra-high risk (UHR) samples	7 prospective studies	56.3%	1171 subjects 12-35 years old	Cannabis users vs. non-users	Lifetime cannabis use and transition to psychosis: 1.143 (0.86 to 1.52) 95% CI. Cannabis abuse/dependence and transition to psychosis: 1.754 (1.14 to 2.71) 95% CI.
Marconi, A., et al. (2016)	Psychosis	Association between the extent of cannabis consumption and psychosis-related outcomes.	10 studies: 6 prospective cohorts; 3 cross sectional; 1 case-control	87.5%	66.816 individuals	Review	A consistent increase in the risk of psychosis-related outcomes with higher levels of cannabis exposure in all the included studies (I2=82%). An OR of 3.90 (2.84 to 5.34) for the risk of schizophrenia and other psychosis outcomes among the most severe cannabis users compared to the nonusers. The pooled OR for presence of psychotic symptoms was 3.59 (2.42 to 5.32) and for a diagnosis of schizophrenia or psychotic disorder was 5.07 (3.62 to 7.09).

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Table 2 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Cairns, K. E., et al. (2014)	Depression	Identify risk and protective factors for depression during adolescence that are modifiable by the young person.	113 publications: 15 studies for cannabis use	78.1%	12-18 years old	Cannabis use: the extent to which the adolescent engages in use of cannabis (in any form).	Cannabis use in adolescence was found to be associated with higher levels of depression. A small but significant size emerged (r=0.118(0.068 to 0.168), with substantial heterogeneity evident (I2=81%). A subgroup analysis by gender revealed a significant interaction, with larger effect size estimates for those studies (n=2) with female samples (p=0.003).
Linscott, R. J., et al. (2013)	Psychosis	Epidemiological evidence on psychotic experiences in children and adults.	61 cohorts*	37.5%	-	-	Cannabis use and prevalence of psychotic experiences: 2.51 (1.84 to 3.43). Cannabis use and incidence of psychotic experiences: 1.77 (1.20 to 2.61).
Large, M., et al. (2014)	Psychosis	Outcomes associated with psychosis and co-morbid substance use.	22 articles*: 11 cross-sectional; 9 longitudinal; 1 patients readmitted within 1 year	78.1%	3302 subjects: 1879 current substance use	Current substance use vs. no substance use.	Positive symptoms and cannabis use (95% CI): 0.38 (−0.02 to 0.78). Negative symptoms and cannabis use (95% CI): 0.07 (-0.24 to 0.38). Depressive symptoms and cannabis use 95% CI: -0.10 (-0.71 to 0.51). Social function and cannabis use (95% CI): -0.20 (-0.56 to 0.16).
Lev-Ran, S., et al. (2014)	Depression	To establish the extent to which different patterns of cannabis use are associated with the development of depression.	14 longitudinal studies	78.1%	76058 subjects Up to 12 years old	Cannabis use (includes any use); Heavy cannabis use (at least one per week)	Heavy cannabis users & develop of depression: OR 1.62 (95% CI 1.21 to 2.16), compared with non-users or light-users. Cannabis users developing depression: OR 1.17 (95% CI 1.05 to 1.30), compared to controls.

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Table 2 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Marangoni, C., et al. (2016)	Bipolar disorder	The role of the environmental exposures as risk factors for bipolar disorder.	**3**/22 longitudinal studies, for cannabis ue.	57.7%	39872: 1849 exposed/cases; 38023 not exposed/controls	-	Study 1: aOR 4.98 (1.80 to 13.81) $p<0.01$ for any use; aOR 8.93 (2.77 to 28.82) $p<0.001$ for 1-4 times/week use. Study 2: OR 2.12 (1.10 to 4.08) $p<0.05$. Study 3: aOR 2.47 (1.03 to 5.92) $p<0.05$ for weekly to almost daily use.
Ruiz-Veguilla, M., et al. (2012)	Psychosis	Neurological soft signs in patients with psychosis and cannabis use	5 cross-sectional studies	68.8%	284 subjects Cases: 92 Controls: 80 Not specified: 112 Mean ages: 29.9, 26.3, 26.9	No consumer, consumer, cannabis use abuser (DSM-IV); Abuse/dependence (DSM-IV); Daily cannabis user (CIDI).	Psyc_Cann+ showed fewer total NSS: Standardized mean difference calculated was 0.46 (95% CI= -0.07 to 0.98). However this difference was not statistically significant ($p>0.05$).
Misiak, B., et al. (2017)		Interactions between genetic variation in candidate genes and environmental factors in patients with schizophrenia spectrum phenotypes and Bipolar Disorder.	62 studies: 21 cannabis use 3 substance abuse	61.5%	**113517 subjects**: 112462 subjects with cannabis use 1055 subjects with substance abuse Adolescents and adults	Cannabis use; Cannabis intake; Lifetime cannabis use (DSM-IV); Cannabis abuse or dependence (DIGS).	Gene x environment interaction that affects on certain individuals with several alleles (for instance, COMT 158Val and DRD2 rs1076560 T) in combination with cannabis use, leading to increased risk of psychosis (schizophrenia and schizophreniform disorder, early onset of psychosis)

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Table 2 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Szoke, A., et al. (2014)	Psychosis	Identify studies that explored the association between cannabis use and psychometric schizotypy and synthetize the results using meta-analytical tools.	29 cross-sectional studies (longitudinal)	81.3%	Ever vs. never use: N ever: 17408 subjects N never: 15087 subjects Current users vs. non-current users: Current: 4120 subjects Non-current: 3143 subjects.	Ever vs. never use Current users vs. non-current users	Life-time use vs. Never use: total (includes positive and negative symptoms and disorganization) CI 95% 0.42 (0.34 to 0.51). Current use vs. Not current use: total (positive and negative symptoms and disorganization) CI 95% 0.21 (0.14 to 0.29). Life-time use vs. Never use: Positive 0.44 (0.32 to 0.57). Current use vs. Not current use: Positive 0.23 (0.15 to 0.31). Life-time use vs. Never use: Negative 0.18 (0.15 to 0.21). Current use vs. Not current use: Negative 0.10 (0.04 to 0.23). Life-time use vs. Never use: Disorganization 0.33 (0.27 to 0.40). Current use vs. Not current use: Disorganization 0.17 (0.15 to 0.37).
Le Bec, P. Y., et al. (2008)	Psychosis	Examine the evidence that cannabis use causes chronic psychotic disorders by using established criteria of causality.	7 prospective cohorts	42.3%	50.275 subjects Up to 11 years old, except two studies that contemplate subjects since the day they were born.	No consensus. (times per month, times per year, frequency of consumption)	Association between cannabis use at least five times per month and psychotic symptoms OR=2.2 (95% CI 1.5 to 3.3). Association between cannabis use up to 50 times OR=3.1 (95% CI 1.7 to 5.5) and cannabis use before 15 years old OR=4.5 (95% CI 1.1 to 18.2) with psychotic symptoms.

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Table 2 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Dowling, N. A., et al. (2017)	Pathological gambling	Identify early risk and protective factors longitudinally associated with the subsequent development of gambling problems.	2/17 longitudinal studies for cannabis	90.6%	- Age average: from 3-21 years at the first evaluation; From 17-39 years at the final evaluation.	-	Cannabis use displayed a small effect size with subsequent problem gambling. There was no heterogeneity in effect size estimates between associations and no significant publication bias. Sensivity analyses suggested that these results are robust to the inclusion of articles using non-standardized measures of problem gambling and adjusted data.
Bouso, J.C., et al. (2018)	Personality disorders	Analyze the relationship between personality and administration of psychedelics/ hallucinogens drugs	18 observational studies	61.5%			Authors did not find clear results referred to isolated cannabis use.
Schlossarek, S., et al. (2016)	Cannabis depen-dence	To identify recent findings regarding psychosocial determinants of cannabis dependence and to summarize them systematically	26 cross-sectional and longitudinal studies	53.8%	Up to 13 years old.	No consensus (daily, frequently, weekly)	The most consistent predictive factors of cannabis dependence were an early onset of cannabis use (at the age of 11–15 years), frequent use, positive psychotropic effect of cannabis, use independent from social contexts and prior drug involvement.
Zammit, S., et al. (2008)	Psychosis	To systematically review the evidence pertaining to whether cannabis affects outcome of psychotic disorders	12 longitudinal studies	69.2%	Not specified	No consensus (regular use, misuse vs. non-misuse, use)	Cannabis use is associated with increased relapse or rehospitalization, decreased treatment adherence and co-occurring cannabis and tobacco users have greater psychiatric severity.

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Table 2 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Peters, E. N., et al. (2012)	Cannabis dependence and drug use	To highlight the clinical needs of co-occurring users and consider whether future interventions ought to be modified to meet these needs	28 cross-sectional and longitudinal studies	57.7%	Adolescents and adults	No consensus (lifetime use, adolescence use, cannabis use, cannabis and tobacco co-occurring use)	Lifetime cannabis and tobacco co-occurring use (CT) is associated with cannabis abuse or dependence and nicotine dependence. Adolescent CT is associated with cannabis (20-24 years) and nicotine (23-27 years) dependence, decreased life satisfaction, fewer years of education and increased depressive symptoms in adulthood. CT is associated with withdrawal syndrome (depressed mood, headaches, sweating/heart-racing, nausea, yawning), anxiety symptoms, fewer years of education, greater psychiatric severity, more legal problems and more likely to have been drunk in the previous 30 days.

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Table 3 Somatic risks.

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Martinasek, M., et al. (2016)	Respiratory	Inhalational effects of inhalational cannabis.	48 articles: 5 case control; 10 cohort studies; 7 cross-sectional; 13 case studies; 5 experimental studies; 1 longitudinal study; 1 retrospective study; 1 secondary analysis.	25%	17.902 subjects Up to 15 years old, except one case study → 13 months	-	There is a risk of lung cancer from inhalational marijuana, an association between inhalational marijuana and spontaneous pneumothorax, bullous emphysema, and chronic obstructive pulmonary disease. A variety of symptoms have been reported by inhalational marijuana smokers, including wheezing, shortness of breath, altered pulmonary function tests, cough, phlegm production, bronchodilation and other symptoms.
Broyd et al. (2016)	Cognition	Effects of cannabis use in human cognition.	105 articles	28.1%	- -	-	Cognitive effects of cannabis exposure are plagued with heterogeneity of both the extent of cannabis exposure in the samples assessed and the instruments of assessing cognitive function. Memory function is the most consistently impaired cognitive domain affected by cannabis. Cannabis-related attentional impairment may reflect residual effects that dissipate gradually as cannabinoids are cleared from the body. Psychomotor function is affected by acute intoxication and that this likely persists for some time after chronic cannabis exposure.

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Table 3 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
							Executive function subdomains are differentially affected by acute administration and chronic exposure to cannabis. Despite a large number of studies of chronic users in the past decade, the extent to which these effects persist in chronic or abstinent users on decision making, reward processing and delay discounting remains unclear.
Wang, T., et al. (2008)	Gastrointestinal and Nervous System	Adverse events related to the medical use of cannabis	31 articles: 23 randomized controlled trials; 8 observational studies.	81.3%	1932 exposed to cannabinoid exposure; 1209 control groups 18-78 years old	From 18 hours - 37 weeks duration of exposure	The rate of non-serious adverse events was higher among participants assigned to medical cannabinoids than among controls (rate ratio [RR] 1.86, 95% confidence interval [CI] 1.57–2.21). The rates of serious adverse events did not differ significantly between these 2 groups (RR 1.04, 95% CI 0.78–1.39). Of the 164 serious adverse events, the most common was relapse of multiple sclerosis (21 events [12.8%]), vomiting (16 events [9.8%]) and urinary tract infection (15 events [9.1%]). Dizziness was the most commonly reported non-serious adverse event (714 events [15.5%]) among people exposed to cannabinoids.

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Table 3 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Kennedy, M. C. (2017)	Cardiovascular	Affectation of cannabis use in exercise performance and sport.	14 articles	15.6%	- 19-59 years old	THC: 7 mg to 20 mg 30-60 mg Cannabis per week: 3.7g +- 0.82g Hashish per week: 15-30 g Joints per day: 5.9 +- 3.1	None showed any improvement in aerobic performance. Exercise induced asthma was shown to be inhibited. Two studies found that marijuana precipitated angina at a lower work-load (100% of subjects) and strength is probably reduced. Relevant to drug testing was that aerobic exercise was shown to cause only very small rises (<1 ng/mL) in THC concentrations.
de Carvalho, M. F. F., et al. (2015)	Cancer	Relationship between marijuana users and the development of head and neck cancer.	6 articles from 9 case control studies.	65.6%	Cases: 5732 Controls: 8199 Up to 15 years old	-	The meta-analysis found no association between exposure and disease (OR = 1.021; IC 95% = 0.912-1.14; p = 0.718). Approximately 12.6% of cases and 14.3% of controls were marijuana users. Despite this evidence, the association of HNC in marijuana users has not been proven even in studies that control for tobacco use.
Nugent. S.M., et al. (2017)	Cognition	Long-term physical and mental health effects of cannabis use in chronic pain and general patient populations (We only focus on harms)	75 articles: **Harms** → 43 publications: 11 systematic reviews, 32 observational studies.	84.4%	- -	-	Limited evidence on the potential benefits and harms of cannabis use in chronic pain populations. Moderate-strength evidence that light to moderate cannabis smoking does not adversely affect lung function over about 20 years. Cannabis use has potentially serious mental health and adverse cognitive effects, although data are insufficient to characterize the magnitude of risk. Exist little methodologically rigorous evidence examines cannabis effects in patients with chronic pain.

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Table 3 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Gurney, J., et al. (2015)	Cancer	Find if there are associations between cannabis exposure and testicular germ cell tumor (TGCT) development	3 case-control articles	81.3%	Cases: 719 Controls: 1419 Up to 18 years old	Ever-use Current use Weekly use >10 years	In terms of overall association, our meta-analysis was inconclusive regarding the association between ever-use of cannabis and development of TGCT (pooled odds ratio [OR], ever-use compared with never use): 1.19, 95 % CI 0.72–1.95), and for the association of former use with TGCT (OR: 1.54, 95 % CI 0.84–2.85). Current use of cannabis increased the odds of TGCT development by 62 % (OR: 1.62, 95 % CI 1.13–2.31). Frequency of cannabis was associated with TGCT development, with weekly (or greater) use appearing to nearly doubling the odds of TGCT development (OR: 1.92, 95 % CI 1.35–2.72). Association between the duration of cannabis use (> = 10 years vs. never use) and TGCT development (OR: 1.50, 95 % CI 1.08–2.09). There was insufficient evidence to conclude that cannabis use was associated with seminoma development. There was evidence of an association be- tween cannabis use and non-seminoma development - with current use more than doubling the odds of tumor development (OR: 2.09, 95 % CI 1.29–3.37). Frequency of use was also strongly associated with non-seminoma development, with those using cannabis on at least a weekly basis having two and a half times greater odds of tumor development compared those who never used cannabis

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Table 3 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Carrigan, N., et al. (2016)	Cognition	Determine whether or not there is a relationship between cognitive failures and different psychological disorders or substance use, and how this relates to objective cognitive outcomes.	21 studies: 2 for cannabis use 2 for polydrug use	15.6%	61 subjects cannabis use 85 subjects polydrug use -	Cannabis use Polydrug use	Daily smoking and alcohol dependence seemed to be associated with increased cognitive failures. Cannabis seemed to have a small detrimental effect on everyday cognition.
Jouanjus, E., et al. (2017)	Cardiovascular	Cardiovascular risk related to the use of cannabis-based products.	115 studies: 29 observational studies 81 case report 3 clinical trials 2 experimental studies	43.8%	24.999 subjects -	Cannabis-based products: **THC**, Sativex, Dronabinol, Nabilone.	An association between exposure to cannabis-based products and cardiovascular disease. This evidence is stronger for ischemic strokes than for any other cardiovascular diseases. Tachycardia and hypertension were often reported.
Macleod, J., et al. (2004)	Social harm	Psychological and social sequelae of cannabis and other illicit drugs use	48 prospective studies	73.1%	89.097 subjects (some studies follow-up is not reported). Up to 15 years old	Any use Weekly use Use on more than 50 occasions Daily use	Cannabis use was consistently associated with reduced educational attainment (substantial strength and magnitude). Cannabis use was consistently associated with use of other drugs (substantial strength and magnitude). Cannabis use was inconsistently associated neither with psychological problems nor with antisocial or otherwise problematic behavior.

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Table 3 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Gates, P. J., et al. (2014)	Nervous System	The effects of cannabinoid administration on slep	39 studies: 11 studies for cannabis administration	59.4%	230 subjects for cannabis use Up to 18 years old	Cannabis use: Use as usual; Unclear dose, reaching as use until "reaching a subjective high"; % mg of THC per 1g joint; 0.7-1.4, 2.5-10, 15, 20, 30, 200, 300 mg THC (oral dose)	Cannabinoid use among recreational users: may interrupt the normal cycles of sleep e particularly SWS sleep, and does not appear to consistently cause any significant change to the time spent asleep or the number of night time awakenings, but may leave an impression of non- restful sleep. Cannabinoid use among users with a medical condition known to disturb sleep: shows some consistency across studies of improved sleep via reduced night time disturbances, although the majority of these studies do not include psychometrically validated measures, and shows relatively inconsistent effects on sleep among studies with objective measures.
Ruisch, I., et al. (2018)	Maternal and fetal health	Highly prevalent and preventable maternal substance use during pregnancy including the use of cigarettes, alcohol, cannabis, and caffeine, and offspring risk of conduct problems.	3/36 longitudinal studies for cannabis use.	81.3%	1684 subjects: 421 cases 1263 controls -	Cannabis use	Present meta-analytic results comprised only three available about THC studies and did not indicate an overall association between cannabis use during pregnancy and offspring conduct problems. OR = 1.29 (95%-CI 0.93–1.81; I2 = 0; three studies). The only available confounder-adjusted data did not reveal a significant association and, moreover, it was suggested by the authors that their unadjusted results may reflect differences in parental tolerance for problem behavior instead of true offspring behavioral differences (O'Connell and Fried, 1991). Odds ratios (ORs) were 2.06 (1.67–2.54, 25 studies) for maternal smoking and OR = 2.11 (1.42–3.15, 9 studies) for alcohol use.

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Table 3 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Bogaty, S., et al. (2018)	Cognition	Evaluate the cognitive differences between cannabis never-using patients and patients who currently use cannabis.	14 studies	50%	1430 subjects Mean age: 15-45 years old	Cannabis users vs. never-using	Cannabis user (CANN+) performed worse on several cognitive domains compared to Never-using cannabis (CANN-). Premorbid IQ reported poorer performance for CANN+ (g=-.40, 95% CI [-0.59- -0.20]. Current IQ reported poorer performance for CANN+ (g=-.17, 95% CI [-0.34- -0.00]. Working Memory reported poorer performance for CANN+ (g=-.76, 95% CI [-1.30- -0.22]. CANN+ outperformed CANN- in tests of conceptual set-shifting. The association between age and performance in CANN+ cognition was varied, with older age predictive of worse performance in processing speed, sustained attention, verbal memory, and better performance in verbal learning and very fluency.
Ghasemiesfe, M., et al. (2018)	Respiratory	To examine the association between marijuana use and respiratory symptoms, pulmonary function and obstructive lung disease.	22 studies: 10 prospective studies 12 cross-sectional studies	87.5%	671 subjects (adolescents and adults)	Current use, Moderate to heavy use	Wheezing (OR 2.011.3 CI95% 1.50-21.706), cough (OR 1.73 CI95% 1.21-2.47), chronic sputum production (OR 1.53 CI95% 1.08-2.18) are associated to current marijuana smoking. Moderate to heavy marijuana smoking is associated with cough (OR 4.37 CI95% 1.71-11.19), sputum production (OR 3.40 CI95% 1.99-5.79), wheezing (OR 2.83 CI95% 1.89-4.23) and dyspnea (OR 1.56 CI95% 1.33-1.83).

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Table 3 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Irner, T.B. (2012)	Maternal and fetal health	To identify relevant published data on adolescents who have been exposed in utero to alcohol and/or other substances and to examine developmental consequences across functions and mental health at this point in life.	25 cross-sectional and longitudinal studies	30.8%	Subjects aged between 4 - 51 years old	Marijuana exposure	Cognitive functioning and behavioral disturbances are the most significant effects due to maternal marijuana use.
Ganzer, F., et al. (2016)	Cognition	To investigate long-term effects of cannabis use after a prolonged duration of abstinence.	38 cross-sectional and longitudinal studies	87.5%	-	Regular consumption of cannabis or marijuana, and at least 14 days of abstinence.	Cannabis use, even after a time of abstinence, impairs attention and conctentration (r= .273, 95%CI .109 to .423). Motor function remains impaired even after a time of abstinence (r=.478, 95%CI .394 to .555). Memory and learning also remain impaired after a time of abstinence (r=0.229, 95%CI .130 to .323).

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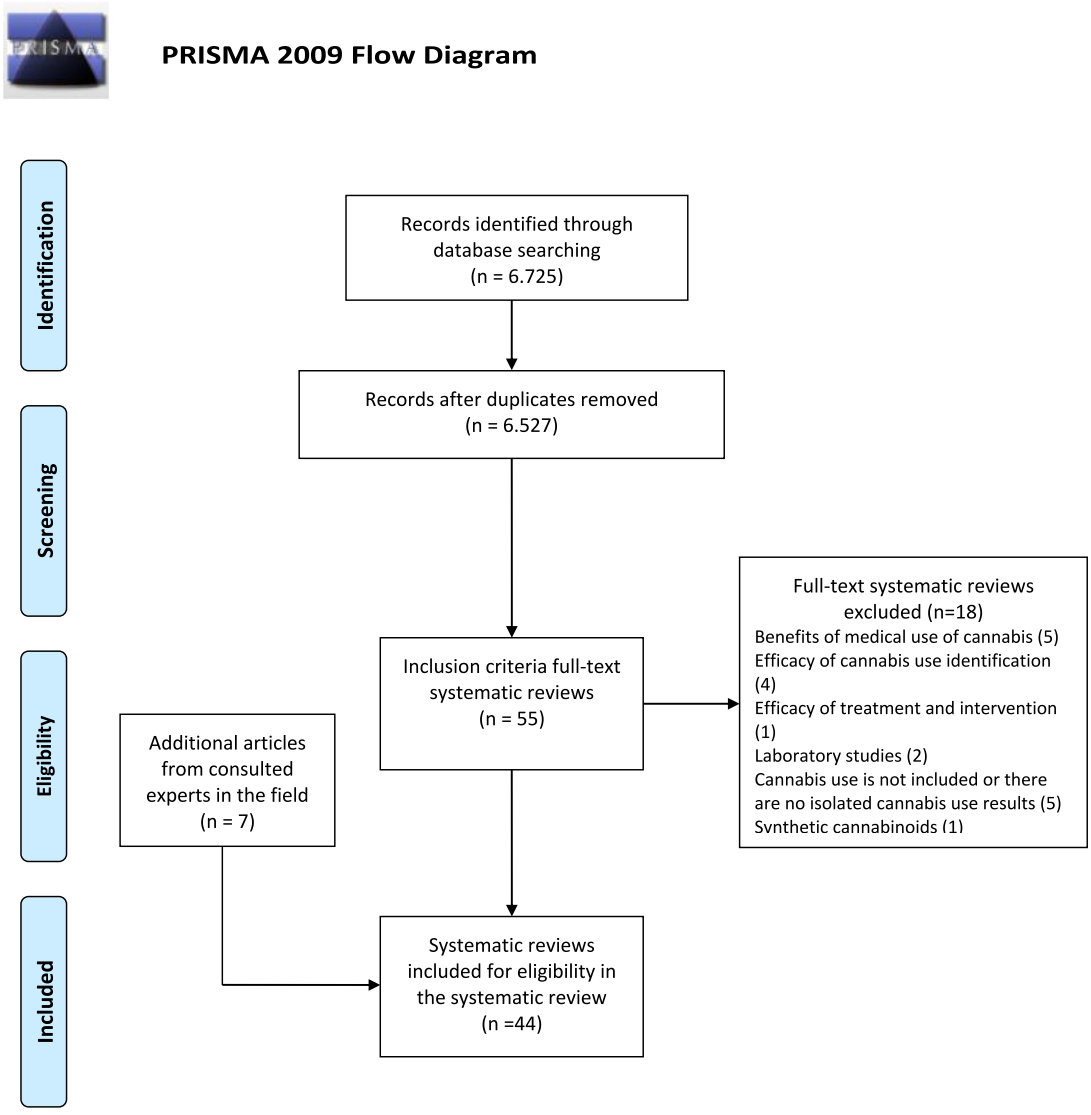

Fig. 1 PRISMA 2009 flow diagram. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

no use) and incidence of psychosis: OR 1.41 CI95% 1.20-2.84 (Moore et al., 2007), OR 1.14 CI95% 0.86-1.52 (Kraan et al., 2016). The association between cannabis use and transitioning to a first episode of psychosis is well documented. Cannabis use has an impact on incidence (OR1.77 CI95% 1.20-2.61) and prevalence (OR2.51 CI95% 1.84-3.43) of psychotic experiences (Linscott and van Os, 2013). Moreover, age at onset of psychosis is 2.7 years earlier for cannabis users (95% CI, −0.526 to −0.301) (Large et al., 2011).

Evidence supports that cannabis use worsens psychosis prognosis. Smoking cannabis is related with fewer total neurological soft signs, defined as minor neurological abnormalities in sensory and motor performance (OR 0.46 CI95% 0.07-0.98) (Ruiz-Veguilla et al., 2012). Moreover, not using cannabis is considered a protective factor on positive (OR 0.42 CI95% 0.34-0.51) and negative symptoms (OR 0.18 CI95% 0.15-0.21) and disorganization (OR 0.33 CI95% 0.27-0.40) (Szoke et al., 2014). In addition, cannabis use is associated with an increased risk of relapse or rehospitalization and lower treatment adherence; although the authors did not provide specific measures of this association (Zammit et al., 2008).

Only one review did not find an association between cannabis use and psychosis. This could be due to that nearly all the reviewed studies had a cross-sectional design and the few longitudinal studies included had limited sample sizes (Large et al., 2014).

3.1.2. Affective disorders (number of systematic reviews and meta-analyses: 4)

Several studies have suggested that cannabis consumption may represent a risk factor for depression (OR 1.17 CI95% 1.05-1.30) (Lev-Ran et al., 2014), mainly after long-term and heavy consumption (at least one joint per week or DSM-IV Cannabis Use Disorder) (OR 1.49 CI95% 1.15-1.94) (Moore et al., 2007) (OR 1.62 CI95% 1.21-2.16)

Table 4 Injury and mortality risks.

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Kuhns, J. B., et al. (2009)	Violence	To synthesize the results of marijuana, cocaine and opiate drug toxicology studies of homicide victims and examine variation in the results across person and setting characteristics.	19 papers: 8/18 independent studies for marihuana use (cross-sectional)	53.1%	16.298 subjects Minors and adults	-	Marijuana toxicology with a range of 0–34%. The random effects mean was 6% [95% confidence interval (CI) = 2–17%, Q (test of homogeneity) = 290.76, df = 7, P < 0.00005]. Positive relationship between proportion testing positive and year of data. For marijuana and cocaine the relationship was small, positive and statistically significant (B = 0.16, Z = 2.40, P = 0.016, n = 13; B = 0.16, Z = 3.55, P = 0.00046, n = 26). A strong curvilinear relationship with the highest toxicology levels occurring during early to middle adulthood. For marijuana the highest toxicology level was for the age category 20–29 (40%). The highest percentage testing positive was: +25 (33%), 30-34, 20-29 and 25-34 category age. Geographic region. Marijuana: United States (7%, [2%-19%, 95% CI]) Other (5%, [1%-30%, 95% CI].
Asbridge, M., et al. (2012)	Traffic events	To determine whether the acute consumption of cannabis (THC) by drivers increases the risk of a motor vehicle collision.	9 observational studies	78.1%	49.411 subjects -	Most studies used 1ng/ml of cannabis or any amount greater than zero as the cutoff for a positive test result with one study using a 2ng/ml cutoff and another using only self-report.	Cannabis was associated with a significantly increased risk of collisions compared with unimpaired driving (OR 1.92 [95% CI 1.35 to 2.73]; P=0.0003). Heterogeneity among the individual study (I =81). Collision risk estimates were higher in case-control studies (OR 2.79 [95% CI 1.23 to 6.33)] P=0.01) and studies of fatal collisions (OR 2.10 [95% CI 1.31 to 3.36]; P=0.002) than in culpability studies (OR 1.65 [95% CI 1.11 to 2.46]; P=0.07) and studies of non-fatal collisions (OR 1.74 [95% CI 0.88 to 3.46]; P=0.11).

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Table 4 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Elvik, R. (2013)	Traffic events	Risk of road accident associated with the use of drugs.	28/66 cross-sectional and longitudinal studies for cannabis use	56.3%	- -	-	Use of drugs while driving tends to have a larger effect on the risk of fatal and serious injury accidents than on the risk of less serious accidents (usually property damage-only accidents). Cannabis and Property damage (OR 1.26 [95% CI, 1.10-1.44].
Hostiuc, S., et al. (2018)	Traffic events	Analyze whether there is a significant association between DUIC (driving under the influence of cannabis) and UTEs (unfavorable traffic events).	24 cross-sectional studies	62.5%	245.779: Controls reported: 31.536 (no data from 6 studies). -	THC blood analysis over 0.5ng/ml (in 3 studies)	Exist significant increases in the effect size for DUIC (driving under the influence of cannabis) tested through blood analysis: odds ratio (OR) of 2.27 and a confidence interval (CI) between 1.36 and 3.80. Death as an outcome, with an OR of 1.56 and a CI between 1.16 and 2.09. Case–control as the type of study, with an OR of 1.99 and a CI between 1.05 and 3.80. Publication bias was very high.
Choenni, V., et al. (2017)	Violence	Association between alcohol and illicit drug use and the perpetration of intimate partner violence (IPV) and child maltreatment (CM).	14/96 cross-sectional studies for cannabis use	12.5%	- -	Cannabis use	IPV perpetration is often associated with cannabis and cocaine use. Studies on the association between illicit drug use and CM are scarce. Studies on overall illicit drug use imply that there is an association with CM. There is some evidence that both stimulants and depressants are associated with CM perpetration.

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Table 4 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Calabria, B., et al. (2010)	Mortality	To review the literature on mortality among people who use cannabis. All-cause mortality, motor vehicle accidents, cancer and suicidal behaviors.	19 cross-sectional and longitudinal studies	21.9%	- -	"Heavy" use: >50 times or >10 joints-years and Weekly use "Light" use: Ever use, less than weekly and any detection of THC.	There is insufficient evidence to assess whether the all-cause mortality rate is elevated among cannabis users in the general population. Case–control studies suggest some association between 'heavy' cannabis users and respiratory and brain cancers and responsibility in fatal motor vehicle accidents. The evidence is as yet unclear as to whether cannabis use increases the risk of suicide. Indirect effects of cannabis use and associated mortality may also exist.
Borges, G., et al. (2016)	Suicide	To review the epidemiological literature on acute and chronic effects of cannabis on suicidality (ideation, attempt and death).	23 longitudinal studies	59.4%	Adolescents Adults	Distinguishes between acute (consumed on a specific occasion and its acute consequences) and chronic use (cannabis use patterns, symptoms of cannabis use disorder and heavy cannabis use).	Cannabis use & suicide ideation: OR=1.43 (1.13 to 1.83). Heavy cannabis use & suicide ideation: OR=2.53 (1.00 to 6.39). Cannabis use & suicide attempt OR=2.23 (1.24 to 4.00). Heavy cannabis use & suicide attempt OR=3.20 (1.72 to 5.94).

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Table 4 (*continued*)

Authors and year of publication	Area	Aim	Number of included papers and type of studies	AMSTAR 2 affirmative punctuation (%)	Number of study subjects and age range	Pattern of use	Results
Li, M. C., et al (2012)	Traffic events	To assess the association between marijuana use and crash risk	2 cross-sectional, 5 case control, 2 cohort design	78.1%	93.200: Drivers up to 15 years old	Marijuana use	All studies except one reported statistically significantly increased risk of crash involvement associated with marijuana use. The summary odds ratio estimated from the random-effects model was 2.66 (95% CI, 2.07-3.41). Two studies provided data for assessing the dose response relation between marijuana use and crash risk. Brault, et al., found that the risk of crash involvement increased progressively with the concentration of 11-nor-9-carboxy-THC (THC-COOH); relative to that for drivers testing negative for the substance, the estimated odds ratios of crash involvement were 1.1 (95% confidence interval: 0.5, 2.6) for those with low THC-COOH concentrations in their urine, 1.8 (95% confidence interval: 1.0, 3.5) for those with medium THC-COOH concentrations, and 3.3 (95% confidence interval: 1.9, 5.9) for those with high THCCOOH concentrations. Fergusson and Horwood (70) found that the risk of crash involvement increased significantly as self-reported frequency of marijuana use in the past year increased.
Coentre, R., et al. (2017)	Depression and suicidal behavior	To assess rate of depressive symptoms and suicidal behavior and to search for the most relevant demographic and clinical factors associated	Prospective	50%	Mean age 28.94	Cannabis use	Prevalence of Suicide attempts: 10,83%; Suicide: 1,51%. Greatest suicide risk was found during the month before and 2 months after first contact; Severity of depressive symptoms and cannabis use are predominant risk factors across time.

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Table 5 Main results.

Main affectations of cannabis use	
Mental health	Psychosis (incidence, early onset, larger effects)
	Affective disorders (development of depression, suicidal ideation, development of bipolar disorder)
	Anxiety (development of anxiety symptoms and higher anxiety outcomes)
Organic/somatic	Respiratory (pneumothorax, emphysema, chronic obstructive pulmonary disease)
	Cancer (lung cancer and testicular germ cell tumor)
	Cardiovascular (tachycardia, hypertension)
	Sport (lower work-load and strength)
	Gastrointestinal (vomiting and diarrhea)
	Nervous system (dizziness, exacerbation of multiple scleroses, non-restful sleep)
	Cognitive (memory, psychomotor function, executive function, deleterious effect, sustained attention and educational attainment)
Injury	Suicidal behavior (ideation and attempt)
	Violence (intimate partner violence and child maltreatment)
	Motor vehicle collision

(Lev-Ran et al., 2014). One study found that cannabis use in any form is associated with higher levels of depression (correlation coefficient r 0.118 CI95% 0.068-0.168) (Cairns et al., 2014) and that co-occurring cannabis and tobacco use in adolescence is associated with increased depressive symptoms in adulthood and decreased life satisfaction, but the authors did not provide specific measures of the association (Peters et al., 2012).

Any use of cannabis has been associated with bipolar disorder (OR 4.98 CI95% 1.80-13.81) (Marangoni et al., 2016). One study found that frequent cannabis use increases the risk of bipolar disorders: 1-4 times of cannabis use per week (OR 8.93 CI95% 2.77-28.82). Another study found that daily use increases the risk for bipolar disorder (OR 2.47 CI95% 1.03-5.92) (Marangoni et al., 2016). Moreover, one study found that cannabis abuse and dependence are risk factors for the development of bipolar disorder (OR 2.12 CI95% 1.10-4.08) (Marangoni et al., 2016).

3.1.3. Anxiety disorders (number of systematic reviews: 3)

Evidence supports that cannabis use is linked with the development of anxiety symptoms in general population (OR 1.15 CI95% 1.03-1.29) (Twomey, 2017), and also when there is co-occurrence of cannabis and tobacco use; although the authors did not provide specific measures of the association (Peters et al., 2012). Moreover, cannabis use is a risk factor for anxiety disorders (OR 2.90 CI95% 1.11-7.57) (Moore et al., 2007).

3.1.4. Pathological gambling (number of systematic reviews: 1)

The relationship between cannabis use and problem gambling remains still unclear. However, evidence supports that cannabis use is one of the multiple risk factors related with problem gambling (Dowling et al., 2017).

3.1.5. Personality disorders (number of systematic reviews: 1)

The association of cannabis use and personality disorders has been scarcely studied and up to date results are inconclusive (Bouso et al., 2018).

3.1.6. Cannabis dependence (number of systematic reviews: 2)

Daily and weekly cannabis use, early onset of use (11-15 years) and positive psychotropic effects of cannabis are predictive factors of cannabis dependence, although the authors did not provide specific measures of association (Schlossarek et al., 2016). Moreover, adolescence co-occurring cannabis and tobacco use are associated with cannabis abuse or dependence at age 24 (OR 27; CI not specified), and nicotine dependence between 23 and 27 years old (OR 1.89; CI not specified). In addition, co-occurring cannabis and tobacco users are more likely to report cannabis withdrawal syndrome symptoms, including depressed mood, headaches, sweating/heart-racing, nausea and yawning; the authors however did not provide specific measures of the association (Peters et al., 2012).

Co-occurring cannabis and tobacco users presented a lower mean of continuous cannabis abstinence during treatment compared to current dependent cannabis users who never smoked cigarettes (2.8 weeks of abstinence vs. 3.7 weeks) or were ex-cigarette smokers (2.8 weeks of abstinence vs. 5.6 weeks) (Peters et al., 2012).

3.2. Organic/somatic risks

Seventeen systematic reviews were included, with a Quality average (AMSTAR 2) of 56.5% affirmative punctuation. Reviews included the following outcomes: respiratory effects, cancer, gastrointestinal alterations, cardiovascular impairment, nervous system disorders, cognitive impairment, sleep disturbances, motor coordination and postnatal consequences.

3.2.1. Respiratory effects (number of systematic reviews and meta-analyses: 3)

There is evidence of a respiratory harm attributable to marihuana smoking. There is an increased risk of lung cancer ranging between 8% and 410% due to the use of inhalational marihuana (after adjusting for confounding factors); being such ample range a result of the heterogeneity of samples and study designs. Besides, inhalational marihuana has an

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impact on the development of spontaneous pneumothorax, bullous emphysema, bronchodilatation and chronic obstructive pulmonary disease. Moreover, a variety of symptoms are associated to current marijuana smoking including wheezing (OR 2.01 CI95% 1.50-2.70), shortness of breath, cough (OR 1.73 CI95% 1.21-2.47), phlegm production and chronic sputum production (OR 1.53 CI95% 1.08-2.18) (Ghasemiesfe et al., 2018; Martinasek et al., 2016). Moderate to heavy marijuana smoking is associated with cough (OR 4.37 CI95% 1.71-11.19), sputum production (OR 3.40 CI95% 1.99-5.79), wheezing (OR 2.83 CI95% 1.89-4.23) and dyspnea (OR 1.56 CI95% 1.33-1.83) (Ghasemiesfe et al., 2018).

Only one review did not find any adverse effect on lung function due to inhalational cannabis use (Nugent et al., 2017).

3.2.2. Cancer (number of systematic reviews and meta-analyses: 2)

Evidence supports that cannabis use has an impact on testicular germ cell tumor (TGCT) development. Cannabis use up to 10 years (OR 1.50 CI95% 1.08-2.09), as well as using it weekly or more often (OR 1.92 CI95% 1.35-2.72), has an impact on TGCT development. More specifically, current cannabis use, defined as using at least on a weekly basis, is a risk factor for non-seminoma development (OR 2.09 CI95% 1.29-3.37) (OR 2.59 CI95% 1.60-4.19) (Gurney et al., 2015).

At the present time, there is no evidence of a relationship between cannabis use and head and neck cancer development (OR 1.021 CI 95% 0.912-1.14; $p = 0.718$) (de Carvalho et al., 2015).

3.2.3. Cardiovascular (number of systematic reviews and meta-analyses: 2)

It is claimed that cannabis use increases the risk for cardiovascular diseases, particularly ischemic strokes (OR 2.68 CI95% 1.03-6.99), hemorrhagic strokes (OR 1.18 CI95% 1.12-1.24), ischemic heart disease (OR 4.8 CI95% 2.9-9.5) and thromboangiitis obliterans (TAO) (OR 3.5 CI95% 1.08-5.08) (Jouanjus et al., 2017).

Marihuana precipitates angina at a lower work-load and probably reduces subject's strength. Also aerobic exercise causes small rises in THC concentrations (<1 ng/mL) (Kennedy, 2017).

3.2.4. Gastrointestinal (number of systematic reviews and meta-analyses: 1)

Intensive vomiting and persistent diarrhea are the most prevalent side effects associated to medical use of cannabis (Wang et al., 2008).

3.2.5. Nervous system (number of systematic reviews and meta-analyses: 2)

Dizziness (15.5%) and relapse of multiple scleroses (12.8%) in patients with this disorder are the most common side effects reported in medical cannabis use (Wang et al., 2008).

Recreational use of cannabis accounts for non-restful sleep, and may particularly interrupt slow wave sleep (Gates et al., 2014).

3.2.6. Cognitive impairment (number of systematic reviews and meta-analyses: 6)

There is enough evidence to endorse the claim of a negative impact of cannabis use on cognition, even after the person is no longer acutely intoxicated ("stoned") by cannabis use. Memory is the most consistently impaired cognitive domain (g = -0.761 CI95% −1.30 to −0.22) (Bogaty et al., 2018). Moreover, cannabis use leads to cognitive adverse effects on multiple aspects of cognition. Cannabis use has detrimental effects on everyday cognition and reduces educational attainment (OR 5.6 95%CI 2.0-1.5) (Macleod et al., 2004), leading to memory and learning deficits ($r = 0.229$, 95%CI 0.130-0.323) (Bogaty et al., 2018; Broyd et al., 2016; Carrigan and Barkus, 2016; Ganzer et al., 2016). Chronic cannabis use alters psychomotor (r= 0.478, 95%CI 0.394-0.555), executive functions (Broyd et al., 2016), attention and concentration ($r = 0.273$, 95%CI 0.109-0.423) (Ganzer et al., 2016). Adolescent co-occurring cannabis and tobacco use is associated with fewer years of education, although the authors did not provide specific measures of the association (Peters et al., 2012).

Evidence supports that an older age of users is predictive of worse performance in processing speed, sustained attention and verbal memory (Bogaty et al., 2018).

3.2.7. Maternal-fetal health (number of systematic reviews and meta-analyses: 2)

Cognitive functioning and behavioral disturbances are the most significant outcomes of impairment due to maternal marijuana use, although the authors did not provide specific measures of the association (Irner, 2012).

The other systematic review is inconclusive regarding the impact of maternal cannabis use on offspring behavior (OR 1.29 CI95% 0.93-1.81; I2 = 0) (Ruisch et al., 2018).

3.3. Injury risks and social consequences

Ten systematic reviews were eligible for the injury dimension and had a quality average of 52.4% affirmative punctuation. Reviews included the following outcomes: impact on suicidal behavior and mortality, intimate partner violence, child maltreatment, motor vehicle collision.

3.3.1. Suicidal behavior (number of systematic reviews and meta-analyses: 3)

Cannabis use has an impact on suicidal behavior. Suicidal ideation and suicide attempts are linked to cannabis use (OR 1.43 CI95% 1.13-1.83) (OR 2.23 CI95% 1.24-4.00). Moreover, depressive symptoms and cannabis use are predominant risk factors for suicide commitment (Coentre et al., 2017). In addition, heavy cannabis use is associated with higher risk of suicide ideation (OR 2.53 CI95% 1.00-6.39) and attempt (OR 3.20 CI95% 1.72-5.94) (Borges et al., 2016). Suicidal ideation is also linked to frequent use (OR=4.55, 95% CI 1.37-15.11) (Moore et al., 2007).

Association of cannabis use and other forms of mortality has been scarcely studied and up to date results are inconclusive (Calabria et al., 2010).

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3.3.2. Violence (number of systematic reviews and meta-analyses: 3)

There is evidence of a relationship between cannabis use and violence. Cannabis use is reported to be associated with intimate partner violence and child maltreatment perpetration, but effect sizes are not provided (Choenni et al., 2017). Moreover, there is a relationship (small, positive and statistically significant) between cannabis use and being a victim of homicide as 6% of them tested positive on marihuana use (CI95% 2–17%) (Kuhns et al., 2009). In addition, co-occurring cannabis and tobacco users have more legal problems and are more likely to have been drunk in the previous 30 days, although these results did not differ from tobacco users. Authors did not provide specific measures of association (Peters et al., 2012).

3.3.3. Motor vehicle collision (number of systematic reviews and meta-analyses: 5)

Evidence clearly supports an association between cannabis use and risk of collision (OR 1.92 CI95% 1.35–2.73). Being considered responsible of the collision (OR 1.65 CI95% 1.11–2.46; $p = 0.07$), non-fatal collisions (OR 1.74 CI95% 0.88–3.46; $p = 0.11$), becoming involved in an accident (OR 2.66 CI95% 2.07–3.41) and increased crash risk (OR 1.92 CI95% 1.35–2.73) are attributable to cannabis use (Asbridge et al., 2012; Elvik, 2013; Li et al., 2012). Fatal collisions are also associated to cannabis use (OR 2.10 CI95% 1.31–3.36) (OR 1.56 CI95% 1.16–2.09) (Elvik, 2013; Hostiuc et al., 2018). Moreover, heavy cannabis use (>50 times by age 18 years, or >10 joints per week) has also an impact on fatal motor vehicle accidents (Calabria et al., 2010).

4. Discussion

This systematic review aimed to identify the impact of cannabis use on different health outcomes in order to generate a global picture of cannabis-related harms. We identified 44 systematic reviews, which included 1,053 articles covering a broad spectrum of negative health outcomes directly linked to cannabis use. However, some difficulties arise when pulling together the results.

Frequency and more particularly quantity of cannabis used are usually vaguely defined. More specifically, there is no consensus on the definition of heavy use and in some cases this variable is not even defined or specified (Borges et al., 2016; Ghasemiesfe et al., 2018; Marconi et al., 2016b; Peters et al., 2012). The revised evidence does not discriminate either between the different types of marijuana (mixed delta-9THC/cannabidiol, mixtures from “skunk”). Patterns of use are not clearly described, and tobacco and alcohol are often confounding factors difficult to isolate. Moreover, the quality of most of the systematic reviews is between low and moderate according to AMSTAR 2 (60.1% affirmative punctuation). Moreover, according to AMSTAR 2, the quality of the reviews varies quite dramatically within the 3 studied domains. Mental health reviews have the highest quality average (65.1%) and scores range between 37.5% and 87.5% (Table 2); reviews included in the organic domain have a quality average of 56.5% and scores range between 81.3% in the case of gastrointestinal disorders and 25% for respiratory problems (Table 3). Injury has the lowest quality average (52.4%), and scores range from 12.5% to 78.1%, with higher quality scores found in studies linking cannabis use to traffic accidents and social sequelae (Table 4). These results compel us to interpret the following conclusions with caution.

Moreover, causal inference is difficult to demonstrate in observational studies of environmental risk factors (Rothman and Greenland, 2005; Vandenbroucke et al., 2016). Despite this, we have screened for those systematic reviews with at least a 70% AMSTAR quality and we have searched for Mendelian Randomization studies (MR). In case there weren’t, the Bradford Hill criterions for causality were applied (Bradford et al., 1965). MR uses genetic variants to determine whether an observational association between a risk factor and an outcome is consistent with a causal effect. Remarkably, these studies are of great importance given their high level of evidence. In line with this, MR showed a strong impact of cannabis use on psychotic disorders (Gage et al., 2017; Vaucher et al., 2018), and a causal relationship between cannabis use and alcohol use and tobacco smoking (Verweij et al., 2018).

According to the Bradford Hill criterions, 11 associated outcomes (anxiety, depression, cognition, TGCT, respiratory outcomes, non-serious adverse events, lung cancer, motor vehicle collision, suicidal ideation, educational attainment and other drugs use) were found (strength), and had at least one longitudinal study that found association (temporality). Then, six of the previous eleven outcomes (motor vehicle collisions, suicidal ideation, anxiety, depression, educational attainment and respiratory outcomes) had two or more prospective studies that support association to cannabis use (consistency).

Regarding these last six final outcomes, we can affirm that there is a causal relationship, since the following Bradford Hill criteria were met: dose-response, plausibility, coherence and experiment (Table 6). Cannabis use effects were comparable with those of tobacco (combustion) and alcohol (cognitive impairment). The criteria of specificity may be hard to reach in this field since cannabis use is often mixed with tobacco, alcohol and other psychoactive substances. Focusing on the mental health domain, we have found a causal association for psychosis, anxiety and depression. In line with these outcomes, several studies have reaffirmed that adolescent cannabis use has a strong impact on psychosis and incidence of schizophrenia (Di Forti et al., 2019; Hall and Degenhardt, 2009; Hjorthoj et al., 2018; Shahzade et al., 2018; Volkow et al., 2016). Recent studies reported that higher levels of cannabis use increase the risk for developing major depression and bipolar disorder, as well as for maintaining high levels of anxiety over time (Jacqueline Duperrouzel et al., 2018; Rasic et al., 2013).

We have found a causal association for lower educational attainment and respiratory outcomes. Additional evidence supports these outcomes, showing that regular cannabis smokers are more prone to report chronic bronchitis and increased respiratory infections (Hall and Degenhardt, 2009; Shahzade et al., 2018). More recent studies report a significant association between marijuana use and respiratory diseases, lung cancer and chronic obstructive pulmonary disease (Berthiller et al., 2008; José Miguel Chatkin et al., 2017). Additionally, reviewed evidence shows that chronic

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Table 6 Causality assessment.

	Strength (Odds Ratio, CI95%)	Temporality (num. cohort studies)	Consistency (Odds Ratio and CI95% prospective studies)	Dose-response	Plausibility	Coherence	Experiment
Anxiety disorder	2.90 (1.11-7.57)[15]	3[15].	Colombia: 1.48 (1.10-2.00); ECA: 2.90 (1.11-7.57); NY State: 1.16 (1.00-1.35)[15]	A biphasic effects of 9-THC on anxiety (lower doses generally being anxiolytic and higher doses being anxiogenic)[87].	Effect of 9-THC on amygdala activation, which play a key role in the processing of fear[87].	Yes**	In a sample of healthy male subjects, a pure, synthetic i.v. preparation of THC elicited anxiety[88].
Depression	CU: 1.17 (1.05-1.30)[15]. HCU: 1.49 (1.15-1.94)[24]; 1.62 (1.21-2.16)[24]. CU in any form: r* = .118 (.068-.168)[24]	8 [1524]	1.70 (1.03-2.79) CHDS[15] 1.62 (1.11-2.36) NY State[15] 4.00 (1.23-12.99) ECA[15] 1.90 (1.10-3.29) Victoria[15] cannabis use in any form: 1.46 (1.00-2.15)[24] 1.62 (1.06-2.48)[24] Heavy cannabis use: 4.00 (1.23-12.99)[24] 2.18 (1.53-3.11)[24] 2.54 (1.40-4.60)[24]	Weekly users of cannabis and subjects with CUD had depressive scores that were higher than the scores of CU in any form	First, "THC acts upon the cannabinoid system in the brain, related to regulation of emotional experience (and therefore of depression). There is evidence linking rimonabant, a cannabinoid CB1 receptor antagonist, and depression. Increased rates of depression have been observed in clinical trials using rimonabant, a finding that has led to the suspension of rimonabant by both the European Medicines Agency and the United States Food and Drug Administration"[8990].Second, "CU causes life events or circumstances that increase the likelihood of depression[8991], meaning that the perceived association between CU and increased risk for depression is socially mediated[89]. CU is associated with reduced educational attainment[92], unemployment and crime[9293], all factors that may increase risks of depression"[91].Third, "there may be a neurobiological link, by which cannabis impacts on serotonin and other neurotransmitters causing an increase in depressive symptoms"[25].	Yes**	"There are human studies showing depressive symptoms following acute administration of rimonabant, implying that cannabinoids may actually have an antidepressant action. There is no evidence of experimental studies"[24].

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Table 6 (*continued*)

	Strength (Odds Ratio, CI95%)	Temporality (num. cohort studies)	Consistency (Odds Ratio and CI95% prospective studies)	Dose-response	Plausibility	Coherence	Experiment
Suicidal ideation	OR 4.55 (1.37-15.11)[15]	3 [15].	Baltimore cohort: 1.80 (1.02-3.17) CHDS cohort: 1.43 (1.22-1.67) ECA cohort: 4.55 (1.37-15.11).	Association with suicidal ideation increases when cannabis use is greater: ever used cannabis before age 16 OR 1.80 (1.02-3.17) vs. cannabis misuse disorder OR 4.55 (1.37-15.11). [15]	Mediated by psychiatric disorders associated to CU[15].	Yes**	Up to our knowledge, there is no evidence of experimental studies indicating cannabis users suicidal ideation after using cannabis.
Respiratory outcomes	Wheezing 2.83 (1.89-4.23)[32] Cough 4.37 (1.71-11.19)[32] Sputum production 3.40 (1.99-5.79)[32] Dyspnea 1.56 (1.33-1.83)[32]	2 [32].	2 cohort studies for each outcome[32]: Cough (overall) 2.04 (1.02-4.06) Sputum production (overall) 3.84 (1.62-9.07)	Association with chronic cough and chronic sputum production increases when CU is more intense[32]: Current marijuana smoking and chronic cough association has an OR 1.73 (1.21-2.47), and chronic sputum production has an OR 2.01 (1.50-2.70). CU at least once a week at least for a year has an increased association with both outcomes, chronic cough OR 2.04 (1.02-4.06) and with chronic sputum production OR 3.84 (1.62-9.07).[32]	"Marijuana cigarettes are believed to contain particulate matter, toxic gases and reactive oxygen species and plycyclic aromatic hydrocarbons at a concentration possibly 20 times that of tobacco smoke. Studies have shown that marijuana is associated with histiopathologic changes in bronchial inflammation that are similar to changes seen with smoking tobacco. THC may have adverse immunomodulatory effects that could lead to infections and cancer"[32].	Yes**	First, "experimental findings in humans are consistent with a major role of the autonomic nervous system in the cardiovascular responses that occur in response to THC"[32]. Second, "marijuana smoke contains particulate matter and compounds that induce oxidative stress and inflammation in the lung. Findings among marijuana users are consistent with chronic airway inflammation and epithelial injury, including basal cell hyperplasia, goblet cell hyperplasia, and subepithelial inflammation, suggesting a mechanistic link between long-term marijuana use and respiratory symptoms"[32].

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Table 6 (*continued*)

	Strength (Odds Ratio, CI95%)	Temporality (num. cohort studies)	Consistency (Odds Ratio and CI95% prospective studies)	Dose-response	Plausibility	Coherence	Experiment
Educational attainment	5.6 (2.0-1.5); 3.1 (1.2-7.9)[40]	2[40]	Christchurch 3.1 (1.2-7.9)[40] Australian schools 5.6 (2.0-1.5)[40]	Any use < 15 years old and OR for school dropout: Christchurch 3.1 (1.2-7.9)[40]. Weekly use at ages 15-17 years and OR for early school leaving[40]: Australian schools 5.6 (2.0-1.5)[40]. Association with school dropout increases when CU is greater: any use <15 years old OR 3.1 (1.2-7.9) vs. weekly use at ages 15-17 OR 5.6 (2.0-15)[40].	"It is plausible that impaired educational outcomes are attributable to a combination of a higher pre-existing risk of educational problems in regular CU, the adverse effects of regular CU on learning in school, increased affiliation by regular CU with peers who reject school, and a strong desire among younger CU to make an early transition to adulthood by leaving school"[94].	Yes**	"In a sample of healthy male subjects, a pure, synthetic i.v. preparation of THC elicited working memory/executive function deficits"[88].
Motor vehicle crash	Risk: 1.92 (1.35-2.73) Fatal: 2.10 (1.31-3.36) Culpability: 1.65 (1.11-2.46) Involved: 2.66 (2.07-3.41)	2[54]	Cohort studies: 2.04 (1.36-3.07)[54]	Association with motor vehicle crashes increases when cannabis use is greater: low concentrations of THC OR 1.8 (1.0-3.5) vs. medium concentrations of THC OR 3.3 (1.9-5.9).	"Cannabis impairs performance of the cognitive and motor tasks necessary for safe driving, increasing the risk of collision"[86]. "Cannabis seems to impair automatic behaviors, such as tracking, at low doses and impair ability to perform more complex tasks at higher doses"[54].	Yes**	"Drivers attempt to compensate by driving more slowly after smoking cannabis, but control deteriorates with increasing task complexity. Cannabis smoking increases lane weaving and impaired cognitive function. Critical-tracking tests, reaction times, divided-attention tasks, and lane-position variability all show cannabis-induced impairment." [90]

CU (Cannabis Use); CUD (Cannabis Use Disorder); HCU (Heavy Cannabis Use: 1 joint/ week or CUD).
* correlation coefficient Pearson r.
** indicating that no strong evidence that our findings are against previous evidence.

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heavy use may impact fluency abilities and acutely impair attention, concentration, decision making, inhibition, impulsivity and working memory (Crean et al., 2011), and similar results have been shown in daily chronic users (10 years or more) (Hall and Degenhardt, 2009). In line with this, young people who use cannabis are at increased risk for poor school performance, reduced educational attainment and early school leaving and (Danielsson et al., 2015; Hall, 2015; Boden et al., 2017; Tu et al., 2008). However, temporality was difficult to establish, since only one of the included studies was longitudinal, and as a consequence chronicity of alterations was not able to define.

Referring to injury, we found a causal relationship between cannabis use and both motor vehicle crashes and suicidal ideation. Recent studies confirm that cannabis use increases the risk of suffering motor vehicle accidents (Balzo et al., 2018; Wettlaufer et al., 2017), but much of this data has been criticized for systematic bias (Rogeberg, 2019).

Moreover, our review found that cannabis use is associated with some other outcomes, even though causality was not well established. Recent studies support that cannabis use leads to cannabis withdrawal syndrome (Budney et al., 2019; Livnea et al., 2019). Also, using cannabis immediately prior to or while gambling was associated with greater gambling amounts, frequency, negative consequences and problem severity (Cronce et al., 2017). In the organic domain, a recent study found that cannabis use during pregnancy was a risk factor leading to adverse outcomes in the newborn (Petrangelo et al., 2018). Another study found that depressive symptoms and shorter breastfeeding in the baby are linked to marijuana use (Ko et al., 2018). In the injury domain, one study showed a significant association between marijuana use and psychological, physical and sexual intimate partner violence perpetration (Shorey et al., 2018). In the same line, a study reported that persistency of cannabis use is associated with an increased risk of subsequent violence (Dugré et al., 2017). Moreover, cannabis use during adolescence increases levels of callous-unemotional traits, which in turn lead to problematic behaviors (Hawes et al., n.d.).

The National Academies of Science (2017) reported evidence concerning to cannabis use related harm and, even though we found similar outcomes, our results partially differ. In fact, our systematic review adds to the NAS report evidence for cardiovascular risk (ischemic strokes, hypertension and TAO), cognitive attainment (fewer years of education, lower education attainment, concentration alteration and detrimental effects on everyday cognition), injury implications (violence perpetration, homicide victims, crash responsibility and crash involvement) and prenatal exposure (cognitive dysfunction and behavioral disturbances) (National Academies of Sciences, Engineering, 2017).

When comparing cannabis-related harms with those associated to alcohol use, evidence is stronger for the latest. Particularly, the following diseases are more intensely related to alcohol rather than cannabis: unipolar depressive disorders, ischemic heart disease, ischemic stroke, road traffic accidents, self-inflicted injuries and violence (Rehm et al., 2009). In the case of tobacco smoking related-harms, evidence is more conclusive than that of cannabis use. Strong evidence supports that tobacco smoking causes lung cancer, chronic obstructive pulmonary disease and coronary heart disease, which are the main causes of death (West, 2017).

This review has several limitations. Firstly, a systematic review of systematic reviews may not include all the relevant recent studies, and some breaking advances on cannabis-related harms might have been excluded. Nevertheless, we can guarantee that the results gathered in our study, and their discussion, are strongly supported by previous systematic reviews. Secondly, gender differences cannot be taken into account, since most studies do not provide results by gender. Further studies in the field should address this issue. Thirdly, dose and frequency are not precisely described in most of the reviewed literature, which limits the accurate interpretation of specific dose-effect relationships. This highlights the pressing need to include data on quantity, frequency and patterns of use in future studies. Despite these limitations, our systematic review of systematic reviews provides a comprehensive overview of the multiple harms related to cannabis use that can pave the way both for future research and policies.

In conclusion, cannabis use is associated to relevant harms in the mental health domain (psychosis, bipolar disorder, depression, anxiety and cannabis dependence), the organic domain (respiratory, cardiovascular, gastrointestinal, nervous system, cognitive functions and some cancers) and injuries (motor vehicle collisions, violence and suicidal behavior). However, evidence of causality for many of these outcomes is missing. Therefore, the reviewed evidence shows that cannabis use related harms are not limited to the more widely-studied psychosis or other mental health issues, and that these effects compel us to considerate cannabis use as a relevant public health problem. However, there is still little data on the dose-dependency of these effects; evidence that is essential in order to define, from a public health perspective, what can be considered risky use of cannabis. This definition should be based on quantitative and qualitative criteria that informs and permits the evaluation of current approaches to a regulated cannabis market.

Funding

This study is funded by the Spanish grant of Plan Nacional Sobre Drogas, Ministerio de Sanidad y Consumo (PNSD 132373 - 2017I053 - 603; Antoni Gual Solé). The conclusions of the article are only the responsibility of the authors and do not necessarily represent the official views of the institutions, who had no further role in study design, collection, analysis and interpretation of the data; in the writing of the paper; or in the decision to submit the paper for publication.

H.L.-P. received funding from the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III through a 'Rıo Hortega' contract (CM17/00123, to Dr. López-Pelayo), FEDER.

This work is supported by the following institutions: Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Hospital Clínic i Universitari de Barcelona and CERCA Programme / Generalitat de Catalunya.

Contributions

MB, AG and HL-P designed the study. EC, HL-P, MB and AG wrote the first draft of the manuscript. All the other authors reviewed and approved the final paper.

Conflict of interest

H.L.-P.: has received travel grants from the laboratories honoraria and travel grants from Janssen and Lundbeck, none of these COI are related to the current research. The other authors declare that they have no known conflicts of interest.

Acknowledgements

CERCA Programme / Generalitat de Catalunya.

Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Hospital Clínic i Universitari de Barcelona.

Plan Nacional Sobre Drogas, Ministerio de Sanidad y Consumo.

Ministry of Economy and Competitiveness, Instituto de Salud Carlos III through a 'Rıo Hortega'

Janssen and Lundbeck.

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Please cite this article as: E. Campeny, H. López-Pelayo and D. Nutt et al., The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.02.003

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