Cannabis sativa use in adolescence and risk of psychosis: a systematic review

Uso de *cannabis sativa* na adolescência e risco de psicose: uma revisão sistemática

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ABSTRACT

Background: Studies have pointed out the increased risk of developing psychosis in adulthood related to *cannabis* use during adolescence. Aim: To conduct a systematic review of the literature on the use of *cannabis* in adolescence and risk of psychosis. Method: We conducted a systematic review in accordance with PRISMA guidelines. We searched by PubMed, PsycINFO, and SciELO database between 2010 and 2019. Results: After an accurate analysis, of the 8.673 records screened articles, we selected and included 32 original studies in this systematic review. The sample in the original papers totaled 81.049 participants, indicating an association between early use of cannabis and the onset of psychosis in 97.3% of the studies, with a robust variety of instruments used. It has been shown that early *cannabis* use, associated to genetic vulnerability, gender, duration of use, environmental and social factors, or the use of other drugs may lead to late development of schizophrenia whether compared with non-users. Conclusion: There is evidence that marijuana use is associated with the occurrence of psychosis in adolescence and later in life. However, other variables, such as social and biological aspects, should be considered. This shows the importance of educational programs of public policies on risks of *cannabis* and clear information to the population about several combination factors that might lead to trigger psychotic disorders, such as schizophrenia.

Keywords: *Cannabis*, adolescence, psychosis, systematic review.

RESUMO
Introdução: pesquisas têm apontado para o risco ampliado de desenvolver transtornos psicóticos na idade adulta relacionados ao uso de *cannabis* durante a adolescência. Objetivo: realizar uma revisão sistemática sobre o uso de *cannabis* na adolescência e o risco de desenvolver psicose. Método: foi realizada uma revisão sistemática de acordo com as diretrizes do PRISMA. As pesquisas foram realizadas nas bases de dados PubMed, PsycINFO e SciELO entre 2010 e 2019. Resultados: Após uma análise precisa, dos 8.673 registros de artigos triados, selecionamos e incluímos 32 estudos originais nesta revisão. A amostra dos artigos originais totalizou 81.049 participantes, indicando relação entre o uso precoce de *cannabis* e o desenvolvimento de psicose em 97,3% dos estudos, com robusta variedade de instrumentos utilizados. Os resultados demonstraram que o uso precoce de *cannabis*, associado à vulnerabilidade genética, gênero, tempo de uso, fatores ambientais e sociais ou o uso de outras drogas podem levar ao aparecimento tardio da esquizofrenia quando comparados aos não usuários. Conclusão: Há evidências de que o uso de maconha está associado à ocorrência de psicose na adolescência e na vida adulta. Porém, outras variáveis, como aspectos sociais e biológicos, devem ser consideradas. Isso mostra a importância de programas educacionais e políticas públicas sobre os riscos do uso da *cannabis* na adolescência, oferecendo informações claras à população sobre as combinações de vários fatores que podem levar ao desencadeamento de transtornos psicóticos, como a esquizofrenia.

Palavras-chave: *Cannabis*, adolescência, psicose, revisão sistemática.

1 INTRODUCTION

Although there is considerable discussion about the medical use of marijuana, there is also a parallel discussion on the potential adverse health effects; therefore, in this article we emphasize the relationship between cannabis and psychosis, particularly in adolescence. Marijuana, whose main substance is delta-9-tetrahydrocannabinol (THC), is derived from *Cannabis sativa*, a Central Asian plant belonging to the Cannabaceae family.[1] As the main substance in *cannabis*, THC still contains approximately 538 chemical elements.[2] It is estimated that 10% of those who try the drug will become daily users.[3]

The risk of developing psychotic marijuana symptoms results from the fact that THC interacts with the largest receptors system in the human body, the endocannabinoid.[4] Although its effects vary from person to person, depending on the quantity, length and frequency of use, increased use of marijuana intensifies the effect caused by THC[5], leading to changes in perceptions and slower reflexes. The effects also include negative cognitive effects in working memory, inhibition control the notion of time[6,7], in addition to an association between abuse of marijuana and vulnerability in adolescence to trigger psychotic episodes.[8,5,9] Early marijuana consumption increases the probability of dependency, generating significant impairments in cognitive, emotional, social, and

mental development.[10] Authors suggest that desire for social acceptance, self-affirmation and individual independence as possibly causes for young people to use drugs, which typically starts with cigarettes, alcohol and then marijuana, and which can consequently lead to the use of multiple illicit drugs during this phase of development.[11]

It has recently been shown that the consistent use of marijuana in early adolescence can lead to brain atrophies such as decrease in gray matter.[12,13] Along these lines, there is agreement that the use of *cannabis* is associated with a greater risk of developing psychotic diseases, including schizophrenia.[14] Exposure to *cannabis* during adolescence is most strongly associated with the onset of psychosis among those who are particularly more vulnerable, such as those who have been abused as children and those who have a family history of schizophrenia.[15] Large, Di Forti, and Murray[16] strongly state that using marijuana in adolescence increases the risks of schizophrenia in adulthood. In addition, they also point to the fact that young people who smoke marijuana are three times more likely to develop psychosis later in life. In a meta-analysis of 66,816 individuals, results demonstrated that higher levels of *cannabis* use were associated with increased risk of psychosis in all included studies.[17]

A logistic regression model resulted in an OR of 3.90 (95% CI 2.84-5.34) for the risk of schizophrenia and other psychosis-related outcomes among heavier cannabis users, when compared to non-users. Current evidence shows that high levels of cannabis use increase the risk of psychotic outcomes and confirms a dose-response relationship between the level of use and the risk of psychosis.[17] Studies have shown a relationship as well between marijuana and the appearance of psychosis, among them schizophrenia, in a minority of individuals with variation in the gene of COMT enzyme (cathecol-O-methyltransferase).[18] This variation creates a relationship between genetic predisposition and environmental exposure to marijuana in the development of psychotic conditions. Therefore, the chance of the disease developing in individuals who have this variation is greater when they use marijuana, unlike those who do not have this genetic variation.

The discussion on the medical use of marijuana has been focused on the social and scientific debate, for possessing components in controlled doses. The therapeutic use of marijuana has been the focus on social and scientific discussion, since in controlled doses if has components that could help in the treatment of several diseases. However, there are still many doubts about the harmful effects on individuals and public health.[19] Cannabidiol (CBD) is one of the components of *cannabis* that helps in the treatment of certain diseases, such as epilepsy. However, the dose level of the substance must be

controlled by a specialist. In research by Pierre[20] the benefits of CBD in psychiatric patients have been questioned. It is worth noting here that the medicinal use is different from recreational use, since the preparation for medicinal use features a specific process, beginning with cultivation of the plant, unlike the preparation for recreational use, in which *cannabis* is mixed with substances considered impure. According to Pierre[20], the use of marijuana by individuals who already have a disorder enables a destructive effect. On the other hand, research suggests that patients with schizophrenia may have some benefit in their treatment using cannabidiol. Nevertheless, the evidence is mixed, and the benefits are uncertain.[21]

In medicinal preparation, in addition to extraction of CBD, other *cannabis* substances are extracted for therapeutic purposes and to help alleviate possible symptoms, thus giving rise to some products. They are: sativex, nabilone, dronabinol, marinol, rimonabant, bedrocan, among others.[22] However, some of the products mentioned have been banned due to side effects, but they could help with treatment for cancer and AIDS, epilepsy, Alzheimer's and for chemotherapy, to name a few. It is therefore imperative that the debate on the medicinal use of *cannabis* not be conflated with the legalization of recreational marijuana. Despite its importance in this field, the risks of recreational marijuana use cannot be neglected, and we therefore focus on this study the impact of recreational *cannabis* and its relationship with psychotic conditions in adolescence.

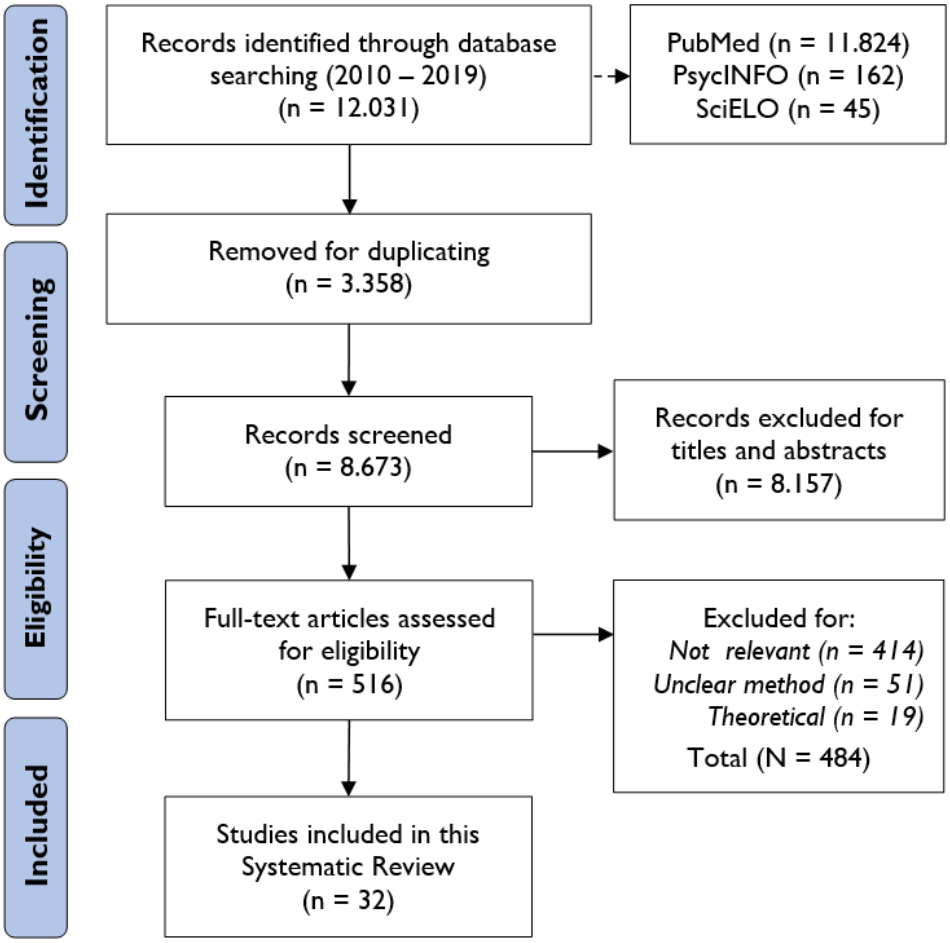
The aim of this systematic review was to verify the *cannabis* use in adolescence and the risk of developing psychosis.

2 METHOD

We conducted a systematic review of the literature on the topic of cannabis as a risk factor for psychosis in adolescence through PubMed, PsycINFO and SciELO databases search, between 2010 and 2019. Thus, we searched for relevant articles using the terms "*adolescence* AND *cannabis*" OR "*cannabis* AND *psychosis*" OR "*adolescence* AND *schizophrenia"*, OR "*cannabis* AND *adolescence* AND *psychosis*" OR "*cannabis* AND *adolescen** AND *psychos**" OR "*cannabis* AND *youth* AND *psychos**" in English, Spanish and Portuguese language. A total of 8.673 studies were found. After exclusion of redundancies and assessing of title, abstract and full text for eligibility, 32 articles were selected through consensus among the authors, according to relevance and contribution to the subject. All of them have been studied critically, considering the design of this

review. The process of data extraction was carried out independently and double-blindly by two reviewers allocated at random.

Figure 1. Flow diagram of included studies in this review.



Elaborated by authors, based on PRISMA.

The search strategy, selection of publications and the reporting of review results were aligned with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[23] (www.prisma-statement.org). Two reviewers critically and independently evaluated all identified documents. Firstly, two reviewers extracted the data, and a third reviewer checked the works and then both reviewers discussed the process. Divergences and discrepancies were resolved through discussions that included the participation of a fourth reviewer.

Studies with different objectives (e.g., not investigating psychosis developing, focusing on other drugs use, not adolescent included) were excluded for not been relevant for this review. In unclear method it was taken into account studies not offering enough details or omitting them (e.g., inclusion criteria), not describing important sample characteristics such as, comorbidities presence or absence. The evaluation was guided by

a PRISMA checklist, assessing the clarity of the research. In addition, PICOS tool (for participants, interventions, comparisons, results, and study design) was used to identify relevant articles. This was designed to reduce the risk of bias in included articles, separately evaluating the evidence and the applicability of the results. The entire process study selection is further detailed in Figure 1.

3 RESULTS

Initially, 8.673 articles were identified, with 8.643 excluded after step-by-step close analysis. Thus, 32 original articles were included for this review published between the years 2010 and 2019. The studies were originated from USA (12), United Kingdom (4), Australia (4), Canada (3), Spain (3), Sweden (3), Brazil (1), Italy (1), The Netherlands (1), and Finland (1).

Table 1. Original studies (n = 32) included in this systematic review.

Author Country	Sample	Design	Measures	Results
Shahzade et al.[24] USA	178 participants 1: healthy controls with cannabis use, 2: schizophrenia patients with cannabis use. 18 – 40 years old.	Cross-sectional, Control Group	DIGS - version IV, SIS	We have found that early use not only increases overall risk, but also signals and amplifies many of the most impairing symptoms. To mitigate this, we propose a model for identifying at-risk individuals while explaining and predicting the particular psychiatric concerns associated with such use. ANOVA testing was performed to test whether the age of first cannabis use differ across the four reason groups. There was a significant difference between the reason groups [F (3, 51) = 4.02, *p* = .01] for age of onset of cannabis use.
Mustonen et al.[25] Finland	6.534, age 15 –16 years	Cross-sectional, Prospective	Register for Health Care, Register of Primary Health Care Visits, PROD-screen,	The risk of psychosis was elevated in individuals who had tried cannabis five times or more (hazard ratio, (HR) = 6.5, 95% CI 3.0–13.9). The association remained statistically significant even when adjusted for prodromal

Author Country	Sample	Design	Measures	Results
			Parental psychosis	symptoms, other substance use and parental psychosis (HR = 3.0, 95% CI 1.1–8.0). Adolescent cannabis use is associated with increased risk of psychosis even after adjustment for baseline prodromal symptoms, parental psychosis, and other substance use.
Mané et al.[26] Spain	284 participants with first episode of psychosis.	Cross-sectional, controlled clinical trial, Control Group	K-SADS SCIDI, PANSS, YMRS, MADR, TGAFS, CGA, MAIDAD,	Statistically significant differences in the age of onset of psychosis per sex (male/female) (23.27 ± 5.99 versus 24.90 ± 5.89; p = 0.025; t = 2.25) and first use of cannabis (yes/no) (21.28 +/- 4.72 vs. 24.55 +/- 6.15; p <0.001; t = -4.76)
McHugh et al.[27] Australia	731 young participants, from 12 to 25 years old, with no risk for psychosis or psychotic disorder.	Longitudinal, random, controlled clinical trial, Control Group, 5-year follow-up	CAARMS, QIDS, SOFAS, YMRS, K10, SPHERE 12, GAD-7, OASIS WHO, WHODAS-12, WHOQOL, SCOFF, WHO-ASSIST, BIS/BAS	Those at risk for psychosis showed higher rates of involvement with cannabis than those in search for help (p = 0.02). Individuals at risk for psychosis showed higher rates of consumption of high-risk cannabis (4.7% at risk for psychosis / 1.6% searching for help) and average-risk cannabis (25.4% at risk for psychosis / 21.2% searching for help); 8.67, p = 0.01.
Carney et al.[28] Australia	801 young participants, from 12 to 15 years old. 279 at risk for psychosis, 59 with psychotic disorder, 452 with no psychosis criterion.	Cross-sectional, Controlled clinical trial.	CAARMS, QIDS, SOFAS, YMRS, K10, SPHERE 12, GAD-7, OASIS, WHO, WHODAS-12, WHOQOL, SCOFF, WHO,	Risk for psychosis (4.45); searching for help (3.20; p = 0.02). A significant higher number of participants at risk for psychosis have used cannabis during their life and currently use marijuana (33%) in comparison to control groups of participants searching for help (26%).

Author Country	Sample	Design	Measures	Results
			ASSIST, BIS/BAS	
Bourque et al.[29] Canada	2,566 young participants, from 13 to 16 years old, evaluated every year for 4 years at medical practices.	Longitudinal, random, controlled clinical trial, 3-year follow-up	DADPA, BSI, CFT, SOPT, DLTCMS, PALP, FASA, SDQ,	A great increase in the use of cannabis from ages 13 to 16 was associated to a higher probability of being linked to an average trajectory of increased psychotic experiences (PE) [odds ratio = 2.59].
Hodgins et al.[9] Sweden	1.992 participants treated from 1968 to 1971, 1,567 treated from 1980 to 1984, and 180 treated in 2004.	Longitudinal, random, controlled clinical trial	K-SADS, SCID - I and II.	Among those who have developed schizophrenia, substance abuse by adolescents was associated to the increase of risk of Substance Use Disorders (SUDs). SUDs were more common in participants with schizophrenia than without. Men (M): Clinical Sample 1 (CS1) + General Population 1 (GP1) = 1.23,4% v. 5,8% (Fisher's Exact Test - FET, $p < 0,001$); M: CS2 + GP2 = 35,7% v. 8,0% (FET, $p = 0,030$); Women (W): CS1 + GP1 = 18,5% v. 6,3% (FET, $p = 0,030$); W: CS2 + PG2 = 35,5% v. 7,7% (FET, $p = 0,001$).
González et al.[30] Spain	268 participants with psychosis and 237 control subjects.	Cross-sectional, controlled clinical trial, Control Group, 3-month follow-up	SCID-I, K-SADS-PL, EuropASI, FHPRD, CGI	The association between cannabis consumption and cognitive deficits shown by the analyzed patients varied depending on their family history (FH). FH patients showed a lower probability of having university education ($p < 0.001$) and a higher probability of using marijuana than controls ($p < 0.001$). On the other hand, control subjects were more often active workers ($p < 0.001$).

Author Country	Sample	Design	Measures	Results
Kelley et al.[31] USA	210 participants with 1st episode of psychosis.	Longitudinal, controlled clinical trial	LSUR, SOS	The onset age is considered an immediate risk. The beginning of cannabis uses before or during adolescence was a predictor of psychosis, unrelated to gender and family history (pre-adolescence p = 0.04; adolescence p = 0.04, and transition phase from adolescence into adulthood p = 0,01).
Buchy et al.[32] USA	735 CHR and 278 control participants	Longitudinal, controlled clinical trial, Control group, At baseline and 6- and 12-month follow-ups	SIPS, SOPS, ADUS	In Clinical High Risk (CHR), individuals with cannabis use are higher than in controls and this pattern persists across 1 year. Evaluation of clinical outcome may provide additional information on the longitudinal impact of substance use that cannot be detected through evaluation of transition/non-transition to psychosis alone.
Smith et al.[33] USA	144 healthy participants, 10 healthy participants with a history of use of cannabis, 28 participants with schizophrenia and no history of use of cannabis.	Cross-sectional, controlled clinical trial, Control Group	SCID, SAPS, SANS, WAIS-III, WMS-III, MR, LDHDBM	It was determined that everyone with a history of cannabis consumption showed morphologic differences in the hippocampus in comparison to healthy individuals. Among schizophrenics (SCZ) with history of use of cannabis (Cannabis Use Disorder – CUD), it was observed that the longest CUD was associated to a shape "more similar to the cannabis shape" of the right hemisphere (r = 0.50, p = 0.04) and a longer CUD abstinence was associated to a shape "less similar to the cannabis shape" of the left hemisphere (r = 0.57, p = 0.03).
Buchy et al.[34]	162 participants	Longitudinal, controlled	SOPS, ADUS	The use during adolescence favors a loss of density of

Author Country	Sample	Design	Measures	Results
Canada	at risk for psychosis and 105 healthy participants.	clinical trial, Control Group		grey matter and a decrease of structural connectivity of the white matter. Age was positively and significantly related to the thalamic connectivity with the anterior cingulate cortex (p = 0,01).
Colizzi et al.[35] Italy/ United Kingdom	272 participants with 1st episode of psychosis, 234 control subjects and 253 healthy participants.	Controlled case study	PSQ, MRCSS, CEQmdv, FTND, SPQ	There was a correlation between cannabis consumption and the D2 Dopamine Receptor (DRD2) gene, therefore showing probability to develop a psychotic disorder. Those with a long-term history of consumption also showed an increased risk for psychosis. Among those who had a history of marijuana use, patients who had a first episode of psychosis were more likely to report daily use than control subjects (63.6% vs. 39.8%; x2 = 14.30, $p < 0.001$).
Mané et al.[36] Spain	48 participants with psychosis and 48 control subjects.	Cross-sectional, controlled clinical trial, Control Group	DSM-IV, PANSS, DQ	The age of onset of psychosis was more significant in users than in non-users. Males represented a higher number of users. Non-psychotic cannabis users – 15.83 (2.53). Cannabis users with first psychotic episode – (p = 0.19, t = 1.31).
Håkansso, Johansson [37] Sweden	Case Study with intervention.	Case study	ECT, EEG, MRI	The adolescent was admitted to a hospital and diagnosed with cannabis-induced psychosis.
Koenders et al.[38] Netherlands	80 users with schizophrenia, 33 non-users with schizophrenia and 84 healthy participants.	Cross-sectional, controlled clinical trial, Control Group	DSM-IV, MRI	In the groups of patients with schizophrenia, lower volumes of grey matter were identified in comparison to the control group. A positive tendency of relation between the frequency of cannabis use and a change in the cortical structure was observed (f = 5,70, p = 0,019).

Author Country	Sample	Design	Measures	Results
Epstein et al.[39] USA	134 patients; 10 to 23 years old. 18 adolescents using cannabis with early schizophrenia, 34 with schizophrenia, 29 cannabis users and 53 healthy individuals.	Cross-sectional, controlled clinical trial, Control Group	SAD, SSACP, SCI-DSM-IV, SCID, WRAT-III, ANT	The use of cannabis during adolescence is associated to schizophrenia and showed a decreased efficiency of attention when compared to adolescents with schizophrenia who do not use.
Donoghue et al.[40] England	Initially 511 participants from the AESOP study.	Epidemiologic, observational, and descriptive study	SCAN, IGC, ICD-10, PPHS, DUP	It is suggested that the consumption of cannabis is associated to an earlier start of schizophrenia. The age of the first use of cannabis is associated to the age of onset of psychosis.
Sara et al.[41] Australia	24.306 participants, from 18 to 50 years old.	Longitudinal, Control Group, 5-year follow-up	ICD-10	Disorders caused by using cannabis predict an increase in the probability of progression to schizophrenia (Univariate Odd Reasons - OR = 1.12; 95% CI, 1.01 - 1.24) while stimulant disorders predicted a decreased probability (OR = 0.81; 95% CI, 0.67 - 0.97).
Bernier et al.[42] Canada	240 participants, 120 healthy participants and 120 young participants with a recent schizophrenia diagnosis.	Cross-sectional, controlled clinical trial	SCID, SCID-1, SCI-PANSS, PSP, BAI, CDRSS, DQuest, MRI	The levels of NAA (N-acetylaspartic acid) in patients with schizophrenia were lower in comparison to the control group.
Davis et al.[43] USA	34.653 adult participants.	Epidemiologic, observational, and Cross-sectional study	AUDADIS-IV, SSCID-II, IPDE, DSM-IV, DIDPD	Indicates that the risk of psychosis and the emergence of a schizotypal personality increase with a higher use of marijuana, no matter the dosage. The relation between

Author Country	Sample	Design	Measures	Results
				the use of cannabis to psychosis was of 1,27 (95% CI, 1,03 – 1,57) for use; 1,79 (95% CI, 1,35 – 2,38) for abuse; and 3,69 (95% CI, 2,49 – 5,47) for cannabis addiction.
Stefanis et al.[44] Australia	997 participants.	Cross-sectional, random	DIP, OPCRIT	The effect of the use in patients in the beginning stages of psychosis remained significant after the family history of schizophrenia. In patients who were addicted to cannabis at some point, the effect of age when they started using cannabis on the duration of pre-morbid exposure to cannabis was only significant, f (8.781) = 1.99, *p* = 0.44, adjusted R2 = 0.01.
Cunha et al.[45] Brazil	28 participants with 1st psychotic episode using cannabis, 78 participants with 1st psychotic episode and no history of use and 80 healthy control subjects.	Epidemiologic, Cross-sectional study, Control Group	MRI, DSM-IV, PANSS, SCID, IRB, SPM2, WMS-III, COWAT	Abnormalities were found in patients with no use of cannabis when directly compared to patients with history of use. The use of cannabis started significantly earlier among patients with a first episode of psychosis and a history of use of cannabis (FEP C+, n = 28). The use of cannabis preceded the beginning of psychosis in all patients. The average age of onset of use was of 15.9 years (D*P* = 3.1), the average duration of exposure to cannabis throughout life was of 6.5 years (D*P* = 4.9) and 64.3% (n = 18) had a history of daily use.
Proal et al.[46] USA	87 healthy participants, 84 participants who did not have psychosis	Cross-sectional, controlled clinical trial, Control Group	DIGS-IV, FIGS	It is suggested that family history is a risk. In this case, genetic load is a higher risk than the use of marijuana. There has been an increase in morbid risk for schizophrenia in relatives of patients from

Author Country	Sample	Design	Measures	Results
	and consumed cannabis, 32 participants with psychosis who did not use cannabis and 74 participants with psychosis who used cannabis.			the sample who used and did not use cannabis, in comparison to their respective non-psychotic control samples (p = 0.002, p < 0.001), respectively).
Leeson et al.[47] United Kingdom	99 patients with 1st psychotic episode.	Longitudinal, controlled clinical trial, Control Group, 2-year follow-up	DIP-DM, AUS, WTAR, WAIS-III, RAVLT, CANTB, APNS, YMRS, HRSD, SFS, NOS, PSAS, SAI, CRS	The use of cannabis was considered among the youngest and the beginning of psychosis was too. Early abstinence is a factor that may originate psychotic symptoms. The age in the first use of cannabis was significantly related to the age in the beginning of prodrome (r = 0.47, p < 0.001) and the beginning of psychosis (r = 0.56, p < 0.001). Both the youngest age of cannabis use (β = 0.92, p < 0.001) and the male sex (β = 4.40, p = 0.002) were included as independent predecessors of the beginning of the earliest psychosis (model R2 = 0.43, f 2.50 = 18.85, p < 0.001).
Anglin et al.[48] USA	804 young participants, from 11 to 35 years old	Longitudinal prospective, random, controlled clinical trial 3-follow-up	DISC-IV, SCID-I/NP, PDQ, SCIPD, CIC-SR, SPD	Cannabis users were more likely to develop anxiety or depressive disorders during adolescence and psychotic symptoms during life. The first use of cannabis, defined as the first use before 14 years of age, along with constant use was evident among only 17.1% (n = 97) of all participants who had

Author Country	Sample	Design	Measures	Results
				ever tried cannabis at any age.
Galvez-Buccollini et al.[49] USA	57 participants with psychosis who used marijuana before developing psychosis.	Cross-sectional, controlled clinical trial	DIGS, FIGS	There was a significant association between age in the beginning of consumption and age in the beginning of psychosis (β = 0,4, CI 95% = 0.1 – 0,8, *p* = 0.015). After adjustments for possible interfering factors, such as sex, age, diagnosis of abuse or alcohol addiction, family history of schizophrenia etc., age in the beginning of cannabis use was significantly associated to age in the beginning of psychosis (β = 0,4, 95% CI = 0,1 – 0,7, *p* = 0.004) and age of first hospitalization (β = 0,4, 95% CI = 0,1-0.8, *p* = 0.008). The average time between the beginning of cannabis use and the beginning of psychosis was of 7,0 ± 4,3.
Ho et al.[50] USA	235 participants with schizophrenia	Cross-sectional, controlled clinical trial, 3-follow-up	CASH, WAIS-R, WAIS-R Span, WAIS-R, Symbol, Trail Making A, Stroop Color, Word Test, Wisconsin Card Sorting Test WCST	The use of cannabis in the context of specific CB1 genotypes may contribute to a deficit of white matter volume and cognitive impairment, therefore increasing the risk of developing schizophrenia. Patients with marijuana abuse/addiction showed lower volumes of frontal White Mass (Adjusted Average = 175.6 versus 180.6cc in patients without marijuana abuse/addiction; f = 3,10, *p* = 0,07) and lower volumes of temporal White Mass (Adjusted Average = 68.6 and 70.0 cc respectively, = 5,49, *p* = 0,02).
Welch et al.[51]	147 participants	Longitudinal, controlled	MRI	People at high risk for schizophrenia are more

Author Country	Sample	Design	Measures	Results
United Kingdom	at high risk for schizophrenia and 36 control subjects	clinical trial, Control Group, 1-year follow-up		vulnerable to the effects of cannabis on the brain. Substance abuse predisposes brain abnormalities and may lead to psychosis. The level of use of cannabis was also significantly and positively related to the volumes of left and right lateral ventricles (r = 0,208, *p* = 0,013; r = 0,226, *p* = 0,007, respectively) and third ventricle (r = 0,271, *p* = 0,001). All individuals with an exposure to cannabis higher than isolated use were compared to those below this cutoff level. The first group showed an increased rate of developing schizophrenia (*p* = 0,029, OR = 3,18; 95% CI = 1,08 – 9,36).
Welch et al.[52] United Kingdom	25 participants at high risk for psychosis, from 16 to 25 years old, with cannabis exposure; and 32 not exposed to cannabis.	Longitudinal, controlled clinical trial, Control Group, 2-year follow-up	MRI	Interactions of the period of exposure to cannabis are also shown, after including covariates. As can be noted, the exposure to cannabis is associated with bilateral thalamic volume loss, with a significant effect on the left (f = 4,47, *p* = 0,04) and highly significant effect on the right (f = 7,66, *p* = 0,008).
Compton et al.[53] USA	109 participants with 1st psychotic episode	Cross-sectional, controlled clinical trial	PAS, SOS, SCID, CORS/TOPE	Participants (12 to 15 years of age) who had used cannabis prior to or at 15 years of age (n = 49) were compared to those who had not used prior to or at 15 years of age (n = 60). Those who had used cannabis showed an average initial adolescent social score of 1,21 ± 0,85 in the Premorbid Adjustment Scale, versus 1,75 ± 1,27 shown by those who had not used it (t = 2,34, df = 95, *p* = 0,02),

Author Country	Sample	Design	Measures	Results
				showing better functioning of social developing among those who had used cannabis. For academic development, users showed 3,59 ± 1,46 versus 2,00 ± 1,33 of non-users (t = -4,52, df = 65, p < 0,001).
Sevy et al.[54] USA	49 participants with positive symptoms of schizophrenia with 1st psychotic episode and use of cannabis and 51 participants with schizophrenia and no use of cannabis. All from 16 to 40 years old.	Longitudinal, prospective, random, clinical trial, 3-follow-up	SADS-C+PD, SANS, SCID-I/P, HCT, ISP, CPT, CPT-IP, TMT, WCST, DMST, CVLT, JLO, WAIS-R, WRAT-3	Individuals with cannabis use disorders (CDUs) were significantly younger at the beginning of the study when compared to the group with no history of abuse (22±4 years vs 25±6 years; p < 0.001) and showed an earlier age in the beginning of psychosis (20±4 years vs 22±7 years; p < 0.01). In the beginning of the study, males (n = 40) showed an earlier age in the beginning of psychosis (19±4 vs 23±5) in comparison to females (n = 9; 21 ± 3 vs 24 ± 4).

Table developed by authors.

Note. The studies used The Diagnostic and Statistical Manual of Mental Disorders (DSM) guidelines (IV or V) for diagnostic criteria and there were no questions regarding the diagnostic method used in these studies. In addition to DSM, a significant number of complementary instruments were used, such as: Multidimensional Assessment Instrument for Drug and Alcohol Dependence (MAIDAD); Alcohol and Drug Use Scale (ADUS); Scale of Prodromal Symptoms (SOPS); The Positive Symptom Scale of the Comprehensive Assessment for At-Risk Mental State (CAARMS); WHO Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST); Detection of Alcohol and Drug Problems in Adolescents (DADPA); Brief Symptoms Inventory (BSI); Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS); Structured Clinical Interview for Diagnostic (SCID); European Adaptation of

a Multidimensional Assessment Instrument for Drug and Alcohol Dependence (EuropASI); Family History of Psychosis-Related Disorder (FHPRD); Scale of the Assessment of Positive Symptoms (SAPS); Scale of the Assessment of Negative Symptoms (SANS); Psychosis Screening Questionnaire (PSQ); *Cannabis* Experience Questionnaire modified version (CEQmdv); Fagerström Test for Nicotine Dependence (FTND); Positive and Negative Syndromes Scale (PANSS); Lifetime Substance Use Recall (LSUR); Symptoms Onset in Schizophrenia (SOS); Schizophrenia for School-Age (SSACP); Schedules for Clinical Assessment in Neuropsychiatry (SCAN); Duration of Untreated Psychosis (DUP); Calgary Depression Rating Scale for Schizophrenia (CDRSS); Drug Questionnaire (DQuest); Diagnostic Interview for Psychosis (DIP); Course of Onset and Relapse Schedule/Topography of Psychotic Episode (CORS/TOPE); Schedule for Affective Disorders and Schizophrenia Change Version (SADS-C+PD); and Premorbid Adjustment Scale (PAS); The Diagnostic Interview for Genetic Studies (DIGS-version IV); The Structured Interview for Schizotypy (SIS).

Table 1 shows in detail the sample, design, measures used, and main results of the original studies included in this systematic review. The total sample of the studies involved 81.049 participants. Regarding methodological design, 12 studies were longitudinal, 15 cross-sectional, 3 epidemiological studies, 1 case-control and 1 case report. Of these, the majority was controlled clinical studies or clinical trial with the presence of a control group. A substantial majority of the studies (97.3%) indicated an association between early use of *cannabis* and the onset of psychosis.

4 DISCUSSION

The objective of this review was to verify the *cannabis* use in adolescence and the risk of developing psychosis. Based on the studies included in this review, 81.049 individuals were evaluated. Of these 32 original surveys, nine presented evidence of psychotic symptoms after the onset use of marijuana.[9,31,35-37,44,47,49,53] In these studies, there is a predominance of men and the ages of the individuals in the samples were not always mentioned, although participants were always identified as young or adult individuals who consumed marijuana in adolescence. Furthermore, in studies by Anglin[48] individuals were between the ages of 11 and 35, in Compton et al.[53] between 15 and 18 and Sara et al.[41] considered those 18 to 50. According to the original studies, a large part of the research indicates that the genetic constitution may influence the onset of psychosis, that is, individuals with genetic vulnerability are at risk when compared with

individuals with no family history[26]. As such, it is understood that the effect of use on patients with genetic vulnerability is greater.[27,28,30,44,46,51,52]

A history of long-term, frequent, or daily use and other already existing disorders may also influence the onset of psychosis.[31,34,43,44,50] Studies have shown the early use of *cannabis* may include psychosis.[9,24,25,31,40,41,47-50,53] Therefore, marijuana is considered a trigger drug for psychosis, both for individuals with genetic vulnerability and those with long-term use. In this case, we analyzed a study that reported the case of an adolescent diagnosed with drug-induced psychosis.[37] The subject described in the study began frequent use of marijuana at age 13, and by 17 began presenting psychotic symptoms. Some of the symptoms consisted of persistent delusions, and strange and paranoid behavior. The teenager received intense treatment and was eventually discharged, but even without the use of the drug, his symptoms persisted. Therefore, marijuana was found to be associated as one of the factors that led to the development of schizophrenia for this adolescent.

In addition, abstinence may have influenced psychotic symptoms. It is also worth noting that the history of cannabis abuse and the onset of psychosis was predominantly found in males.[9,36,37,50,54] Additionally, it was observed that that for patients with psychosis associated with marijuana usage, such usage started in adolescence and they developed the symptoms subsequently. Some studies have found that marijuana users with episodes of psychosis have a reduction in brain volume when compared to patients with schizophrenia who did not try the drug, in addition to the brain abnormalities[33,38,42], changes in cognitive functioning and development of depressive symptoms.[29] The effect of marijuana on the body can affect the structures of the frontal, temporal and median lobe. In addition, it may cause morphological changes in the volume and shape of the hippocampus when compared with healthy individuals.[32]

It is worth noting that the effects can cause irreversible damage to the brain.[43] It is also known that cannabinoids increase the activity of dopaminergic neurons in the mesolimbic pathway, therefore, the use of cannabis further increases the activity in the dopaminergic system, so it would be possible to explain the persistence, even if short term, of the psychotic symptoms and experiences.[29] However, marijuana use is not the only factor to be considered, biological, environmental, and social factors are also present.[54,55] Therefore, it can be theorized that the combination of environmental and social factors and the use of *cannabis* lead to the onset of psychotic disorders, such as schizophrenia. It is important here to differentiate psychosis from schizophrenia. Many

long-term users may experience psychotic episodes sporadically without an accurate diagnosis of the disorder, but the episodes tend to repeat themselves over time in a more severe and intense manner and corroborate the diagnosis of schizophrenia. This is due to changes in the nervous system, caused by genetic and aforementioned factors together with cerebral and biochemical changes in neurotransmitters.

Given the fact that schizophrenia is a chronic disease, with a complex nature that affects not just the individual, but all their surroundings, the affected individual will need help stabilizing the symptoms. Independent of continued use of marijuana, symptoms tend to worsen.[56,57] Considering this discussion, it is extremely important to cite health care models. Measures to prevent further damage are essential. Prevention and health promotion are concepts that must be present in society, since use can be prevented, thereby also preventing the appearance of schizophreniform symptoms in the future. In terms of original studies, few studies did not find evidence of an association between *cannabis* and onset of psychosis.[39,45] In these two studies, results showed that the use of marijuana does not affect the brain and its structures, but rather has a moderate effect on attentional performance in adolescents and that abnormalities are found in individuals with schizophrenia and not in users with schizophrenia; that is, the authors attribute the abnormality to disease, not the use of the drug itself. It can be theorized that the studies encountered individuals with greater damage from the disease, or that the marijuana was not entirely impure; the medical form of *cannabis*, as mentioned above, can be used, and is already used, in many countries Additionally, the studies may have concluded that the symptoms and effects of marijuana use were similar to the symptoms of schizophrenia and therefore found no concrete evidence to make such a relationship.

4.1 LIMITATIONS AND STRENGTHS

This systematic review was carried out in accordance with PRISMA guidelines (http://prisma-statement.org/) and used the PICOS tool to identify relevant articles, however, it has not been registered in PROSPERO (International prospective register of systematic reviews). Although we assessed the risk of bias in included articles, some studies might have been suffered from bias due extensive reading of this paper. Nevertheless, in our point of view, it has not affected the results, once several research included have suggested relationships between *cannabis* use in adolescence and psychosis in adulthood. We carefully screened, made eligible and extracted the data in

large search in databases, based on the independently and double-blindly using allocated randomly way, in order to provide a formal assurance and accuracy for further analysis.

5 CONCLUSION

There is evidence that marijuana use is associated with the occurrence of psychosis both in adolescence and later in life. However, other variables should be considered, such as social and biological aspects. This study reinforces the fact that guidance programs for educating on the risks of cannabis use are needed as public policies, demonstrating to the population the risk of a combination of various factors in the use of marijuana in the appearance of psychotic disorders, such as schizophrenia, in this population.

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CONFLICTS OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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