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High-Risk Cannabis Use: A Proposal of an Operational Definition through Delphi Methodology for Scientific Consensus

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Abstract

Introduction: Cannabis ranks as one of the most widely used psychoactive substances worldwide. Its usage has been reported as a risk factor for developing a variety of physical and mental health issues, alongside social and economic problems. According to the World Health Organization (WHO), hazardous (or high-risk) substance use is defined as "a pattern of substance use that increases the risk of harmful consequences for the user." The primary objective of this study was to achieve a consensus on an operational definition of high-risk cannabis use suitable for a European jurisdiction (Spain). ***Methods:*** A three round Delphi study was conducted. The Delphi technique entails group decision-making and iterative forecasting by consulting a panel of experts and conducting systematic feedback rounds. An online survey was distributed among a diverse expert panel comprising professionals from Spain working on fields related to cannabis use (research, policy planning, and clinical professionals). One-hundred ninety-nine invitations were sent to experts, of which forty-five (22.6%) accepted to participate. All participants were provided the option to revise a background document with the latest compiled scientific evidence and guidelines related to health and social conditions associated to cannabis usage. This background document also proposed the quantification of dose using a standardized unit established for the population of Spain (the Standard Joint Unit or SJU) based on quantity of cannabis main psychoactive constituent, 9-tetrahydrocannabinol (9-THC) (1 SJU = 1 joint = 0.25 g of cannabis = 7 mg of 9-THC). Three rounds of Likert scale and

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open-ended questions were administered until consensus, defined as ≥75% agreement, was attained. ***Results:*** Consensus was reached on defining high-risk cannabis use as the usage of more than 4 SJU (>28 mg THC) per week or any use of cannabis with potency >10% THC. Concurrent use of cannabis with other drugs was also considered high risk, while the smoked route was considered the riskiest administration route. It was also agreed that vulnerable groups for high-risk cannabis use (for whom any pattern of cannabis use represents high risk of harm) include individuals under the age of 21, pregnant or breastfeeding women, individuals with psychiatric history, those with medical health issues related to cannabis use, professional drivers and heavy machine operators. ***Conclusion:*** This operational definition of high-risk cannabis use for Spain elucidates usage patterns and individual vulnerability factors predictive of heightened harm. Its adoption holds potential to inform decision-making among individuals, professionals, and policy-makers, facilitating evidence-based interventions aimed at prevention and risk reduction.

Introduction

Cannabis ranks as one of the most prevalent psychoactive substances consumed globally. In 2021, more than 4% of the world population aged 15–64 (219 million people) had used cannabis [1]. Research indicates a distinct correlation between cannabis consumption and various health concerns, including psychiatric disorders, sleep disturbances, cognitive impairment, respiratory issues, cancer, cardiovascular complications, and gastrointestinal disorders. Furthermore, cannabis use poses a risk factor for motor vehicle accidents, suicidal behavior and violence [2]. The health risks associated with cannabis use [2–4] are a global public health problem [5]. In Europe, around 8% of adults (22.6 million aged 15–64) are estimated to have used cannabis in the last year. It is estimated that around 1.3% (3.7 million) of adults (aged 15–64) are daily or almost daily cannabis users [6]. Spain accounts for 66% of the number of cannabis seizures in the European Union. This reflects Spain's role, as a transit country for cannabis trafficking and as a production area, although significant cannabis production takes place across the European Union [7]. In Spain, in 2022, among the population aged 15–64, 40.9% reported having used cannabis at some point in their life, 10.6% reported having consumed it in the last 12 months and 8.6% in the last 30 days [6]. These rates are some of the highest in Europe [8].

Cannabis policy regarding legalization changed in recent years and there is a renewed debate on the regulation of cannabis use and its supply [5]. So far, Canada, Uruguay, Malta, and Germany allow the recreational use of cannabis [9]. Also, recreational cannabis use has been legalized in 24 US states [10–12]. Other countries such as Luxembourg, Colombia, or Mexico are planning a legal market for recreational use [13–16].

Changes in social perception, availability and legal status highlight the need for prevention policies that need to be designed taking into account previously validated strategies for other legal drugs such as alcohol. According to the World Health Organization (WHO), hazardous (or high-risk) substance use is defined as "a pattern of substance use that increases the risk of harmful consequences for the user. Unlike harmful (or problematic) use, hazardous use refers to patterns of use that are of public health importance despite the absence of any current disorder in the individual user" [17–19]. The concept of hazardous (or high-risk) substance use needs to include: (a) specific vulnerable groups that have individual, non-modifiable risk factors (among whom any pattern of substance consumption implies health risks); (b) recommendations for the general population on: riskier patterns of use (frequency, dose, potency), riskier routes of administration (RoA) and risks of concomitant use of other drugs.

In summary, from a public health point of view, universal, and selective intervention might benefit from the implementation of a clear definition of high-risk cannabis use (patterns of cannabis use that increase the risk of adverse effects on health) [20]. Moreover, a specific definition of high-risk substance use facilitates sending clear messages for universal prevention among the general population while also allowing selective preventive interventions to be carried out among vulnerable groups.

An operational definition of high-risk cannabis consumption continues to exhibit certain challenges up to the present day. A systematic review identified at least 22 definitions of risky use. The most frequent was weekly cannabis use. There were no definitions that included both quantity of main psychoactive substance (9-tetrahydrocannabinol [9-THC or THC]) and frequency of use [18].

The Standard Joint Unit or SJU (7 mg 9-THC, 250 mg hashish/marijuana) was defined in 2017 for the population of Spain and aims to facilitate data collection and report on risky use [21]. It has been recognized internationally as a tool in the context of a broader standard cannabis unit [22]. Additionally, a recent consensus of

international experts determined that the standardization of measurements of cannabis use should help determine risky cannabis use [23, 24].

This study aims to fill the gap of an operational definition of high-risk cannabis use for a European jurisdiction (Spain) to achieve an expert agreement that includes: (1) components of risky use for the general population: riskier patterns of use (frequency, dose, potency), riskier RoA, risks of concomitant use of other drugs, and (2) vulnerable groups.

Methods

The study aimed to achieve a consensus on an operational definition of high-risk cannabis use among a diverse expert panel comprising professionals from various fields engaged in cannabis use disorder research, policy planning, and treatment (such as psychology, medicine, public health, addiction research, and social sciences) using the Delphi method. The Delphi method involves a series of multiple rounds of questionnaires with controlled feedback, enabling participants to reconsider their positions and share perspectives on subsequent rounds. It relies on the involvement of experts, ensuring that the responses come from well-informed sources, adding credibility to the findings and recommendations. These characteristics make the Delphi technique particularly suitable for gathering comprehensive, well-rounded, and unbiased opinions from experts [25].

All participants were provided with a comprehensive description of the study's objectives and information about the Delphi process. They were also offered the option to read a background document (see online suppl. material S1; for all online suppl. material, see https://doi.org/10.1159/000540541) which gathered the latest scientific evidence and guidelines related to health and social conditions associated to cannabis usage. This background document reviewed the concept of high-risk substance use according to the World Health Organization. It also provided information about the case of alcohol, in which high-risk use is an internationally recognized concept with consensus on measuring quantity (using standard drink units), frequency and considering vulnerable groups even if there is variation across jurisdictions. The document also cited sources that have provided cannabis high-risk use recommendations and highlighted the gap in linking previously proposed standardized quantities for cannabis use, citing the concept of the Standard Joint Unit (SJU) as a tool to help facilitate the discussion on THC quantity of use [22]. The document provided synthesized evidence of cannabis harmful effects on mental and physical health [2], including the cognitive and behavioral harms from early, chronic and acute use [26]. Summary for scientific evidence of mental, physical and social consequences of cannabis use was provided in tables, showing previously proposed cut-off points for quantity and frequency that might predict higher risk of harm. Sources for all the studies were provided. Different domains of high-risk use were proposed as a way to frame the discussion: patterns of use, route of administration, concomitant use of other substances, characteristics of vulnerable groups.

Participants

Potential expertise was identified as at least 1 year of experience in working with people suffering cannabis-related health harms and/or having published at least one peer-reviewed article about cannabis-related harms in a scientific journal. Experts were sourced from diverse channels, including scientific and professional associations and networks (psychiatry, family medicine, and epidemiology), editorial boards of addiction research magazines, universities, and hospitals. Additionally, potential participants were identified through bibliographic searches, LinkedIn connections, and personal referrals from contacted experts. All individuals received an initial invitation letter through e-mail outlining the study's criteria. They were provided with a comprehensive overview of the study's objectives and the Delphi process and requested to furnish sociodemographic and professional details.

One-hundred ninety-nine invitations were sent to experts. Forty-five accepted to participate (22.6%). Of those who accepted, forty-two completed round 1 (93.33%), thirty-eight responded to round 2 (84.44%), and thirty-six did round 3 (80.00%). See Figure 1.

Among responders of all three rounds, 38.9% were women, mean age of 47.3 years old (SD 10.2). They reported a mean of 16.1 (SD 12) years of experience in clinical tasks and 13.0 (SD 9.2) in research. See Table 1.

Procedure and Data Analysis

The Delphi study took place from February to April 2022. To keep anonymity between participants, the study was administered through an online platform, ensuring no direct interaction among participants. The identity of the experts remained undisclosed to anyone except the research team, and the feedback provided was anonymous (showing the percentage of answers from the expert panel) to safeguard the independence of participants' opinions.

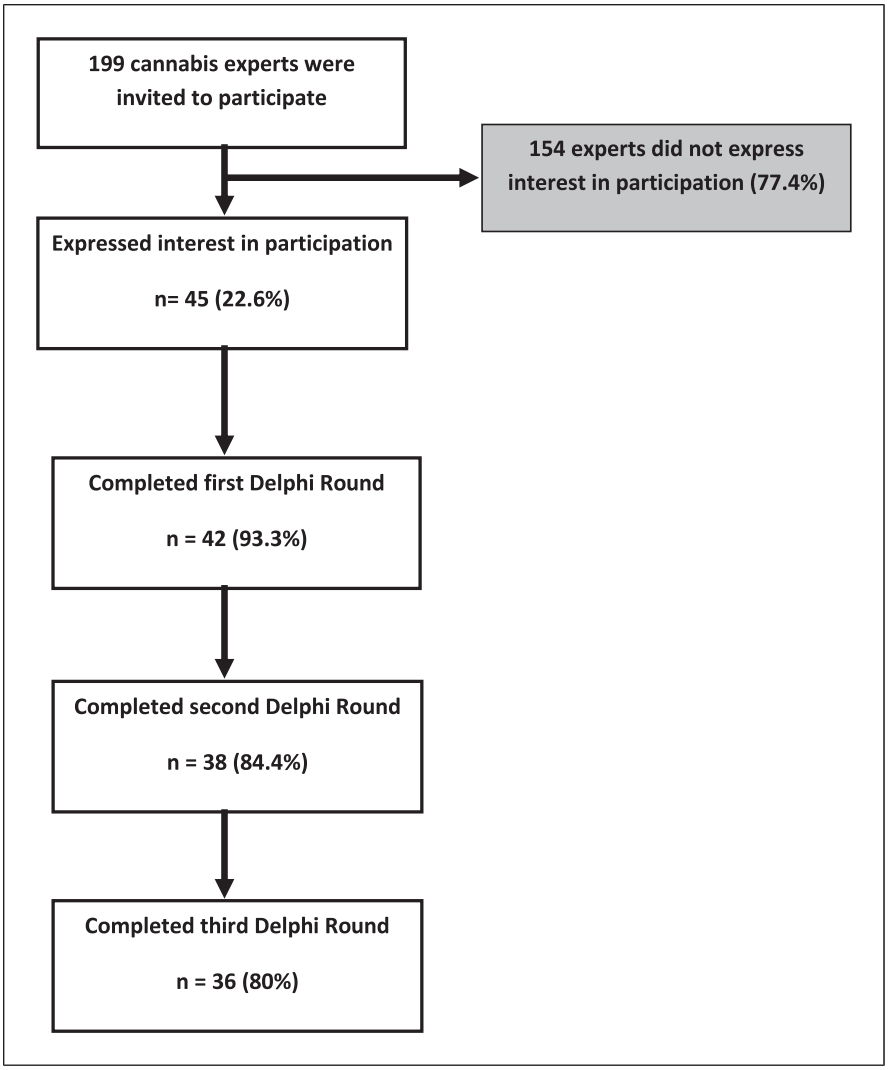

Fig. 1. Flowchart of invited experts and final participants in Delphi Rounds.

The study lasted 3 months. All the material and questionnaires were presented in Spanish. The answers for each Delphi round were collected via an online survey system (www.qualtrics.com). A link to access this online platform was sent to each expert through e-mail. For a detailed description of questions, see online supplementary material S2.

For all rounds, questions were constructed and grouped using the domains defined in the background document (patterns of use, route of administration, concomitant use of other substances, characteristics of vulnerable groups). Participants were asked to provide their individual opinions on each proposed dimension of risky use using either dichotomic responses (Yes/No) or a Likert scale with five options to closed-ended questions. The Likert scale was structured such that options 1 and 2 ("totally disagree" and "somewhat disagree") represented disagreement, options 4 and 5 ("totally agree" and "somewhat agree") represented agreement, and option 3 ("nor agree nor disagree") did not count towards agreement or disagreement.

Consensus in this study was characterized by an accord among a minimum of 75% of participants in any round (given the absence of a universally agreed-upon definition of consensus [27], and considering the findings from prior research [28]). If a question achieved consensus, it was unnecessary to revisit it in subsequent rounds. In the first round, participants were allowed to suggest additional categories or questions for the following rounds via one open-ended question domain.

Table 1. Profile of cannabis experts that participated in Delphi consensus

	Expressed interest in participation (n = 45)	Completed all 3 Delphi rounds (n = 36)
Gender (feminine), *n* (%)	19 (42.2)	14 (38.9)
Age, years	M = 47.7 (SD = 10.2)	M = 48.4 (SD = 9.9)
Professional background, *n* (%)		
Primary care	3 (6.7)	2 (5.6)
Nursing	2 (4.4)	2 (5.6)
Epidemiology	5 (11.1)	3 (8.3)
Pharmacy	1 (2.2)	0 (0)
Pneumology	1 (2.2)	1 (2.8)
Psychology	11 (24.4)	7 (19.4)
Psychiatry	14 (31.1)	14 (38.9)
Basic Research	2 (4.4)	2 (5.6)
Others	6 (13.3)	5 (13.9)
Specialized in addictions, *n* (%)	35 (77.8)	30 (83.3)
Professional experience in years		
Clinical	M = 16.6 (SD = 12.5)	M = 18.3 (SD = 12.0)
Academical	M = 13.3 (SD = 9.4)	M = 12.9 (SD = 9.6)
Percentage of working hours dedicated to diverse professional tasks (professional dedication)		
Clinical practice	M = 44.8 (SD = 36.0)	M = 50.4 (SD = 34.0)
Research	M = 33.5 (SD = 30.4)	M = 28.0 (SD = 28.1)
Teaching	M = 28.3 (SD = 25.6)	M = 26.5 (SD = 24.7)
Management	M = 15.7 (SD = 17.8)	M = 15.2 (SD = 17.9)

Data are reported as mean (M) with standard deviation (SD) for continuous variables or percentages (%) with counts for categorical variables unless otherwise specified.

The second and third rounds also provided anonymous feedback to each participant by informing them of the percentages answered by the rest of the expert panel for every question of the previous round in which no consensus was reached (questions with less than 75% agreement). The research team made a qualitative analysis for every domain of questions in which items which could be considered nested into another one would be removed when there was consensus on both of them. All responses were coded in Excel (2019) and a descriptive analysis was performed using the Statistical Package for Social Sciences (SPSS, version 24).

Results

Consensus derived from three rounds is presented according to the following dimensions of harm associated to cannabis use: components of risky use for the general population ("riskier patterns of use according to frequency, potency and quantity," "riskier routes of administration," "risks of concomitant use of other drugs"), and vulnerable groups (Table 2; Fig. 2). Tables in online supplementary material (S3–S5) include more detailed information of each round's results.

Components of Risky Use for the General Population

Riskier Patterns of Use: Frequency, Quantity, and Potency

In round 1, there was consensus in avoiding a definition of risky use according to frequency alone (78.6% agreement) and the need of a definition based on different levels/dimensions (78.6% agreement). Daily or almost daily use (76.2% agreement) and also weekly use (81% agreement) got consensus. However, in round 1, there was no consensus on the role of potency and quantity. Consequently, these areas were explored again in round 2.

In this second round, a multidimensional definition with frequency and dose (quantity of delta-9-THC in time units) got consensus (83.3% and 89.2% agreement,

Table 2. Summary of consensus statements

Dimension	Criteria	Definition	Round in which consensus was achieved	% of agreement (round in which consensus was achieved)
Pattern of use	Frequency	Not alone	Round 1	78.6
	Potency	>10% of delta-9-THC	Round 3	86.1
	Frequency and quantity	≥5 SJU per week	Round 3	94.4
RoA	Smoking	It is the RoA with higher risk, especially if is mixed with tobacco	Round 1	85.7
	Other RoA	There is no absolutely zero risk for any RoA	Round 1	90.5
Concomitant use of other drugs	Drugs	Any use of other psychoactive substances with cannabis is a risk	Round 1	90.5
	Alcohol	Use of alcohol and cannabis at the same time is a risk	Round 1	95.2
	Synthetic cannabinoids	Use of cannabis and SC is a risk	Round 1	88.1
Specific vulnerable groups	Mental health	Any use if history of personal mental health problems is a risk	Round 1	100
		Any use if history of familiar mental health problems is a risk	Round 1	83.3
	Physical health	Any use if physical disease related to cannabis use is a risk	Round 1	95.2
	Pregnancy	Any use during pregnancy is a risk	Round 1	100
	Breastfeeding	Any use if current breastfeeding is a risk	Round 1	100
	Professional drivers or hazardous machine users	Any use among professional drivers or hazardous machine users	Round 1	97.6
	Age[a]	Under 21 years old any consumption is high risk Under 18 years old any consumption is high risk	Round 1	88.1/95.2

RoA, Route of Administration; SC, synthetic cannabinoids. [a]No consensus in the age range between 21 and 25 years. Despite both age under 21 and age under 18 years old got consensus, following a pragmatic conservative approach it was accorded that younger than 21 years old would be considered the cut-off age for vulnerability.

respectively), but no consensus was reached regarding THC potency (70.3% agreement). Regarding frequency in round 2, when responders could choose only one option (weekly use; daily or almost daily; frequency is not relevant), weekly use (78.4% agreement) got consensus, but not daily or almost daily (21.6% agreement). In this second round, no consensus was reached regarding a specific cannabis dose that suggests higher health risk (options: ≥2 SJU per day, ≥1 SJU per day, ≥5 SJU per week, ≥10 SJU per week).

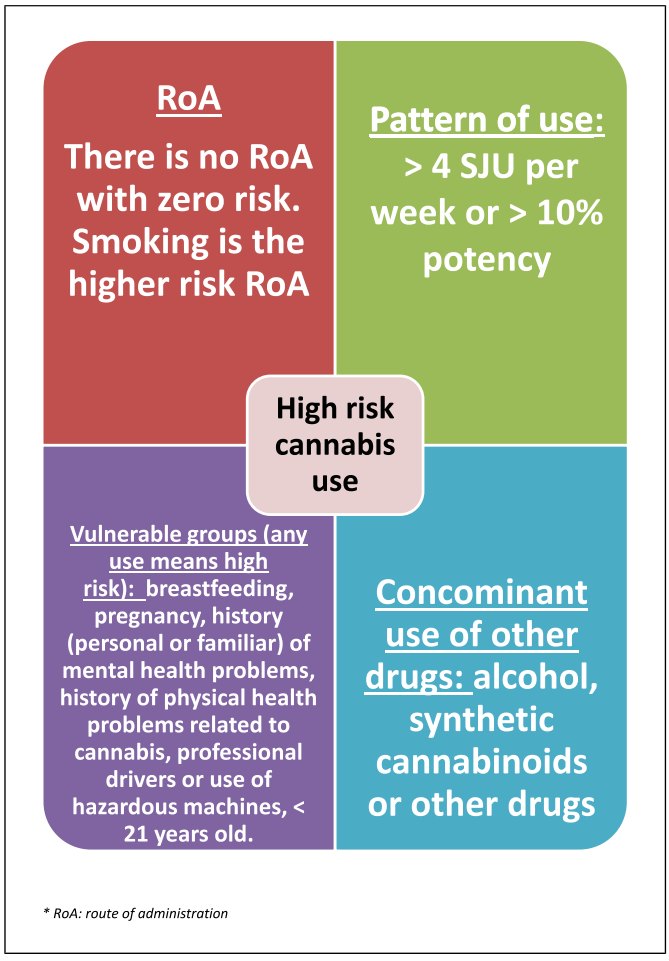

Fig. 2. Operational definition of high risky cannabis use according to Delphi results.

Consequently, considerations regarding dose and potency of cannabis which entail higher health risks were again explored in round 3. In the last round, a dose ≥5 SJU per week was considered risky use (94.4% agreement), and any use of cannabis with potency THC >10% was considered risky use (86.11% agreement).

Routes of Administration

In round 1, consensus was reached in the following two statements: "There is no Route of Administration (RoA) with absolutely zero risk" (90.5%) and "Smoking is the RoA with higher risk, especially if it is mixed with tobacco" (85.7%). In an open-ended question, nobody reported any other RoA to be considered risky. No other statements or questions regarding RoA needed to be proposed in rounds 2 or 3.

Concomitant Use of Other Drugs

In round 1, "Any use of other psychoactive substance" (90.5% agreement), "Use of alcohol and cannabis at the same time" (95.2% agreement), or "Use of synthetic cannabinoids" (88.1% agreement) were acknowledged as risky cannabis use. No other statements or questions regarding the concomitant use of cannabis and other drugs needed to be proposed in rounds 2 or 3.

Vulnerable Groups

In round 1, consensus was reached in six vulnerable groups (any pattern of use of cannabis represents a high risk of developing health harms in these groups): pregnancy (100% agreement), breastfeeding (100% agreement), professional drivers or hazardous machines users (97.6% agreement), family history of mental health problems (83.3% agreement), personal history of mental health problems (100% agreement), personal history of physical diseases related to cannabis use (95.2% agreement).

In round 1, both age <18 years old and <21 years old were considered vulnerable groups (95.2% and 88.1% agreement, respectively), but there was no agreement if the age range between 21 and 23 years old should be considered a vulnerable group. Consequently, age as a vulnerability factor was further explored in subsequent rounds. In round 2 no consensus was reached either between the following options: younger than 18 years old, younger than 21 years old, younger than 23 years old, and younger than 25 years old. Consequently, it was decided that in the final round, only the most voted options in round 2 (younger than 18 years old, younger than 21 years old) would be offered. Nonetheless in round 3, none of the options by themselves reached consensus: 36.11% of the experts agreed for younger than 21 years old, and 63.89% agreed for younger than 18 years old. Therefore, a pragmatic conservative approach was followed: it was accorded that younger than 21 years old would be considered the cut-off age for vulnerability.

In the second round, the dimension of history of personal mental health was further explored by specific psychiatric disorders. The following ones reached consensus: schizophrenia and other psychotic disorders (100% agreement), bipolar disorders (100% agreement), depressive disorders (97.4% agreement), cannabis use disorder (97.4% agreement), other substance use disorders (97.4% agreement), attention deficit (with or without hyperactivity) disorders (92.1% agreement), impulse-control disorders (92.1% agreement), anxiety disorders (92% agreement), gambling (84.2% agreement).

Also in this second round, the dimension of physical diseases related to cannabis use was further explored, and

consensus was reached in the following specific physical conditions: pulmonary cancer (91.2% agreement), other pneumological diseases (COPD, spontaneous pneumothorax, etc.) (89.2% agreement), other respiratory symptoms (sibilants, dyspnea, sputum, etc.) (89.1% agreement), testicular cancer (81.0% agreement), other types of cancer (80.1% agreement), ictus (83.8% agreement), other neurological diseases (75.7% agreement), ischemic heart attack (81% agreement), cognitive impairment (83.8% agreement), thromboangiitis obliterans (75.7% agreement).

In the second round, the following conditions were also considered a risk factor for problems related to cannabis use: driving under the influence of cannabis (100% agreement), history of self-harm or suicidal behavior (89.4% agreement), social vulnerabilities (86.8% agreement), history of violent behavior (81.6% agreement), and history of suffering violence (79% agreement). In the third round, no other new conditions got consensus.

Discussion

A consensus of 36 researchers, clinicians and policymakers working in the field of cannabis-related conditions, recruited within the geographical framework of a European country (Spain), was conducted using Delphi methodology. It reached the following conclusions:

In consistency with previous literature [2], and keeping in mind that there is no safe level of cannabis use, the following patterns of cannabis consumption represent a higher risk of experiencing adverse health consequences.

Among the General Population

- Use of >4 SJU (>28 mg THC) per week,
- Any use of cannabis with potency >10% THC,
- Although there is no route of administration with zero risk, the riskier route of administration seems to be smoked,
- Concomitant use of cannabis with other drugs (including alcohol and synthetic cannabinoids).

Any Pattern of Cannabis Use Should Be Considered High Risk among the following Vulnerable Groups

- Women who are pregnant or breastfeeding, people with (personal or familiar) history of mental health problems (schizophrenia and other psychotic disorders, depressive disorders, bipolar disorders, anxiety disorders, gambling, impulse-control disorders, cannabis use disorders, other substance use disorders, attention deficit with or without hyperactivity-disorders, self-harm and suicidal behavior),
- History of organic health problems related to cannabis (pulmonary cancer, other pneumological diseases (COPD, spontaneous pneumothorax, etc.), other respiratory symptoms (sibilants, dyspnea, sputum etc.), testicular cancer, other types of cancers, stroke and other neurological diseases, ischemic heart attack, cognitive impairment, thromboangiitis obliterans),
- Professional drivers or users of hazardous machines,
- People aged <21 years old.

These identified patterns of high-risk cannabis use, expert-agreed and evidence-based, could be used to create preventive guidelines to better inform the population of Spain (both general and susceptible to experience cannabis-related health harms) about cannabis patterns of use and possible health risks.

In fact, evidence suggests that the lifestyle decisions and actions that people make, which exert key influences on the prevention and management of chronic diseases, are affected by their level of health literacy (HL) [29]. Likewise, the level of literacy also influences beliefs about drugs and attitudes toward their use [30]. In a simplified way, HL could be defined as the ability of people to access, understand, evaluate, and communicate information about health [31]; it is not only about knowledge, but about critical ability to use this knowledge in order to improve one own's health.

Individuals' level of HL has an impact on their health status. Those with lower levels of HL have worse health outcomes than those with higher levels [29]. Several systematic reviews and meta-analyses demonstrate that group and individual interventions in primary care and community settings aimed at improving HL can be effective in generating sustained changes in behavioral risk factors such as diet, exercise, or drug use [32, 33]. In summary, improving the HL of the general population is associated with improved health as well as harm reduction [34].

A previous initiative similar to the one proposed here are the Canadian Lower-Risk Cannabis Use Guidelines (LRCUG), originally published in 2011 [35] and updated in 2017 [36] and 2022 [37]. They were agreed between 6–11 experts on the basis of narrative review (2011, 2022), systematic review plus quality-grade evidence on behavioral factors (2017), and iterative scientific expert consensus (2022). The LRCUG are also based on global evidence about health harms related to cannabis use. To the best of our knowledge, they are the first international effort to combine evidence-based data and expert consensus in order to provide recommendations on lower risk patterns of cannabis use. In that sense, their value as a public health tool is enormous. Similarly to our consensus they include recommendations on the frequency of use

and low-potency cannabis, but they do not contain suggestions on specific cut-off points for dose or quantity of cannabis main psychoactive substance (9-THC), potency, or age of use involving higher health risks, mainly because, appropriately, available evidence so far is considered inconclusive to establish measurable thresholds that could enable consumers to consistently mitigate the risks of negative outcomes [37]. They rightly reflect on the challenge of defining and guiding individuals toward adopting "lower-risk" patterns of cannabis use with clarity, avoiding excessive precision or claims of universality [38]. In conclusion, they include cautious recommendations, globally useful and generalizable.

This cannabis expert consensus for Spain aims to be a complimentary effort to generate recommendations regarding high-risk cannabis consumption based on global scientific evidence, but also adapted to a specific sociocultural context, as has been done previously for other addictive substances such as alcohol [39]. Although available evidence might be ambiguous to define thresholds, specific numerical cut-off points facilitate clarity and ease of use when communicating high-risk cannabis use recommendations to users, clinicians and policy-makers. Indeed, as seen with other substances (such as alcohol), definitions of high-risk consumption patterns that have specific cutoff points, with standardized units of consumption quantities, are useful (operational) for users, clinicians, and policy-makers in making health-related decisions [39–41].

So, combining available evidence and expert opinion, the presented operational definition of high-risk cannabis use opts to prioritize a pragmatic approach and proposes specific cut-off points for frequency and dose that hold higher health risks (>4 SJU or 28 mg THC per week), potency of cannabis involving high risk of cannabis health-related harms (>10% THC) and age of use that can involve higher health risks (<21 years old). For this operational definition of high-risk cannabis use for Spain, considering the dose of psychoactive substance was especially relevant. The quantification of dose was facilitated in this context by the existence of a standardized unit (the Standard Joint Unit or SJU) based on quantity of cannabis main psychoactive constituent, 9-THC (1 SJU = 1 joint = 0.25 g of cannabis = 7 mg of 9-THC) to measure cannabis quantities in Spain. This SJU was established in 2017 by previous research in our group, consisting of a naturalistic study of a convenience sample recruited in universities, leisure spaces, mental health services and cannabis clubs in Spain. Adults, reporting cannabis use in the last 60 days, answered a questionnaire on cannabis use and were asked to donate a joint. The donated joints were then analyzed for their 9-THC and cannabidiol content [21]. SJU has shown to be a useful quantification tool suitable for research and clinical settings [42]. The fact that the vast majority of cannabis in Spain is consumed smoking joints [43], also facilitated to define pragmatic cut-off points for quantity, frequency, and potency that predict higher risk.

But there are many peculiarities of cannabis use that present challenges in the development of standard units globally: different RoA (smoking, vaping, edible, dabbing), concurrent use with other substances or heterogeneity of quantities or interactions among different cannabinoids (THC/cannabidiol). Nonetheless, in recent years, several proposals of standardized measures to quantify cannabis use have been developed by different research groups across the globe. For instance, besides the SJU, another proposal is the standard THC unit (5 mg THC for all cannabis products and methods of administration), based on review of the existing literature [22]. Also recently, it has been proposed to establish a standard THC unit for Canada as 2.5 mg THC for all cannabis products and RoA [44].

LRCUG have been endorsed by several leading Canadian organizations with health, substance use and addiction focus or mandate. They were also included in education and prevention strategies devised by different levels of government as part of the implementation of cannabis legalization in Canada [45]. Also, a recent study analyzed data from the US nationally representative survey, National Epidemiologic Survey on Alcohol and Related Conditions (2001–2005), and following recommendations from the Canadian LRCUG evaluated how lower-risk cannabis use (late initiation and low use frequency) was associated with the risk of developing cannabis abuse/dependence over a 3-year follow-up period compared to 12-month abstinence (controls) or higher risk cannabis use (early initiation and higher use frequency). It was found that following recommended use patterns can significantly lower one's risk of cannabis abuse/dependence [46].

Few other examples backed by rigorous scientific evidence exist regarding health risks related to cannabis and patterns of use. In 2023, the American Society of Regional Anesthesia and Pain Medicine published guidelines for the management of the perioperative patient on cannabis and cannabinoids. Although these guidelines are based on a review of the literature and expert consensus based on Delphi methodology, they are aimed at the clinical practice of Anesthesia professionals, not at the general population [47]. In a recent Canadian study, the authors conducted a digital assessment using the Google search

engine to identify lower-risk substance use guidelines (LRSUGs) that could be identified by youth when searching for official sources of information related to commonly used substances, including cannabis. Although 23% of the 100 identified guidelines were focused on cannabis, very few cited evidence in support of the information they provided [48].

On another note, the quantitative thresholds regarding dose, frequency, potency, and age proposed in this consensus are similar, albeit not identical, to those proposed in previous literature exploring cannabis health-related harms (which was included in the Background document that was sent to the experts that participated in our study). For instance, diverse frequencies of cannabis use have been previously linked with psychotic disorders: less than once per month [49], daily [50], from once per week to daily [51], or weekly [52]. Frequencies that have previously been described to increase the risk for developing cannabis use disorders are 2–3 times per month [53], weekly [54], or daily –at least 1 SJU [55]. Lastly, in 2021, our group conducted an online survey about cannabis use and health-related harms among 2,124 adults living in Spain who used cannabis at least once during the last year. It was found that using cannabis on 3 out of 4 days was associated with an 8-fold probability of scoring 4+ on the Severity Dependence Scale (OR 8.33, 95% CI: 4.91–14.16, $p < 0.001$), which is indicative of a cannabis use disorder. Also, a start of regular cannabis use before the age of 25 combined with using cannabis at least once per month was associated with a higher probability of risky alcohol use (OR 1.33, 95% CI: 1.12–1.57, $p = 0.001$) [26].

Identification of vulnerable groups among whom any pattern of cannabis use might increase the risk of experiencing cannabis use-related harms is also especially relevant from a public health point of view. The proposed vulnerable groups in this operational definition might include a considerable proportion of the population (e.g., according to WHO 1 in every 8 people in the world lives with a mental disorder, around 12.5% of the global population [56]), but given the relevant and extensive possible harms of cannabis use on global health [9, 57], and given the high prevalence of use of this substance [1, 43], the presented expert consensus favored conservative recommendations, to try to promote caution regarding the use of cannabis.

For instance, the health effects of cannabis use appear to be more severe at early ages of use. For example, it is estimated that up to 8% of the incidence of schizophrenia in the population could be related to cannabis use in young people [58]. It has even been shown that even occasional cannabis use can produce structural and cognitive changes in the adolescent brain [59, 60]. And early onset of cannabis use can lead to a more rapid development of dependence than in adults [9, 57]. But we also should keep in mind that although previous evidence suggested that the earlier the onset of cannabis use the higher the risk for adverse health consequences, according to recent refinements provided by the latest studies the role of "early-age-onset" as an independent determinant of adverse outcomes has become more ambiguous. Current evidence suggests the increased importance of frequency of use and the potency of cannabis used, the adverse impacts of which might increase if cannabis use is also initiated at a young age [61, 62].

Conversely, our study presents several limitations that should be pointed out. On the one side, although in the survey it was specifically agreed that a dose ≥5 SJU per week was considered risky use, it was decided that in the final operational definition of high-risk cannabis use the equivalent cut-off point of >4 SJU per week would be used since we believe that to report quantity in this manner is more straightforward from a public health point of view. Also, not all the factors that reached consensus in the Delphi survey were included in the final proposal of an operational definition of high-risk cannabis use. For instance, although in round 2 "social vulnerabilities" and "history of violence" reached consensus, the team finally concluded that these concepts were ambiguous and might promote stigma, so they were excluded.

Since the included cannabis experts were all from Spain, the proposed definition of cannabis high-risk use might not be applicable in other sociocultural contexts. As with other definitions involving changing substance consumption patterns (such as guidelines on risky alcohol use), a specific definition of high-risk cannabis use might need to be adapted to different geographical realities. Although questions included in Delphi rounds were based on current international evidence, the final recommendations included in this proposal are highly influenced by experts' opinions, with their consequent limitations. Also, given the characteristics of the Delphi methodology used to achieve consensus, the authors and initiators might have exerted some influence on the process through the proposals they have put forward.

Nonetheless, to the best of our knowledge, the proposed operational definition of high-risk cannabis use is one of the few evidence-based and expert-agreed guides currently available on factors that influence cannabis health harms. The presented operational definition aims to be a complimentary effort to past similar guidelines to generate recommendations regarding high-risk cannabis

consumption based on global scientific evidence, but also adapted to the specific sociocultural context of a European jurisdiction (Spain). This proposal includes experts' consensus on defined quantitative thresholds for age of use, potency, quantity, and frequency of use that might predict a higher risk of harm. Moreover, quantity of use is assessed with a standardized unit [21].

The proposed definition of high-risk cannabis use is one of the first steps needed to inform individuals' decisions, professionals, and policy-makers about cannabis use and related health harms. Additionally, this specific definition of high-risk cannabis use supports the implementation of evidence-based prevention and risk reduction prevention programs.

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Statement of Ethics

This study protocol was reviewed and approved by the local Ethics Committee for Clinical Research of Hospital Clinic de Barcelona, Approval No. HCB/2017/0795. Written informed consent was obtained from participants to participate in the study. All experts who participated in the consensus were also specifically asked for permission to publish their names and affiliations; the list of participants' names in the Acknowledgement section includes the identities of only those experts who participated in the consensus who explicitly gave their written consent to be made public. This study was performed in accordance with the guidance on Good Clinical Practice (CPMP/ICH/135/95) and with the ethical principles stated in the Declaration of Helsinki 1964, as revised at the 64th World Medical Association (WMA) General Assembly in Fortaleza, Brazil, October 2013.

Conflict of Interest Statement

C.O. has received travel grants from Lundbeck, which had no bearing on the research of this study. A.G. has received honoraria, research grants and travel grants from Lundbeck and D&A Pharma, which had no bearing on the research of this study. M.B.O. has received travel grants from Lundbeck and Camurus and CME-related honoraria from Novo Nordisk, all outside the subject of this article. H.L.P. has received honoraria and travel grants from Lundbeck, which had no bearing on the research of this study. The authors declare no competing interests related to this work.

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Author Contributions

CRediT author statement: *Clara Oliveras*: data curation, formal analysis, investigation, methodology, writing – original draft, writing-review and editing; *Pablo Rodrigo Guzman Cortez*: writing – original draft, and writing – review and editing; *Laura Nuño*: data curation, formal analysis, investigation, methodology, writing – review and editing; *Joan Colom*: conceptualization, writing – review and editing; *Cristina Casajuana Kögel*: conceptualization, writing – review and editing; *Francisco Pascual*: writing – review and editing; *Sergio Fernández-Artamendi*: writing – review and editing; *Antoni Gual*: conceptualization, data curation, investigation, methodology, writing – review and editing; *Mercè Balcells-Oliveró*: conceptualization, data curation, investigation, methodology, supervision, writing – original draft, writing – review and editing; *Hugo López-Pelayo*: conceptualization, data curation, formal analysis, investigation, methodology, supervision, writing – original draft, and writing – review and editing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to containing information that could compromise the privacy of research participants but are available from the corresponding author (C.O.) upon reasonable request.

References

1 United Nations Office on Drugs and Crime (UNODC). World drug report 2023: executive summary. Vienna, Austria; 2023. https://www.10.30875/9789287053978-05.zhtml
2 Campeny E, López-Pelayo H, Nutt D, Blithikioti C, Oliveras C, Nuño L, et al. The blind men and the elephant: systematic review of systematic reviews of cannabis use related health harms. Eur Neuropsychopharmacol. 2020;33:1–35. https://doi.org/10.1016/j.euroneuro.2020.02.003
3 Solmi M, De Toffol M, Kim JY, Choi MJ, Stubbs B, Thompson T, et al. Balancing risks and benefits of cannabis use: Umbrella review of meta-analyses of randomised controlled trials and observational studies. BMJ. 2023; 382:e072348. https://doi.org/10.1136/bmj-2022-072348
4 National Academies of Sciences. Engineering and M. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington (DC), USA; 2017. https://doi.org/10.17226/24625
5 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Cannabis legislation in Europe; 2018. https://doi.org/10.2810/4682
6 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Cannabis – the current situation in Europe (European drug report 2023) [Internet]. 2023 [cited 2024 Mar 11]. Available from: https://www.emcdda.europa.eu/publications/european-drug-report/2023/cannabis_en
7 European monitoring Centre for drugs and drug addiction. European Drug Report 2023: Trends and developments [internet]. 2023. https://doi.org/10.2810/161905
8 Manthey J, Freeman TP, Kilian C, López-Pelayo H, Rehm J. Public health monitoring of cannabis use in Europe: prevalence of use, cannabis potency, and treatment rates. Lancet Reg Health Eur. 2021;10:100227. https://doi.org/10.1016/j.lanepe.2021.100227
9 United Nations Office on Drugs and Crime. World drug report 2022: Drug market Trends of cannabis and opioids. 2022. Available from: https://www.unodc.org/unodc/en/data-and-analysis/wdr-2022_booklet-3.html
10 Bort R, Garber-Paul E, Ward A. The United States of weed [Internet]. Roll Stone. 2023 [cited 2024 Feb 5]. Available from: https://www.rollingstone.com/feature/cannabis-legalization-states-map-831885/
11 Matthews AL, Hickey C. More US states are regulating marijuana. In: See where it's legal across the country [Internet]. CNN; 2023. [cited 2024 Feb 5]. Available from: https://edition.cnn.com/us/us-states-where-marijuana-is-legal-dg/index.html
12 Wikipedia. Legality of cannabis by U.S. jurisdiction [Internet]. 2024. [cited 2024 Apr 23]. Available from: https://en.wikipedia.org/wiki/Legality_of_cannabis_by_U.S._jurisdiction
13 CNBC. These European countries are pushing to legalize weed — but the EU is not on board [Internet]. 2023 [cited 2023 Jun 17]. Available from: https://www.cnbc.com/2023/05/11/germany-czechia-luxembourg-netherlands-push-to-legalize-cannabis.html
14 CNN. This country calls time on the 'war on drugs' [Internet]. 2022 [cited 2023 Jun 17]. Available from: https://edition.cnn.com/2022/08/21/americas/colombia-marijuana-bill-war-on-drugs-intl-cmd/index.html
15 The Guardian. "This is another revolution": could legalisation of cannabis transform Mexico's economy? [Internet]. 2023 [cited 2023 Jun 17]. Available from: https://www.theguardian.com/global-development/2023/jan/05/legalisation-cannabis-transform-mexico-economy
16 Spanish National Plan on Drugs. Cannabis-Aspectos Regulatorios (Plan Nacional Sobre Drogas) [Internet]. 2024. Available from: https://pnsd.sanidad.gob.es/fr/profesionales/cannabis/PaisesRegulados/home.htm
17 World Health Organization (WHO). Lexicon of alcohol and drug terms. Geneva; 1994.Available from: https://apps.who.int/iris/handle/10665/39461
18 Casajuana C, López-Pelayo H, Balcells MM, Miquel L, Colom J, Gual A. Definitions of risky and problematic cannabis use: a systematic review. Subst Use Misuse. 2016; 51(13):1760–70. https://doi.org/10.1080/10826084.2016.1197266
19 Anderson P, Gual A, Colom J. Clinical guidelines on identification and Brief interventions Barcelona; 2005. Available from: https://inebria.net/wp-content/uploads/2017/09/cg_1.pdf
20 Balcells-Oliveró M, Oliveras C. Defining cannabis risky use: Building the plane while you fly it. Eur Neuropsychopharmacol. 2023; 69:84–6. https://doi.org/10.1016/j.euroneuro.2023.02.003
21 Casajuana Kögel C, Balcells-Olivero MM, López-Pelayo H, Miquel L, Teixidó L, Colom J, et al. The standard joint unit. Drug Alcohol Depend. 2017;176:109–16. https://doi.org/10.1016/j.drugalcdep.2017.03.010
22 Freeman T, Lorenzetti V. Standard THC units': a proposal to standardize dose across all cannabis products and methods of administration. Addiction. 2020;115(7):1207–16. https://doi.org/10.1111/add.14842
23 López-Pelayo H, Matrai S, Balcells-Olivero M, Campeny E, Braddick F, Bossong MG, et al. Supporting future cannabis policy: developing a standard joint unit: a Brief backcasting exercise. Front Psychiatry. 2021;12: 675033. https://doi.org/10.3389/fpsyt.2021.675033
24 López-Pelayo H, Matrai S, Balcells-Olivero M, Campeny E, Braddick F, Bossong MG, et al. Standard units for cannabis dose: Why is it important to standardize cannabis dose for drug policy and how can we enhance its place on the public health agenda? Int J Drug Policy. 2021;97:103350. https://doi.org/10.1016/j.drugpo.2021.103350
25 Yousuf MI. Using experts' opinions through Delphi technique. Pract Assessment, Res Eval. 2007;12(4).

26 López-Pelayo H, Campeny E, Oliveras C, Rehm J, Manthey J, Gual A, et al. Early, chronic, and acute cannabis exposure and their relationship with cognitive and behavioral harms. Front Psychiatry. 2021;12:643556. https://doi.org/10.3389/fpsyt.2021.643556
27 Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014;67(4):401–9. https://doi.org/10.1016/j.jclinepi.2013.12.002
28 Nuño L, Guilera G, Rojo E, Gómez-Benito J, Barrios M. An integrated account of expert perspectives on functioning in schizophrenia. J Clin Med. 2021;10(18):4223. https://doi.org/10.3390/jcm10184223
29 DeWalt DA, Berkman ND, Sheridan S, Lohr KN, Pignone MP. Literacy and health outcomes: a systematic review of the literature. J Gen Intern Med. 2004;19(12):1228–39. https://doi.org/10.1111/j.1525-1497.2004.40153.x
30 Von Wagner C, Knight K, Steptoe A, Wardle J. Functional health literacy and health-promoting behaviour in a national sample of British adults. J Epidemiol Community Heal. 2007;61(12):1086–90. https://doi.org/10.1136/jech.2006.053967
31 Wharf Higgins J, Begoray D, MacDonald M. A social ecological conceptual framework for understanding adolescent health literacy in the health education classroom. Am J Community Psychol. 2009;44(3–4):350–62. https://doi.org/10.1007/s10464-009-9270-8
32 Gordon CS, Jones SC, Kervin L. Effectiveness of alcohol media literacy programmes: a systematic literature review. Health Educ Res. 2015;30(3):449–65. https://doi.org/10.1093/her/cyv015
33 Taggart J, Williams A, Dennis S, Newall A, Shortus T, Zwar N, et al. A systematic review of interventions in primary care to improve health literacy for chronic disease behavioral risk factors. BMC Fam Pract. 2012;13:49. https://doi.org/10.1186/1471-2296-13-49
34 Bröder J, Okan O, Bauer U, Schlupp S, Pinheiro P. Advancing perspectives on health literacy in childhood and youth. Health Promot Int. 2020;35(3):575–85. https://doi.org/10.1093/heapro/daz041
35 Fischer B, Jeffries V, Hall W, Room R, Goldner E, Rehm J. Lower Risk cannabis use Guidelines for Canada (LRCUG): a narrative review of evidence and recommendations. Can J Public Heal. 2011;102(5):324–7. https://doi.org/10.1007/BF03404169
36 Fischer B, Russell C, Sabioni P, van den Brink W, Le Foll B, Hall W, et al. Lower-risk cannabis use guidelines: a comprehensive update of evidence and recommendations. Am J Public Health. 2017;107(8):e1–12. https://doi.org/10.2105/AJPH.2017.303818
37 Fischer B, Robinson T, Bullen C, Curran V, Jutras-Aswad D, Medina-Mora ME, et al. Lower-Risk Cannabis Use Guidelines (LRCUG) for reducing health harms from non-medical cannabis use: a comprehensive evidence and recommendations update. Int J Drug Policy. 2022;99:103381. https://doi.org/10.1016/j.drugpo.2021.103381
38 Holmes J, Angus C, Meier PS, Buykx P, Brennan A. How should we set consumption thresholds for low risk drinking guidelines? Achieving objectivity and transparency using evidence, expert judgement and pragmatism. Addiction. 2019;114(4):590–600. https://doi.org/10.1111/add.14381
39 Spanish Ministry of Health. Límites de Consumo de Bajo Riesgo de Alcohol. In: Actualización del riesgo relacionado con los niveles de consumo de alcohol, el patrón de consumo y el tipo de bebida; 2020. Available from: https://www.sanidad.gob.es/areas/promocionPrevencion/alcohol/documentosTecnicos/limiteConsumoBajoRiesgo.htm
40 NHS. UK low risk drinking guidelines. [Internet]Available from: https://www.nhs.uk/better-health/drink-less/
41 Government of Canada. Canada low-risk alcohol drinking guidelines [Internet]. Available from: https://www.canada.ca/en/health-canada/services/substance-use/alcohol/low-risk-alcohol-drinking-guidelines.html
42 Madero S, Oliveras C, Pons MT, Sague M, López-Pelayo H, Gual A, et al. Cannabis use the week before admission to psychiatric inpatient service as a marker of severity. J Psychiatr Res. 2020;129:40–6. https://doi.org/10.1016/j.jpsychires.2020.05.028
43 National Plan on Drugs. Spanish Ministry of Health. ESTADÍSTICAS 2023. Alcohol, tabaco y drogas ilegales en España. Madrid, Spain. 2023. Available from: https://pnsd.sanidad.gob.es/
44 Wood S, Gabrys R, Freeman T, Hammond D. Canada's THC unit: Applications for the legal cannabis market. Int J Drug Policy. 2024;128(May):104457. https://doi.org/10.1016/j.drugpo.2024.104457
45 Fischer B, Malta M, Messas G, Ribeiro M. Introducing the evidence-based population health tool of the lower-risk cannabis use guidelines to Brazil. Braz J Psychiatry. 2019;41(6):550–5. https://doi.org/10.1590/1516-4446-2018-0239
46 Chen T, Hassan AN, Le Foll B. 3-Year follow-up of lower risk cannabis use patterns: evidence from a longitudinal survey. Can J Psychiatry. 2022;67(1):48–56. https://doi.org/10.1177/0706743721996118
47 Shah S, Schwenk ES, Sondekoppam RV, Clarke H, Zakowski M, Rzasa-Lynn RS, et al. ASRA Pain Medicine consensus guidelines on the management of the perioperative patient on cannabis and cannabinoids. Reg Anesth Pain Med. 2023;48(3):97–117. https://doi.org/10.1136/rapm-2022-104013
48 Moebes ZR, Card KG, Koenig B, Benoit C. Lower-risk substance use guidelines accessible by youth. Subst Abus Treat Prev Policy. 2023;18(1):10–2. https://doi.org/10.1186/s13011-023-00516-3
49 Van Os J, Bak M, Hanssen M, Bijl RV, De Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol. 2002;156(4):319–27. https://doi.org/10.1093/aje/kwf043
50 Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. Addiction. 2005;100(3):354–66. https://doi.org/10.1111/j.1360-0443.2005.01001.x
51 Rössler W, Hengartner MP, Angst J, Ajdacic-Gross V. Linking substance use with symptoms of subclinical psychosis in a community cohort over 30 years. Addiction. 2012;107(6):1174–84. https://doi.org/10.1111/j.1360-0443.2011.03760.x
52 Bechtold J, Hipwell A, Lewis DA, Loeber R, Pardini D. Concurrent and sustained cumulative effects of adolescent marijuana use on subclinical psychotic symptoms. Am J Psychiatry. 2016;173(8):781–9. https://doi.org/10.1176/appi.ajp.2016.15070878
53 Callaghan RC, Sanches M, Kish SJ. Quantity and frequency of cannabis use in relation to cannabis-use disorder and cannabis-related problems. Drug Alcohol Depend. 2020;217:108271. https://doi.org/10.1016/j.drugalcdep.2020.108271
54 Coffey C, Carlin JB, Lynskey M, Li N, Patton GC. Adolescent precursors of cannabis dependence: findings from the Victorian adolescent health cohort study. Br J Psychiatry. 2003;182:330–6. https://doi.org/10.1192/bjp.182.4.330
55 Casajuana C, López-Pelayo H, Miquel L, Balcells-Oliveró MM, Colom J, Gual A. Quantitative criteria to screen for cannabis use disorder. Eur Addict Res. 2018;24(3):109–17. https://doi.org/10.1159/000488346
56 World Health Organization (WHO). Mental disorders: key facts [Internet]. 2022. [cited 2024 Jul 5]. Available from: https://www.who.int/news-room/fact-sheets/detail/mental-disorders
57 United Nations Office on Drugs and Crime. World drug report 2022: executive summary / policy Implications. Vienna, Austria; 2022. Available from: https://www.unodc.org/unodc/en/data-and-analysis/wdr-2022_booklet-1.html
58 Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, et al. Effects of cannabis use on human behavior, including cognition,motivation, and psychosis: a review. JAMA Psychiatry. 2016;73(3):292–7. https://doi.org/10.1001/jamapsychiatry.2015.3278
59 Orr C, Spechler P, Cao Z, Albaugh M, Chaarani B, Mackey S, et al. Grey matter volume differences associated with extremely low levels of cannabis use in adolescence. J Neurosci. 2019;39(10):1817–27. https://doi.org/10.1523/JNEUROSCI.3375-17.2018

60 Suerken CK, Reboussin BA, Egan KL, Sutfin EL, Wagoner KG, Spangler J, et al. Marijuana use trajectories and academic outcomes among college students. Drug Alcohol Depend. 2016;162:137–45. https://doi.org/10.1016/j.drugalcdep.2016.02.041

61 Lorenzetti V, Hoch E, Hall W. Adolescent cannabis use, cognition, brain health and educational outcomes: a review of the evidence. Eur Neuropsychopharmacol. 2020;36:169–80. https://doi.org/10.1016/j.euroneuro.2020.03.012

62 van der Steur SJ, Batalla A, Bossong MG. Factors moderating the association between cannabis use and psychosis risk: a systematic review. Brain Sci. 2020;10(2):97. https://doi.org/10.3390/brainsci10020097