

UNIVERSIDADE FEDERAL DE MINAS GERAIS
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA MOLECULAR
FACULDADE DE MEDICINA

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FATORES ASSOCIADOS AO DESENVOLVIMENTO DE TRANSTORNOS PELO
USO DE MACONHA

BELO HORIZONTE
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FATORES ASSOCIADOS AO DESENVOLVIMENTO DE TRANSTORNOS PELO
USO DE MACONHA

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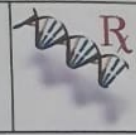
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PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA MOLECULAR



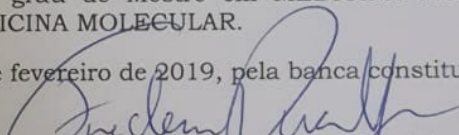
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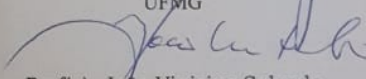
**FATORES DE RISCO E DE PROTEÇÃO PARA A EXPERIMENTAÇÃO E
PARA OS TRANSTORNOS PELO USO DE MACONHA: REVISÃO
SISTEMÁTICA E ESTUDO TRANSVERSAL**

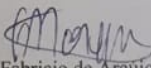
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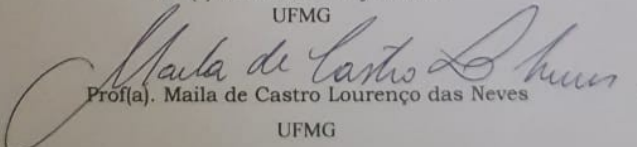
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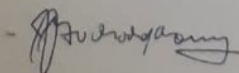
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Belo Horizonte, 27 de fevereiro de 2019.

Aos meus pais,
a quem dedico todas as minhas conquistas.

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RESUMO

Introdução: a maconha é a substância ilícita mais usada no mundo. As taxas de uso dessa substância e transtorno por uso de maconha (TUC) aumentaram na última década, paralelamente à recente aceitação por parte da população do uso da substância. **Objetivo:** realizar revisão bibliográfica sistemática sobre os fatores de risco para a experimentação de maconha (EM) e o TUC. Avaliar a prevalência e os fatores associados ao TUC em uma amostra representativa da população de Belo Horizonte. **Resultados:** em nossa revisão foram encontrados 14 estudos publicados entre 2010 e 2018 que avaliaram os fatores associados à EM e 17 artigos que avaliaram os fatores associados ao TUC. Sexo masculino, renda alta, idade jovem, desvio de conduta, busca de sensações, desempenho escolar abaixo da média, depressão, pais com transtorno por uso de substâncias (TUS), uso de drogas por pares, baixo controle por parte dos pais e fatores relacionados ao uso de outras substâncias são fatores de risco para EM. Fatores como religiosidade, bom relacionamento familiar e viver em um ambiente que valoriza importância da escola são fatores de proteção contra EM. Fatores como sexo masculino, idade jovem, trauma infantil, crise financeira, busca de sensações, desvio de comportamento, transtornos de humor, transtornos ansiosos, TDAH, pais com TUS, fatores relacionados ao uso de substâncias e uso precoce de maconha constituem risco para TUC. Religiosidade é um dos pontos de proteção para TUC. No presente estudo epidemiológico, foram avaliados 7.643 indivíduos. Apurou-se que 11,9% da população estudada experimentaram maconha e 22,9% destes desenvolveram TUC. Indivíduos do sexo masculino, solteiros, sem prática religiosa, que fizeram uso precoce de maconha e com transtorno pelo uso de outras substâncias apresentaram chance significativamente aumentada de desenvolver TUC. **Conclusão:** os fatores de risco para TUC avaliados na população de Belo Horizonte são semelhantes aos encontrados na literatura.

Palavras-chave: Fatores de risco. Maconha. Experimentação. Transtorno pelo uso de maconha.

ABSTRACT

Introduction: Cannabis is the most commonly used illicit substance in the world. Rates of cannabis use and cannabis use disorder (CUD) have increased in the last decade, in parallel with the recent acceptance by the population of substance use. **Objective:** To perform a systematic literature review on the risk factors for cannabis experimentation (CE) and TUC. To assess the prevalence and factors associated with TUC in a representative sample of the population of Belo Horizonte **Results:** Our review we found 14 studies published between 2010 and 2018 that evaluated risk and protective factors for CE and 17 articles that assessed the risk and protective factors for CUD. Males, high income, young age, misconduct, sensations seeking, below average school performance, depression, parents with substance use disorder (SUD), drug use by peers, low parental control, and factors related to the use of other substances were a risk factor for CE. Factors such as religiosity, good family relationship and living in an environment that values the importance of the school were protective factors for CE. Factors such as male gender, young age, childhood trauma, financial crisis, search for sensations, behavioural deviance, mood disorders, anxiety disorders, ADHD, parents with SUD, factors related to substance use, and early use of cannabis were a risk factor for CUD. In our epidemiological study, we evaluated 7,643 individuals. We found that 11.9% of the studied population experimented cannabis and 22.9% of them developed CUD. Being male, single, without religion, using cannabis before 16 years and other substance use disorders had a significantly increased chance of developing CUD. **Conclusion:** The risk factors for CUD evaluated in the population of Belo Horizonte are similar to those found in the literature.

Keywords: Risk factors. Cannabis. Experimentation. Cannabis Use Disorder. Systematic review. Cross-sectional study.

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LISTA DE ABREVIATURAS E SIGLAS

a.C. – Antes de Cristo

ADHD – Attention deficit hyperactivity disorder

APA – American Psychiatric Association

AUD – Alcohol use disorder

CE – cannabis experimentation

CI – Confidence interval

CBD – Canabidiol

CID-10 – Classificação Internacional de Doenças

CRR – Centro Regional de Referência em Drogas

CUD – Cannabis use disorder

d-9-THC – delta-9-tetra-hidrocanabinol

DSM – Manual diagnóstico e estatístico

DSM – III, IV, 5 – Diagnostic and Statistical Manual of Mental Disorders - third, fourth and fifth edition

EM – Experimentou maconha

NIDA – National Institute Drug Abuse

NR – Not Reported

OMS – Organização Mundial da Saúde

OR – Odds ratio

PTSD – Post Traumatic Stress Disorder

SD – standard definition

SEUD – Sedative use disorder

THC – tetra-hidrocanabinol

TUC – Transtorno pelo uso de cannabis

TUC – Transtorno pelo uso de maconha

TUS – Transtornos por uso de substâncias

UNODC – United Nations Office on Drugs and Crime

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¹ Este trabalho foi revisado com base nas novas regras ortográficas aprovadas pelo Acordo Ortográfico assinado entre os países que integram a Comunidade de Países de Língua Portuguesa (CPLP), em vigor no Brasil desde 2009. E foi formatado de acordo com a ABNT NBR 14724 de 17.04.2017.

1 INTRODUÇÃO

A *Cannabis sativa*, ou maconha, é uma planta herbácea, da família das Canabiáceas (Cannabaceae). Ela é cultivada em diversas partes do mundo. A planta caracteriza-se por ter folhas finamente recortadas em segmentos lineares; flores unissexuais e inconspícuas; e pelos granulosos. As plantas femininas segregam uma resina. A utilização da planta se faz, sobretudo, pela extração das fibras do caule, conhecidas como cânhamo; e a resina pode ter propriedades psicoativas (ATAKAN, 2012).

1.1 História

Segundo historiadores, os primeiros registros do uso da *Cannabis sativa* foram para a fabricação de papel e datam de 8.000 anos a.C, na China. Os próprios chineses também descobriram outras formas de uso da planta, principalmente para produção de artigos têxteis e a ação medicinal.

Séculos mais tarde, outros povos aproveitaram as qualidades da planta, fosse ela consumida como alimento, medicamento ou usada como combustível. Sua grande importância histórica se deve ao fato de a maconha ter a fibra natural mais resistente e forte do que todas as outras, podendo ser cultivada em praticamente qualquer tipo de solo.

Da China ela se espalhou para a Índia, o Oriente Médio, o Norte da África. De lá desceu rumo à África Subsaariana e subiu até a Europa, via Turquia. O frio europeu parece ser uma das razões pelas quais a erva não era fumada no continente.

Em tempos passados a maconha somente poderia ser "colhida" na Europa e em regiões circunvizinhas no período entre setembro e dezembro. Na década de 90 iniciou-se o cultivo artificial da maconha, quando foram introduzidas técnicas de hidroponia e iluminação artificial (ATAKAN, 2012).

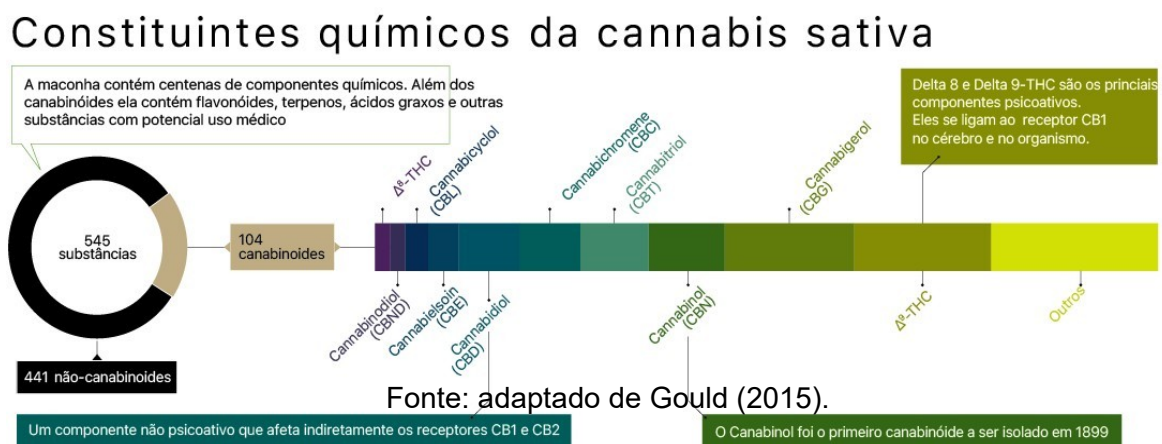
Na América a maconha era utilizada como fonte de fibras para a confecção de cordas e roupas. Seu óleo era empregado na fabricação de tintas (CERMAK,2020). No Brasil a maconha era cultivada na época das capitânicas, sendo que era principalmente utilizada para produção de cordas e roupas. No entanto, é possível que a planta já fosse utilizada como hipnótico pelos primeiros escravos há mais tempo (ZUARDI,).

Atualmente, poucas plantas são tão controversas ou veneradas como a *Cannabis sativa*.

1.2 Constituintes químicos da cannabis

A Cannabis sativa é uma planta que possui centenas de constituintes químicos (FIG. 1). O primeiro composto isolado em forma pura da planta foi o canabinol (WOOD, THOMAS BARLOW; SPIVEY; EASTERFIELD, 1899) Inicialmente, o canabinol foi considerado o principal composto psicoativo da planta. Mais tarde descobriu-se que seus efeitos psicoativos eram mínimos (ZUARDI, 2008). O segundo composto isolado foi o canabidiol (CBD), por Mechoulam e Shvo e 1963 (TODD; ADAMS ; R. GHOSH; WILKINSON, 1963). Somente no ano de 1964 Gaoni e Mechoulam conseguiram isolar o principal composto psicoativo, o delta-9-tetra-hidrocanabinol (d-9-THC) (MECHOULAM; GAONI, 1965).

Figura 1: Componentes químicos encontrados na planta Cannabis sativa



1.3 Efeitos fisiológicos

A estrutura química do tetra-hidrocanabinol (THC) se assemelha à substância nomeada anandamida, o primeiro endocanabinoide descrito. Devido a tal semelhança, o THC é capaz de se ligar a moléculas chamadas receptores canabinóides nos neurônios, causando uma série de sinais e sintomas mentais e físicos. O THC é capaz de exercer efeitos em áreas cerebrais relacionadas ao prazer, memória, pensamento, atenção, movimentos, coordenação, sensorio e percepção temporal (NATIONAL INSTITUTE ON DRUG ABUSE, 2019).

1.4 O uso da cannabis como droga psicoativa

A cannabis sativa é a droga psicoativa mais comumente utilizada no mundo após o álcool e o tabaco. No ano de 2018, cerca de 192 milhões de pessoas usaram cannabis, o que corresponde a 3,9 por cento da população global com idade entre 15–64 (UNITED NATIONS OFFICE ON DRUGS AND LABOR, 2020).

Denomina-se carreira de uso de drogas a passagem de uma pessoa pelos diferentes estágios relativos ao uso de drogas. Essa carreira inicia-se com a experimentação, passa pelo abuso e evolui para um transtorno pelo uso de drogas, com todas as consequências somáticas, psicológicas, sociais e econômicas que advêm destes dois últimos transtornos.

Por não se tratar de um único comportamento nem de um único transtorno, vários fatores psicossociais foram associados a cada um desses estágios (CASTALDELLI-MAIA et al., 2017)

Para fins de pesquisa e delimitação de agravos à saúde, são definidos alguns padrões de uso de drogas:

- a A experimentação;
- b o uso ocasional;
- c o uso regular; e
- d os transtornos pelo uso de drogas (CANOLETTI; SOARES, 2005).

1.4.1 Experimentação de maconha

A experimentação de uma droga pode ser conceituada como seu primeiro uso durante a vida (“EMCDDA | Methods and definitions,” 2012).

Nos Estados Unidos, no ano de 2014, a prevalência nacional estimada do uso de maconha entre pessoas com idade ≥ 12 anos era de 8,4%. De 2002 a 2014, a prevalência de uso de maconha aumentou em 35,0% (de 6,2% em 2002 para 8,4% em 2014; $p < 0,001$) entre pessoas com idade ≥ 12 anos (AZOFEIFA et al., 2016). Dados do relatório mundial da United Nations Office on Drugs and Crime (UNODC) também revelam o crescimento do consumo mundial dessa droga, com uma expansão do consumo de aproximadamente 16% na última década (VEREINTE NATIONEN BÜRO FÜR DROGENKONTROLLE UND VERBRECHENSBEKÄMPFUNG, 2018).

A experimentação de maconha é um processo importante do ponto de vista da prevenção de uma série de consequências negativas e pode preceder o uso futuro de

outras drogas de alto risco, como cocaína, crack ou heroína (ELLICKSON, 2004). Alguns autores sugerem que a maconha possa ser uma “porta de entrada” para outras drogas (SECADES-VILLA et al., 2015).

O termo “porta de entrada” sugere um caminho que leva a outros desfechos (APA DICTIONARY OF PSYCHOLOGY, 2014). Álcool, tabaco e maconha são as drogas mais usadas no mundo (VEREINTE NATIONEN BÜRO FÜR DROGENKONTROLLE UND VERBRECHENSBEKÄMPFUNG, 2018). A experimentação dessas três drogas está associada ao aumento da chance de abuso de drogas mais potentes, ou seja, drogas com maior potencial de induzir sintomas de dependência ao longo da vida (ROCHE et al., 2019). O mecanismo de porta de entrada é uma teoria que tenta explicar a associação entre o uso de drogas como álcool, tabaco e maconha e o uso subsequente de outras drogas ilícitas. No entanto, a natureza dessa associação ainda não é clara (NKANSAH-AMANKRA; MINELLI, 2016).

Essa teoria é demonstrada por mecanismos bioquímicos, de modo que a associação entre uso de maconha e o consumo subsequente de outras drogas estaria ligado a um efeito biológico, “sensibilização” ou “priming” dos circuitos envolvidos no mecanismo de dependência química, sobretudo quando o primeiro uso ocorre na adolescência (VOLKOW et al., 2014). Adicionalmente, a literatura sugere que outros fatores, além da teoria de porta de entrada, predizem a progressão do uso de drogas menos potentes para o uso de drogas mais potentes, como cocaína e opioides (SPOONER; HETHERINGTON; NATIONAL DRUG AND ALCOHOL RESEARCH CENTRE (AUSTRALIA), 2004). Esses fatores são: a) a idade em que os adolescentes têm oportunidades de usar maconha e outras drogas; b) oportunidades associadas, ou seja, um ambiente que oferece a oportunidade de usar tanto maconha quanto outras drogas; c) a disposição de usar drogas que é compartilhada entre os indivíduos que iniciam o uso de qualquer droga (SPOONER; HETHERINGTON; NATIONAL DRUG AND ALCOHOL RESEARCH CENTRE (AUSTRALIA), 2004).

O uso de maconha tem sido associado a comportamentos de risco e prejuízo social, incluindo abandono escolar (MCCAFFREY et al., 2009), comportamento sexual de risco (ANDRADE; CARROLL; PETRY, 2013), comportamento agressivo (MOULIN et al., 2018), acidentes de trânsito (ASBRIDGE; HAYDEN; CARTWRIGHT, 2012), violência e tentativas de suicídio (MAHARAJH; KONINGS, 2005). Esses fatores ocorrem mais frequentemente em indivíduos acometidos por doença psiquiátrica preexistente (SERAFINI et al., 2013).

Alguns pesquisadores sugerem que o uso precoce de maconha, que é definido como qualquer uso até os 16 anos (MELCHIOR et al., 2017), associa-se a alterações nos circuitos neurais, refletindo mudanças na eficiência do processamento neural (GILMAN, 2017). Essa sensibilização precoce parece favorecer o desenvolvimento de dependência química durante a vida adulta. Além disso, as diferenças na integridade do tecido cerebral após o uso mais pesado de maconha, durante a adolescência, predizem futuros comportamentos de risco e transtornos psiquiátricos, como o transtorno pelo uso de maconha (TUC) e psicose (BATTISTELLA et al., 2014).

1.6 Uso regular de maconha

O uso regular de maconha é definido como consumo da droga por duas ou mais ocasiões ao mês, durante um período de seis ou mais meses (CREEMERS, 2010). O uso regular dessa substância psicoativa foi associado ao desenvolvimento de problemas físicos, psicológicos e sociais, como a ruptura de laços familiares e prejuízo do desempenho escolar e laboral (TURNER; SPITHOFF; KAHAN, 2014).

O uso de maconha foi relacionado ao aumento dos custos em saúde pública, à perda de produtividade e à redução do potencial de trabalho devido a problemas de saúde. Isso resulta em um impacto relevante para a economia da sociedade (ECKER; RICHTER; BUCKNER, 2014; HASIN, 2018; SCHUBART et al., 2010).

1.7 Transtorno por uso de Cannabis

A Associação Americana de Psiquiatria define o diagnóstico dos transtornos devidos ao uso de substâncias psicoativas como uma condição complexa em que há o uso descontrolado de uma substância, apesar das consequências prejudiciais. (AMERICAN PSYCHIATRIC ASSOCIATION; COLON-RIVERA; BALASANOVA, 2020).

Os transtornos são descritos pela Classificação Internacional de Doenças (CID-10) como mentais e comportamentais, devido ao uso de substâncias psicoativas. O termo engloba ao menos sete diagnósticos distintos:

- a A intoxicação aguda;
- b o uso nocivo para a saúde;
- c a síndrome de dependência;
- d a síndrome (estado) de abstinência;
- e a síndrome de abstinência com delirium;

- f o transtorno psicótico; e
- g a síndrome amnésica.

Outra classificação nosológica para os transtornos pelo uso de substância é descrita no Manual Diagnóstico Estatístico (DSM), da American Psychiatric Association (APA). Em sua quarta edição, o DSM-IV define como transtornos por uso de substâncias (TUS) para a maconha dois diagnósticos distintos: a dependência e o abuso.

Na edição seguinte, o DSM 5, APA, optou por combinar a maioria dos critérios do abuso e da dependência em um único transtorno (QUADRO 1). Na DSM 5 a APA também excluiu o critério relativo aos problemas legais presente no DSM-IV e acrescentou os critérios para fissura ou desejo compulsivo e da abstinência de maconha, estes inexistentes na DSM-IV (HASIN, 2018). O grupo de trabalho da APA justificou essa mudança em razão dos sintomas de dependência e abuso formarem um constructo unidimensional e não bidimensional. Além disso, essa decisão baseou-se em dados empíricos que sugerem que qualquer uso de maconha pode ter consequências negativas para o indivíduo.

Quadro 1: Transtornos por uso de maconha segundo o DSM-IV e DSM-5

	Abuso - DSM IV *		Dependência - DSM IV **		DSM-5 TUS***
Uso lesivo	X		-		X
Problemas interpessoais ou sociais relacionados ao uso	X		-		X
Negligência a leis relacionadas ao uso	X		-		X
Problemas legais	X		-		-
Abstinência	-		-		X
Tolerância	-		X		X
A substância é frequentemente consumida em maiores quantidades ou por um período mais longo que o pretendido	-		X		X
Existe um desejo persistente ou esforços malsucedidos no sentido de reduzir ou controlar o uso da substância	-		X		X
Muito tempo é gasto em atividades para a obtenção/utilização da substância ou na recuperação de seus efeitos	-		X		X
Problemas físicos ou psicológicos	-		X		X

relacionados ao uso				
Persistência do uso, apesar da consciência dos problemas relacionados À substância	-		X	X
Fissura ****	-		-	X

Adaptado de Hasin (2018).

*Um ou mais critério para abuso em um período de 12 meses.

**Três ou mais critérios para dependência em um período de 12 meses.

***Dois ou mais critérios para transtorno por uso de substâncias em um período de 12 meses.

****Novo critério adicionado no DSM-5.

O transtorno pelo uso de maconha (TUC) é definido como o uso problemático de maconha que leva a comprometimento ou sofrimento clinicamente significativo caracterizados pelo controle prejudicado, uso continuado, apesar dos problemas sociais, médicos, desejo, tolerância e abstinência (HASIN, 2018).

Os dados epidemiológicos indicam que a maioria dos que utilizam cannabis não tem problemas relacionados ao seu uso, mas um subgrupo vulnerável (10 – 30%) pode desenvolver sinais e sintomas do TUC (AMERICAN PSYCHIATRIC ASSOCIATION, 2013; FARMER et al., 2014; HASIN, 2018). No entanto, Cerdà e colaboradores (2020), em um estudo multinível que envolveu 505.796 de entrevistados comparando o uso de maconha antes e depois da legalização da maconha recreativa nos Estados Unidos, evidenciou que a proporção de entrevistados com idade entre 12 e 17 anos relatando transtorno por uso de cannabis aumentou de 2,18% para 2,72 %, enquanto a proporção de entrevistados com 26 anos ou mais que relataram uso frequente de maconha aumentou de 2,13% para 2,62% e aqueles com transtorno por uso de cannabis, de 0,90% para 1,23% (CERDÁ, MAGDALENA et al., 2020).

São fatores de risco para o desenvolvimento de TUC:

- a Transtornos devido ao uso de outras substâncias psicoativas;
- b comorbidades psiquiátricas;
- c estressores agudos e crônicos;
- d predisposição genética para desenvolver esse transtorno;
- e uso precoce de maconha (antes dos 16 anos de idade) (SCHLOSSAREK et al., 2016).

O transtorno pelo uso de maconha está associado a comorbidades graves, como transtornos de humor e psicose, além de prejuízo cognitivo e consequente déficit no

desempenho escolar ou de trabalho (FERGUSON; BODEN; HORWOOD, 2015; MEIER et al., 2012). Esses transtornos associam-se também a alta prevalência de desemprego e baixos salários (CARLINER et al., 2017). Além disso, dados do Relatório Mundial sobre Drogas revelam o impacto dos transtornos por uso de maconha sobre o risco de doenças infecciosas e clínicas e reportam o aumento do risco de doenças cardiovasculares e infecciosas pelo uso dessa substância (UNITED NATIONS OFFICE ON DRUGS AND LABOR, 2020).

A etiologia do TUC é complexa e multifator(AGRAWAL; LYNSKEY, 2006; HABERSTICK et al., 2014; VERWEIJ et al., 2010) e ainda pouco compreendida. A existência de polimorfismos dos genes CNR1 (gene que codifica o receptor cannabinoide 1), CNR2 (gene que codifica o receptor cannabinoide 2), FAAH (gene que codifica a enzima hidrolase amida de ácido graxo), MGLL (gene que codifica a lipase monoglicerídeo), TRPV1 (gene que codifica o receptor vaniloide 1), GABRA2 (gene que codifica o ácido gama-amino butírico) e GPR55 (gene que codifica receptor órfão 55 acoplado a proteína G) pode aumentar o risco de desenvolvimento de um TUC (AGRAWAL; LYNSKEY, 2009) Por exemplo, os indivíduos com polimorfismos do gene CNR1(T/C) apresentam sintomas de abstinência mais intensos (HAUGHEY et al., 2014).

Além dos fatores biológicos, fatores ambientais como a perda dos pais antes dos 15 anos e o baixo nível socioeconômico podem aumentar o risco de TUC até três vezes (VON SYDOW et al., 2002)

Uma revisão sistemática publicada em 2010 reuniu estudos que identificaram fatores associados à experimentação e ao transtorno pelo uso de maconha em gêmeos. Foram encontrados 28 estudos disponíveis avaliando a experimentação de maconha e 24 sobre o TUC. Foi avaliada a influência de fatores genéticos e fatores ambientais na iniciação do uso de maconha e no uso problemático dessa substância. Os resultados indicaram que a vulnerabilidade ao início do uso de maconha e o transtorno pelo uso dessa substância foram significativamente influenciados tanto por fatores genéticos quanto ambientais (VERWEIJ et al., 2010). No entanto, houve tendência a acentuado componente ambiental compartilhado e menos influência genética para iniciação da maconha em comparação ao uso problemático por indivíduos do sexo feminino.

O objetivo do presente estudo foi avaliar os fatores associados à experimentação de maconha e aos transtornos por uso de maconha e identificar, entre os indivíduos que experimentaram maconha, aqueles com mais probabilidade de desenvolver transtornos por uso de maconha com base em revisão bibliográfica e estudo de base epidemiológica.

Dessa forma, apresenta-se este trabalho em dois tempos. Num primeiro, revisão da literatura sobre os fatores de risco para experimentação e para TUC. Num segundo, apresentação dos dados de uma pesquisa epidemiológica transversal realizada na população de Belo Horizonte e avaliação dos fatores associados ao desenvolvimento de TUC. Por fim, são tecidas as conclusões e sugeridas perspectivas de trabalho.

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2 JUSTIFICATIVA

As taxas de uso de maconha e transtorno devido ao consumo dessa substância aumentaram na última década, paralelamente à sua recente aceitação por parte da população (HALL, WAYNE; LYNSKEY, 2016). Essa mudança possivelmente se deve à reduzida percepção da população de que o uso da maconha representa aumento da chance de consequências negativas, incluindo transtorno pelo seu consumo (SALLOUM et al., 2018). No entanto, as evidências mostram que a experimentação está associada ao risco de uso regular; e o uso regular está associado ao risco de comprometimento cognitivo (DERVAUX A; KREBS MO; LAQUEILLE X, 2014), aumento do risco de transtornos psicóticos (JÓNSSON; BIRGISDÓTTIR; SIGURÐSSON, 2014) e outros

problemas de saúde mental (MAMMEN et al., 2018) baixo nível de escolaridade (CURRAN et al., 2016) e desemprego (LAUDET, 2012).

A distinção entre o uso não problemático de maconha e o transtorno pelo seu consumo pode ser complicado, porque é difícil atribuir problemas sociais, comportamentais ou psicológicos à substância, especialmente no caso de uso de outras drogas - DSM-5 (COMPTON, WILSON M.; BALER, 2016; HASIN et al., 2016), tornando-se complexa a mensuração de que existe comprometimento funcional, condição fundamental para a definição de doença. Ao mesmo tempo, como se percebe na prática clínica, é contraditório classificar como uso não problemático determinados modos de consumo, mesmo que não preencham critérios para transtornos por uso de substâncias, tendo em vista que existem consequências negativas. A intoxicação aguda (mesmo considerando o primeiro uso), o uso regular e o uso precoce isoladamente se associam a problemas sociais, físicos e psicológicos (VOLKOW et al., 2014).

Tendo em vista as consequências da substância, é relevante conhecer o que faz com que alguns indivíduos se iniciem na maconha e o que faz com que um subconjunto desenvolva um transtorno. Nesse sentido, o conhecimento dos fatores associados à experimentação e aos transtornos pelo uso é importante para a identificação de grupos de maior vulnerabilidade, possíveis alvos de políticas públicas; e também para o conhecimento de possíveis consequências do uso, desde a experimentação e uso precoce ao uso regular e ao transtorno pelo uso.

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3 OBJETIVOS E HIPÓTESES

3.1 Objetivo geral

Avaliar a prevalência e os fatores associados ao uso de maconha na população de Belo Horizonte a partir de revisão bibliográfica sistemática sobre os fatores de risco para a experimentação e o TUC.

3.2 Objetivos específicos

Identificar a prevalência e os fatores associados ao TUC em uma amostra representativa da população de Belo Horizonte.

4 RESULTADOS

4.1 artigo 1 - Risk and protective factors for experimentation and development of cannabis use disorder: A systematic review

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Introduction

Cannabis is the most commonly used illicit substance in the world (1). The United Nations Office on Drugs and Crime (1) points out that 3.9% of the world's population between the ages of 15 and 64 has used cannabis at least once in 2016. That is equivalent to around 192.2 million people. Those estimates point to a 16% increase of users between 2006 and 2016. This increase seems to be higher in Asian and African countries, followed by governments in the Americas and Europe. In Brazil, according to data from IBGE, cannabis is the illicit substance with the highest prevalence of use among the general population. Of all the adult population, 5.8% declared to have used the substance at some point in their lives - in other words, 7.8 million adult Brazilians have used cannabis at least once in their lives (2).

Among the adverse short-term effects arising from the use of cannabis are hyperemesis, impairment of coordination and performance, anxiety, suicidal thoughts, and psychotic symptoms(3). The use of cannabis is associated with short-term impairment of several domains of cognitive functions, primarily episodic memory, working memory, capacity for planning, and decision making, in addition to modifying the pattern of response to stimuli with increased latency (3). Cannabis use is also associated with increased impulsiveness(4), besides impairing attention and concentration(5). Some of the individuals who experiment with cannabis feel anxiety and may suffer panic attacks and hallucinogenic symptoms in their first use(6). The hallucinogenic symptoms usually appear according to the potency, in other words, the concentration of THC and other cannabinoids of the ingested drug or in individuals who are vulnerable to the development of psychosis (7).

The studies carried out in the '70s, and '80s suggest that few cannabis users developed a cannabis use disorder (CUD) (8), contributing to the reduced perception of the risks by the users. However, recent data from the USA showed that 3 out of 10 cannabis users developed a CUD (9).

Thus, considering the reading material, the use of cannabis is associated with a series of risks and negative consequences. Furthermore, it is one of the most commonly used drugs, making it a severe public health issue. Our central hypothesis is that there are differences between the factors associated with cannabis experimentation (CE) and CUD. Among individuals who experiment with cannabis, some factors favor the development of CUD. Therefore, the objective of this study was to evaluate the factors associated with CE and CUD in the reading material through a systematic review.

Materials and Method

To structure this review, we used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for the systematic review(10). The authors did systematic searches in the PubMed, Scielo and Cochrane Database bases using the following terms MeSH: (cannabis or marijuana or hemp) and (initiation or experimentation or smoking) and (protective or risk or predictor) and (factors or factor). To evaluate the articles regarding factors associated to CUD, the authors carried out a systematic search in the same database using the following terms MeSH: (cannabis or marijuana) and (dependence or abuse or use disorder) and (protective or risk or predictor) and (factors or factor). We took into account all articles published between 2010 and 2018, and we carried out a manual search of relevant systematic searches. The choice of the period for the searches was due to the publication of a review about the topic in 2010 (11).

Two reviewers (KSP and JK) evaluated the titles and summaries pointed out in the searches independently and included the articles that met the inclusion criteria. The complete text of the potentially relevant studies was recuperated and evaluated by the two reviewers. The selection of studies was carried out using standard selection criteria for assessing the eligibility.

In the selection of studies of the factors associated with CE and CUD, the studies which were included in the review met the following criteria: (1) longitudinal or cross-study studies; (2) Exposure to one or more factors associated with CE or CUD; (3) Studies carried out in humans; (4) Studies in Portuguese or English.

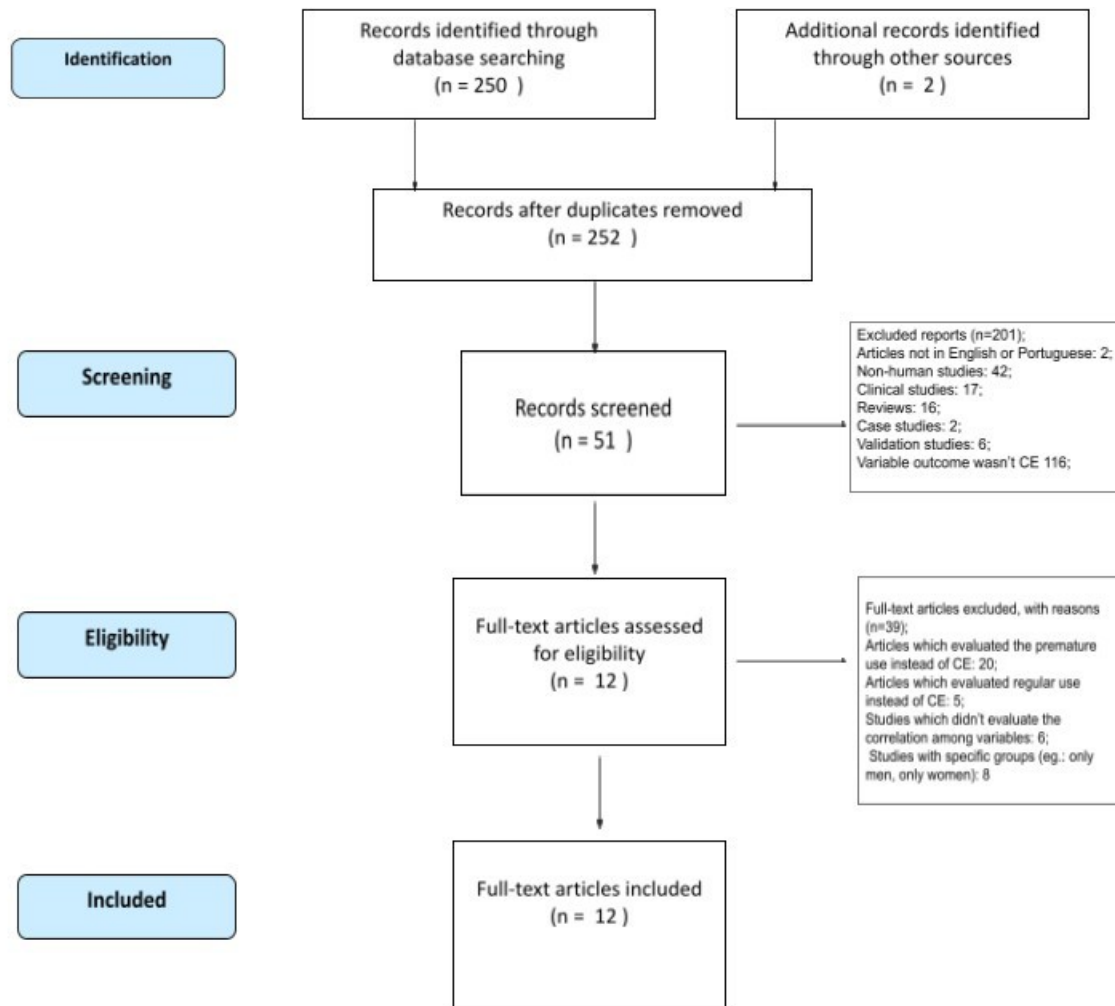
Results

Risk and protective factors for CE

The search for reading material turned up 252 references. After evaluating the titles and summaries of the selection, we chose 51 articles potentially relevantly and excluded 201 studies. After applying our evaluation criteria, 12 references were included, represented in the flow chart (Figure 1).

Figure 1: Analysis flow and inclusion of articles for review (CE).

Figura 2: Analysis flow and inclusion of articles for review (CE).



We found four cross-studies and eight longitudinal studies that evaluated these risk factors. We presented the data from these studies in table 1, which will be described in groups in the following subchapters. The risk and protection factors for CE can be divided into the following: demographics, environmental, individual traits and vulnerability, comorbid and in association with the use of other drugs.

Table 1: Factors associated with CE in the evaluated studies

Author	Design	Sample	Mean age	Association Variable	Risk Measure (OR (95% CI))
Cavazos-Rehg (2011)	Cross-Study	2,312	NR	Number of sexual partners (More than 6 in relation to 0) and Age 13-14	2.9 (1.9–4.5)
				Number of sexual partners (More than 6 in relation to 0) and Age>15	5.4 (2.5–12.0)
				Number of sexual partners (More	12.7 (4.2–38.2)

				than 6 in relation to 0) and Age <=12	
Cerde (2013)	Longitudinal	499	6.7 at inclusion	Symptoms of Conduct Disorder	1.39 (1.22–1.58)
				Depression	1.06 (1.02–1.10)
				Symptoms of anxiety	NS
Glasheen (2017)	Cross-Study	88,689	NR	Income	NS
				Not enrolled or employed - Age between 18 to 20 years old	0.79 (0.63–0.99)
				Residential transience (more than 3 times) - Age between 14 to 15 years old	1.34 (1.13–1.59)
				Residential transience (more than 3 times) - Age between 16 to 17 years old	1.27(1.04–1.56)
				Depression - Age between 14 to 15 years old	2.18(1.83-2.61)
				Depression - Age between 16 to 17 years old	1.72(1.49-1.98)
				Depression - Age between 18 to 20 years old	1.73(1.43-2.08)
				Doesn't live with mother - Age between 12 to 13 years old	1.71(1.14-2.57)
				Doesn't live with mother - Age between 14 to 15 years old	1.29(1.06-1.56)
				Doesn't live with mother - Age between 16 to 17 years old	1.26(1.04-1.51)
				Doesn't live with mother- Age between 18 to 20 years old	NS
				Doesn't live with father - Age between 12 to 13 years old	1.57(1.19-2.08)
				Doesn't live with father - Age between 14 to 15 years old	1.43(1.24-1.65)
				Doesn't live with father -Age between 16 to 17 years old	1.36(1.23-1.51)
				Doesn't live with father - Age between 18 to 20 years old	NS
				Female Sex - Age between 12 to 13 years old	NS
				Female Sex - Age between 14 to 15 years old	NS
Female Sex - Age between 16 to 17 years old	NS				
Female Sex - Age between 18 to 20 years old	0.86(0.77-0.96)				
Hines (2016)	Cross-Study	3,824	32.1 (mean) SD = 3.04	Sex (female)	0.69 (0.64–0.75)
				Parental conflict (high)	1.09; p<0.05
				Parental alcohol problems	OR= 1.19 (1.08–1.30)
				Parental drugs problems	OR= 7.29 (1.74–30.62)
				Frequent Childhood Religious Attendance	0.74 (0.68–0.80)
				Conduct disorder	5.57(1.52–20.47)
Jensen	Longitudinal	454	15.69	Male sex	NS
				Ethnicity	NS

(2017)					
				Sensation Seeking x Neighborhood Disadvantage	1.03; p=0.007
				Parents with TUS	3.72; p=0.002
				Sensation Seeking	NS
Jovic (2014)	Cross-Study	4,175	NR	Female Sex	NS
				High Socio-Economical Status. (parents' jobs, family car ownership, bedroom occupancy, family holidays, and computer ownership)	2.1 (1.4–3.2)
				Age (years old)	1.8 (1.6–2.0)
				Family Structure (mono-parental)	1.4 (1.1–1.7)
				Family Structure (Stepfamily - a family that is formed on the remarriage of a divorced or widowed person and that includes one or more children.)	1.7 (1.3–2.2)
				Low parental monitoring	2.4 (1.9–2.9)
				Good communication with mother	0.8 (0.7–0.9)
				Environment which considers education as a priority	0.4 (0.3–0.6)
				School performance under the mean according to teachers	1.3; p<0.05
				Perceived demand from school	1.5 (1.1–2.0)
				Legleye (2011)	Longitudinal
Male sex	1.23 (1.18–1.28)				
Pampati (2018)	Longitudinal	1,775		Frequent consumption of alcohol	(OR=1.40, p<0.001)
				Use of cigarettes before age of 15 (Yes)	OR = 2.04 (p=0,006)
Pinchevsky (2012)	Longitudinal	1,253	NR	Peer cannabis uses	1,04 (1,03-1,05; p <0,001)
Schmits (2015)	Longitudinal	877	15.61 (mean) SD=0.81	Male sex	NS
				Age	NS
				Use of cannabis between partners (Yes)	1.06; p <0.001
				Depression	NS
				Social phobia	OR=0.98 p = 0.02
				Expectations of effects or desire	OR= 1.11; p =

					0.02
				Negative expectations of effects	OR= 0.80; p = <0.001
				Consumption of alcohol	OR= 1.16; p = <0.001
Silins (2013)	Longitudinal	2,045	27 (mean) SD = 1.5	Male sex	1.56 (1.04 – 2.33)
				Ethnicity	NS
				Religiousness	0.88 (0.82- 0.94)
				Sensation Seeking	1.24 (1.12 – 1.38)
				Harmful consumption of alcohol	2.42 (1.54 – 3.80)
				Consumption of tobacco	4.72 (2.33 – 9.55)
				Consumption of tobacco	4.98 (2.31-10.76)
Tucker (2012)	Longitudinal	20,745	NR	Male sex	NS
				Ethnicity	NS
				Age	0.91 (0.84 – 0.99)
				Characteristics of surroundings; Unemployment rate	1.03 (1.01 - 1.06)
				Ratio of friends who use compulsively use illicit substances	1.77 (1.25 – 2.49)
				Presence of both parents at home	NS
				Low level of control from parents	1.11 (1.01 – 1.22)
				Delinquency	1.10 (1.08 - 1.12)
				Involvement in conflicts at school	1.10 (1.05 - 1.14)
				Compulsively used illicit substances at the time of inclusion	1.91 (1.39 - 2.63)

Legend: NS = Not Significant

* At risk neighborhood: defined as region at high risk of development of delinquency and use of substances, operating through mechanisms such as exposure and social disorganization.

Sociodemographic Factors

Of the sociodemographic factors the male sex, young age and high income, measured based on the parent's job and the presence of household appliances at home, appear more frequently when associated with CE.

Eight studies evaluated the association between sex and the risk of experimenting with cannabis (12,13,14,15,16,17,18,19) three of them were cross-studies and five longitudinal. Five studies point out that CE is associated with male sex, and two found no significant association between male sex and CE. Three studies found that female individuals present a reduced chance of CE (15,17,18). Jovic and colleagues (15) found in a cross-study that being of the female sex is associated with a chance of CE 0.9 times the chance of male experiencing the drug. Hines and colleagues (17) found in a cross-study involving 3,824 those of the female sex present a chance of CE 0.69 times the male's chance of CE. Glasheen and colleagues (18) in a cross-study involving 88,689 participants between ages 12-20 found that, in individuals between ages of 18-20, being a woman is associated with a chance of CE 0.86 times the male's chance of CE. In a longitudinal study involving 2,045 individuals, Silins and collaborators (13) found that the chance of CE in man is 1.56 times the women's risk of CE. Legleye and collaborators (12) found that being of the male sex is 1.23 times more likely to be associated with a chance of CE than women. There was no significant difference between sex and among lower age groups. Jensen and collaborators (14, 19) in a longitudinal study found no significant association between male sex and the risk of CE. Tucker and colleagues (14) in a cross-study, also found no significant association between the male sex and the risk of CE.

Three studies evaluated the association between income and risk of CE (12,15,18). Two of these were cross-studies, and one was longitudinal. Jovic and collaborators (15) in a cross-study, evaluated the socioeconomic level of the participants taking into account the job of the parents, family property and presence of household appliances and classified the socioeconomic level in three categories: low, intermediary or high. This study found that individuals who belonged in the upper-income category were 2.1 times more likely to experiment cannabis than those of other groups. Legleye and colleagues (12) in a longitudinal study involving 29,393 people, found that individuals who belonged to a low socioeconomic level (according to the jobs held by their parents) are 0.63 times as likely to experiment cannabis as individuals who belong to higher levels. Cristie Glasheen and colleagues (18) found in a cross-study that there is no association between the level of income the risk of Cannabis experimentation.

Three studies evaluated the association between ethnicity and the risk of CE (13,14) and all were longitudinal. None of the selected studies found a significant association between ethnicity and Cannabis experimentation. Two studies evaluated the

association between age and the chance of CE. One of them is a cross-study and the other longitudinal. Tucker and colleagues (14) in a longitudinal study, found that the lower the age, the higher the chance of CE, whereas, Jovic found that the higher the age, the greater the risk of CE.

The studies, which evaluated the chance of CE according to sex, were homogeneous concerning the lower tendency of women to experiment with cannabis. The differences between sexes may occur because men had more opportunities to experiment with drugs (20). The studies also suggest that individuals on high-income levels are more likely to experiment with cannabis. This data is consistent with previous studies which show that a high income can increase the likelihood of the use of drugs due to an increase in purchasing power (21).

Environmental Factors

Seven studies evaluated the association between environmental factors and CE (14, 15, 16, 17, 18, 19, 22). Four of those are cross-studies and three are longitudinal. The environmental factors found were: the characteristics of the neighbourhood area and family structure; the monitoring of the parents; and the features of the pair.

Jensen and collaborators (19) evaluated 454 individuals in a longitudinal study with an average age of 15.7 and found that individuals who live in neighborhood disadvantage, defined as region at high risk of development of delinquency and use of substances, and which possess personalities characterized by the sensation-seeking are 1.03 times as likely to experiment cannabis as individuals who live in neighborhoods with fewer risks and without these personality traits. Tucker and collaborators (14) in a longitudinal study involving 20,745 participants, found that individuals who live in an area with high unemployment rate are 1.03 times as likely to experiment cannabis as individuals who live in areas with lower unemployment rates.

Four studies evaluated the characteristics of family structure and its association with CE. Studies took into account family characteristics like the presence of either birth parents at home or parental divorce. Tucker and collaborators (14) found in a longitudinal study that living with both parents at home is associated with a risk of CE 0.76 times the chance of those who live with only one parent. Glasheen and colleague (18), evaluated in a cross-study the influence of the presence of the parents in CE risk among individuals according to age groups. The authors found that not living with their mother is associated

with an increased risk of CE between ages of 12 to 18, mainly between ages 12 to 13 where the risk of CE is 1.71 times greater than in individuals who live with their mother.

Furthermore, according to the study, not living with their father is associated with an increased risk of CE between the ages of 12 to 18, mainly between the ages of 12 to 13 where the risk of CE increases in 1.57 times. Jovic and collaborators (15) found in a cross-study that individuals who come from a mono-parental family, in other words, with only one of the parents present, are 1.4 times more likely to experiment cannabis as individuals who live with both parents. Those same authors evaluated belonging to a Stepfamily is associated with a chance of CE 1.7 times greater than individuals who belong to a family of non-divorced parents. Hines and collaborators (17) evaluated the association between parental conflict and the risk of CE and found that the presence of conflict is associated with a chance of CE 1.09 times greater than those whose parents are not in conflict.

Two studies evaluated the association between parental monitoring and the risk of CE. Tucker and collaborators (14) describe that low parental supervision is associated with a chance of experimentation 1.11 times more likely than those individuals whose parents maintain high control. Jovic and collaborators (15), demonstrated in a cross-study a risk of CE 2.4 times greater in individuals which reported low control by parents concerning those who reported high monitoring. This monitoring refers to the concept of family support, an idea that the authors of this article chose to consider as a social backbone, whose members possess well-defined economic and familiar roles (23).

A cross-study identified environmental factors that act as protective factors for CE. Jovic and collaborators (15) found that individuals with excellent communication with their mothers are 0.8 times as likely to experiment with cannabis as those individuals who reported bad relationships. Jovic and collaborators also found that individuals who live in an environment that considers education as a priority the chance of CE are 0.4 times the chance of individuals who do not live in a situation such as this.

Three studies evaluated the association between the characteristics of the partners and the risk of cannabis initiation. Tucker and colleagues (14) found that the high rate of partners which compulsively use illicit substances increases the risk of CE in 1.77 times. Schmits and collaborators (16) found that the use of drugs by partners is associated with being 1.06 times more likely to be at risk of experimenting cannabis as those individuals whose friends do not use drugs. Pinchevsky and colleagues (22) found in a longitudinal study that peer cannabis use increases the risk of CE 1.04 times concerning individuals belonging to groups of individuals who do not use this substance.

The results presented concerning environmental factors highlight the importance of family support and structure regarding the risk of CE. These studies are consistent with previous studies that found that a family environment characterized by good relationships contributes to healthy development and protects individuals from the use of drugs and other risky behaviors through factors such as supervision, discipline and social inclusion (24). The studies found that the use of drugs by partners is associated with CE; this factor is as a facilitating factor of drug use (23). The number of evidence found concerning this association highlights the importance of the environment in this stage of drug use.

Individual traits and vulnerability

Six studies evaluated the association between individual characteristics and CE (13,14,15,17,19,25) of those, three were longitudinal studies and three were cross-studies. Two studies found an association between family factors and CE (17,19).

Tucker and colleagues (14) showed in a longitudinal study that high levels of delinquency is associated to a 1.10 times greater chance of CE compared to those without delinquent behavior. Tucker and collaborators also observed that the involvement of conflicts at school is associated with a 1.10 times greater chance of CE compared to individuals who do not present conflicts at school. Silins and colleagues (13) found that religiosity is associated with a chance of CE 0.88 times the chance of those who do not present religiosity. Hines and colleagues (17) found in a cross-study that religiosity is associated with a risk of CE 0.74 times the chance of those who do not present religiosity.

Cavazos-Rehg and collaborators (25) found in a cross-study that number of sexual partners (greater than 6) of individuals between that ages of 13 and 14 is associated with a risk of CE 2.9 times greater than individuals who had no sexual partners. Cavazos-Rehg and colleagues also found that the number of sexual partners greater than 6 in individuals younger than 12 years of age is associated with a 12.7 times greater chance of CE than individuals who had no sexual partners. In that, same study the likelihood of CE was 5.4 times greater in subjects who had more than six sexual partners at an age higher than 15 years old in relation to individuals of the same age group who had yet to become sexually active.

Silins and colleagues (13) found in a longitudinal study that traits of the sensation seeking is associated with a 1.24 greater risk of CE compared to individuals without these traits. Jensen and collaborators (19) found in a longitudinal study no significant association between CE and the sensations seeking. Jovic and colleagues (15) also found in a cross-

study that performance at school below the average is associated with a chance of CE 1.3 times greater than individuals whose school performance was within the average.

Jensen and collaborators (19) found that individuals whose parents had some type of disorder due to substance abuse were 3.7 times more likely to experiment with cannabis as those whose parents had no disorder. Hines and collaborators (17) found in a cross-study that individuals whose parents had problems due to drug use are 7.29 times more likely to experiment with cannabis as those whose parents didn't use drugs.

The relative results regarding the influence of individual factors are consistent with the theoretical studies in respect to the experimentation of illicit substances. The experimentation is dependent on individual factors that work as hinderers or facilitators for the use of these substance (26,27). Thus, religiosity, a protective factor found in our study, works as cultural hindering factor for the use of drugs. On the other hand, the search for novelty and delinquency are facilitators for the use of drugs (27). The studies that evaluated family factors point to a possible biological influence associated to drug experimentation but also to possible behavior and rules of the family environment that may behave as a facilitating factor for drug experimentation.

Psychiatric comorbidities and factors related to the use of substances

Four studies evaluated the association between the presence of comorbidities and CE, two of which were cross-studies and two longitudinal studies (16,17,18,29). Four studies assessed the association between the use of other psychoactive substances and CE (13, 14, 16, 28).

Glasheen and colleagues (18) showed that the presence of a depressive episode increases the chance of CE 4.09 times concerning individuals who weren't depressed. Cerda and collaborators (29) showed in a longitudinal study involving 499 individuals that the presence of depression made it 1.06 times more likely the chance of CE.

Schmits and collaborators (16) found in a longitudinal study involving 877 participants that social phobia is associated with a chance of CE 0.98 times the probability of individuals who do not present the disorder, but found no significant association between the presence of anxiety symptoms and CE. Cerda and colleagues (29) found in a longitudinal study that there was no significant association between anxiety symptoms and cannabis initiation.

Hines and collaborators (17), found in a cross-study that the diagnosis of conduct disorder is associated with a risk of CE 5.57 times greater than those without the disease.

Cerda and collaborators (29) found in a longitudinal study that individuals with conduct disorder are 1.39 times more likely to experiment cannabis for each symptom present concerning individuals without the trait.

Silins and colleagues found that individuals who smoke tobacco cigarettes are 4.98 times more likely to experiment cannabis than individuals who do not smoke tobacco (13). Pampati and collaborator (28) found in a longitudinal study that the use of cigarettes before the age of 15 is associated with a 2.04 times higher likelihood of CE compared to individuals who do not smoke tobacco cigarettes. Silins and colleagues, found in a longitudinal study that the use of tobacco is associated with 4.72 times greater likelihood of CE compared to individuals who do not smoke tobacco cigarettes. Silins and collaborators (13) found in a longitudinal study that individuals who harmfully used alcohol, defined as a pattern of use which harms their physical and mental health, were 2.42 times more likely to experiment with cannabis than individuals who didn't use harmful illicit substances. Tucker and colleagues found in a longitudinal study that individuals who compulsively consumed alcoholic beverages at the beginning of the study were 1.91 times more likely to experiment with cannabis than individuals who did not consume illicit substances. Schmits and collaborators found in a longitudinal study that consumption of alcohol is associated with a risk of CE 1.16 higher than individuals who do not use alcohol. None of the presently identified studies within this review found an association between the use of other substances such as cocaine and crack as a risk factor of CE.

The association between conduct disorder and the increased risk of CE was found by previous studies which justify that the association of the presence of personality traits present in individuals with conduct disorder correlate individual features of sensation seeking and the predisposition to use illicit drugs (30). The association between depression and CE is adequate according to theoretical models of emotional dysregulation. Wang and collaborators (31) proposed a model, according to which, depression was positively associated to emotional dysregulation, which in turn was associated to a greater tendency toward maladaptive coping responses to negative emotions, such as the use of drugs. Concerning the anxiety disorders, there was controversy as to its association with the risk of CE. A study showed an association between social phobia and CE, is that the disease worked as a protective factor in that study, and another found no significant association between anxiety disorders and CE. The decreased risk of CE in individuals with social phobias can be understood as possible lesser involvement of these individuals in groups which could influence their decision for the use of drugs. It is also according to cognitive models of anxiety which propose that

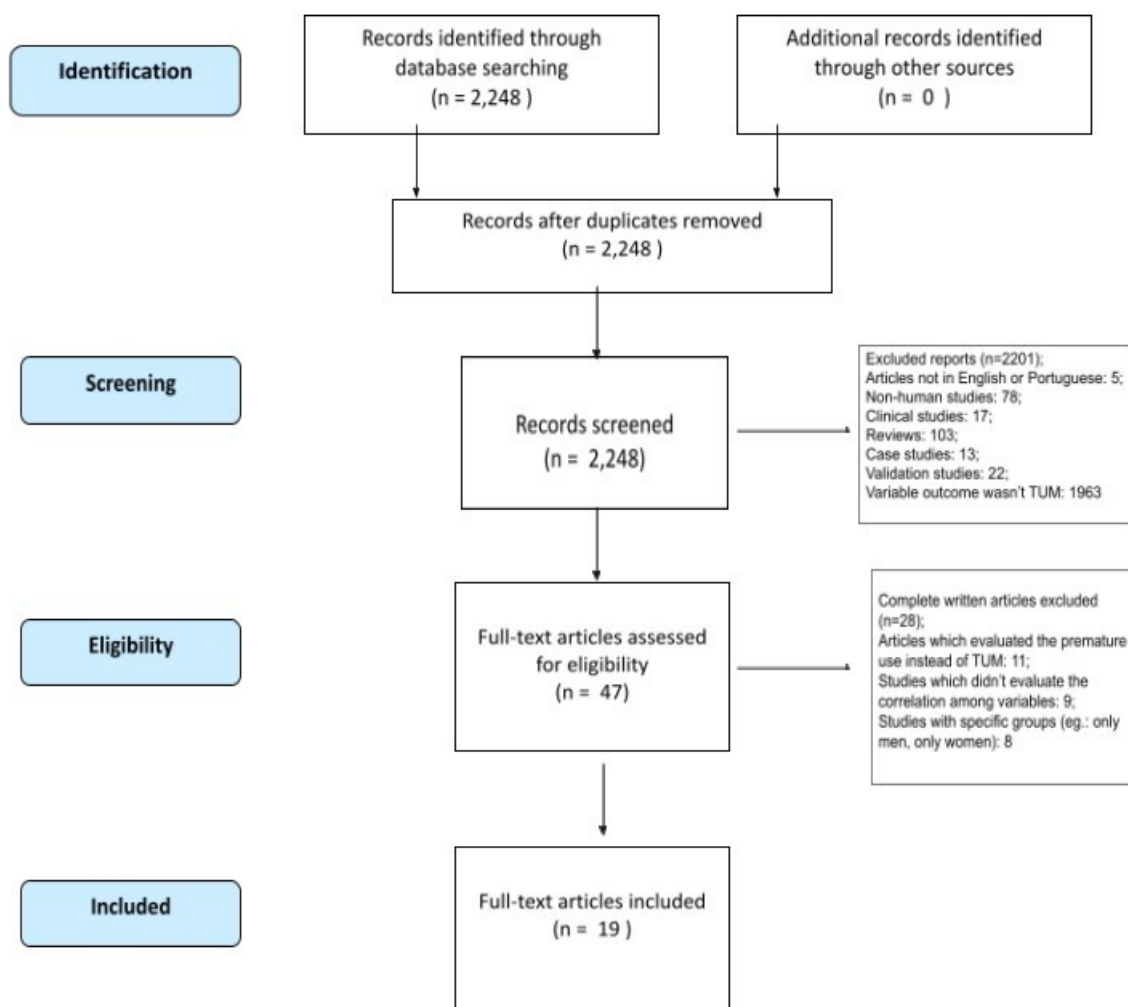
individuals with anxiety possess a higher tendency of aversion to risk (32). Thus, it's possible that these individuals show a greater reluctance to the risks associated with drug use (33).

The studies that evaluated the association between factors related to the use of other substances and CE corroborates with previous studies which proposed that the sequence of use of drugs starts with alcohol and tobacco, followed by cannabis, which precedes the use of cocaine and crack in most individuals (34).

Risk and protective factors for CUD

The search for reading material turned up 2,248 references, after evaluating the titles and the summaries we found 47 potentially relevant articles and excluded 2,201 studies. After using our evaluation criteria, 19 references were included, as shown in the flowchart (Figure 3).

Figura 3: Analysis and inclusion flow of articles for CUD.



We found two cross-studies and 17 longitudinal studies which evaluated these risk factors. We summarized the data of these studies in Table 3, which will be described in the group below. The risk and protection factors for CUD can be divided in the following: demographics, environmental, individual traits and vulnerability, and comorbid and factors related to drug use.

Table 2: Factors associated with CUD in the evaluated studies

Author	Design	Sample	Mean age (years old)	Outcome	Variable	Risk Measure: OR (95% CI)
Abajobir (2017) (36)	Cohort	2,526	NR	Cannabis Abuse (DSM-IV)	Neglect	2.63 (1.18–5.89)
					Having suffered any childhood maltreatment	1.79 (1.08–2.96)
					Sexual abuse	NS
					Physical abuse	NS
					Emotional abuse	NS
Behrendt (2012) (37)	Cohort	3,021	NR	CUD (DSM-IV)	Externalizing Disorder	1.69 (1.2–2.2)
					Age of first time using Cannabis:	0.77 (0.7–0.8)
					Paternal alcohol dependence	1.47 (1.01–2.1)
					Age at first alcohol or nicotine used	NS
					Maternal alcohol dependence,	NS
					Parental illegal drug dependence	NS

Brook (2011) (38)	Cohort	883	14.1 (mean)	CUD (DSM-IV)	Many psychological symptoms	1.21 (1.05–1.39)
					Frequent arguments with partner	1,84 (1,09–3,10)

					High levels of deviance	1.81 (1.21–2.71)
					Frequent acts of violence	1.19 (1.01–1.42)
					Problems resulting from Cannabis use	2.69 (1.33–5.46)
					Skipped work (Frequent)	1.55 (1.10-2.19)
					Association with drug using peers (High)	1.45 (1.07-1.96)
					Gender (Male)	3.88 (2.00 – 7.54)
					Age (Older)	0.60 (0.41 – 0.87)
					Ethnicity	NS
					Personality Attributes	NS
					Satisfaction with partner and Marital harmony (High),	NS
					Ego integration or impulsivity (High)	NS
					Illegal drug use (High)	NS
					Work achievement (High)	NS
					Socioeconomic status	NS
					Neighborhood - Drug offering (High) or Drug availability (High)	NS
					Nicotine dependence or alcohol use (High)	NS
Cornelius (2010) (35)	Cohort	693	10-12 (at inclusion)	CUD (DSM-III-R)	African-American Ethnicity	(Wald=14.2, p<0.001)
					Sex (male)	(Wald=12.0, p=0.001)
					Peer deviation	(Wald=63.4, p<0.001)
					Family history of substance abuse	(Wald=6.9, 0.009)

Foulds (2017) (39)	Cohort	1,011	18 (at inclusion)	Cannabis Dependence	Sensation seeking	3.6 (2.4 - 5.6)
Gao (2010) (40)	Cohort	422	36.4 (mean)	Cannabis Dependence	History of physical abuse	3.47 (1.39–8.67)
					Bipolar disorder	2.43 (1.10–5.33)
					Generalized anxiety disorder	3.28 (1.21–8.86)
					History of cocaine dependence	4.87 (2.32–10.22)
					History of cocaine abuse	2.39 (1.02–5.58)
					Gender (Male),	NS
					History of panic disorder	NS
Kaynak (2013) (41)	Cohort	1,253	18.21 (mean), SD=0.51	Cannabis Dependence	Sex (male)	1.97 (1.10 - 3.52)
					Sensation seeking	1.16 (1.01 - 1.33)
					High school cannabis use	13.13 (6.44 - 26.77)
					Importance of religion:	0.45 (0.25, 0.82)
					Ethnicity	NS
					Mother's education	NS
					parental monitoring	NS
Kirisci (2013) (42)	Cohort	339	10 (at inclusion)	CUD (DSM-III-R)	Age of first cannabis use	0.85 (0.79 - 0.91)
					Age of first alcohol use:	0.88 (0.78 - 0.99)
Kosty (2015) (43)	Cohort	1,709	16.6 (mean) SD = 1.2	CUD (DSM-III-R)	Parent had a history of CUD	1.93 (1.30–2.88)
					Parent had a history of antisocial personality disorder	1.73 (1.06–2.82)
					Parent had a history of hard drug use	1.96 (1.32–2.90)

					disorders	
					Parent history of Alcohol use disorder, depression or anxiety disorder	NS

Lee (2017) (44)	Cohort	674	14.1 (mean) SD=1.3 - at inclusion	CUD (DSM-5)	Sex (male)	2.99 (1.90 - 4.70)
					Higher educational level (years of study)	0.85 (0.77 - 0.95)
					Increase of alcohol consumption over time	15.54 (1.95 - 124.14)
					Ethnicity	NS
LeTendre (2017) (45)	Cohort	11,279	12 (at inclusion)	Cannabis Dependence (DSM-IV)	Age(years)	0.81 0.76 – 0.85
					Sex (male)	2.47 (2.14 – 2.85)
					Adverse experiences at childhood	1.47 (1.31 – 1.65)
					Religiosity	0.92 (0.88 – 0.95)
					Heavy consumption of alcohol	1.08 (1.02 – 1.16)
					Use of other drugs	1.56 (1.20 – 2.03)
					Education or Ethnicity	NS
Marel (2018) (46)	Cross-study	8,841	35.9 (mean)	CUD (DSM-IV)	Major depressive episode	2.15 (1.44 – 3.20)
					Bipolar disorder	1.95 (1.02 – 3.71)
					Generalized anxiety disorder	3.28 (1.21–8.86)
					Panic disorder	1.97 (1.41 –2.75)
					Social phobia	2.45 (1.72 –3.50)
					Agoraphobia	3.06 (1.65 –5.66)
					PTSD	1.79 (1.16 –2.72)
					Psychostimulants use	3.28 (2.31 – 4.65)
					Stimulant use disorder	18.29 (9.77– 34.23)
					SUD	3.43 (2.49 – 4.74)
Daily smoking	1.56 (1.09 – 2.23)					

					Sedative use	3.66 (2.12 – 6.35)
					Opioid use	3.85 (2.42 – 6.12)
					AUD	10.92 6.00 – 19.90
					SEUD	8.54 3.51 – 20.75
					ODD	6.88 (2.82 – 16.79)
					Alcohol use	NS
Ottosen (2016) (47)	Cohort	729,56	5 (at inclusion)	Abuse of marijuana (DSM-III)	ADHD in women	7.15 (5.07-10.09)
					ADHD in men	4.20 (3.36-5.24)
Pingault (2013) (48)	Cohort	1803	20.88 (mean), SD = 0.85	Cannabis Dependence (DSM-III-R)	Oppositional Defiant Disorder	2.33 (1.40–3.87)
Van der Pol et al (2013) (49)	Cohort	600	NR	Cannabis Dependence	Living alone	2.66 (1.38 - 5.14)

					Continual smoking	2.04 (1.16 - 3.58)
					Sex (male)	1.8
Haberstick (2014) (50)	Cohort	15,5	NR	CUD (DSM-IV)	Ethnicity, Age, Education, Marital Status, socioeconomic level.	NS
Van Ryzin (2014) (51)	Cohort	998	NR	Cannabis Dependence (DSM-IV)	Early substance use	3.32(1.02 - 13.60)
Walsh (2014) (52)	Cross-study	315	NR	Cannabis Dependence (DSM-IV)	PTSD symptoms	2.6 (1.2– 5.9)

Legend: ADHD = Attention deficit hyperactivity disorder; AUD = Alcohol use disorder. CI = Confidence interval. CUD = Cannabis use disorder. DSM – III, IV, 5 = Diagnostic and Statistical Manual of Mental Disorders - third, fourth and fifth edition. NR = not reported. OR = Odds ratio. PTSD – Post Traumatic Stress Disorder. SEUD = Sedative use disorder. SD standard definition.

Sociodemographic Factors

Eight studies evaluated the influence of sociodemographic factors in the risk of developing CUD(35,38,40,41,44,45,50,51). Five of those indicate that the male sex (35,41,44,45,50) is associated with the increased risk of CUD, and two of them indicated that male sex is not associated with a chance of CUD (40,51). Seven evaluated the

association between ethnicity and CUD(35,38,40,41,45,50,51). However only one showed a significant association (35). None of the studies that evaluated the association between socioeconomic level and the chance of CUD, found a significant association (38,50). Four studies assessed the association between education and CUD(44,45,50,51) however only one showed a significant association. Three studies evaluated the influence of age in the risk of developing CUD(38,45,50) and two of those found a significant association(38,45).

LeTendre and colleagues (45) found in a longitudinal study involving 11,279 individuals that being of the male sex increases the risk of CUD 2.47 times compared to women. Kaynak and colleagues (41) found that being male increases the risk of CUD in two times compared to women. Lee and colleagues(44) found that being male increases the risk of CUD in three times compared to women. Haberstick and colleagues(50) found in a longitudinal study that male sex is associated with a risk of cannabis abuse and dependence 1.8 and 1.4 times the chance of women, respectively.

Lee and colleagues(44) showed that academic level in years of study is associated with a decreased chance of CUD. Individuals with high educational level present a risk of CUD 0.85 times the likelihood of individuals without schooling, for each year of education. Letendre and colleagues showed that more upper age in years is associated with a decreased chance of CUD. Older individuals present a risk of CUD 0.81 times the chance of younger individuals, for each year (45).

The male sex, low level of schooling and younger age appear to be associated with an increased risk of CUD. Of the studies which evaluated the association between ethnicity and the chance of TUC, only one found an increase in the chance of the disorder in individuals of African-American ethnicity, the origin of this association is still uncertain, although this association may occur due to higher levels social vulnerability among individuals who declared themselves as non-caucasian(53).

Comorbidities

Ten studies evaluated the influence of the presence of comorbidities in the risk of developing CUD (35,37,38,40,43,46,47,48,52). Of those, two was cross-study and eight were longitudinal. The two cross-studi(46,52) reported that post-traumatic stress disorder is associated with an increased risk of CUD, while one of them also showed the increased chance of CUD in the individuals with major depressive disorder, bipolar disorder, generalized anxiety disorder, panic disorder, social phobia, agoraphobia(46). One longitudinal study showed that post-traumatic stress disorder constitutes a risk factor for

CUD (35). Two longitudinal studies evaluated the likelihood of CUD in individuals with mood disorders(40,54). Two studies assessed the possibility of CUD in individuals with anxiety disorders (40,54), four showed increased risk of CUD in individuals with externalizing disorders in infancy and adolescence(37,43,48,54) one showed that antisocial personality disorder is associated with an increased chance of CUD(43) one found an association between attention deficit hyperactivity disorder (ADHD) and an increased risk of CUD(47).

Walsh and colleagues, in a cross-study, evaluated a sample of 1,317 individuals and found those who have PTSD are 2.6 times more likely to develop CUD when compared to those who do not present PTSD(52). Marel and colleagues, in a cross-study, evaluated 8,841 individuals and found that major depressive episode is associated with 2.15 times increased risk of CUD(46). The authors also found a chance of CUD in individuals with bipolar disorder 1.95 times greater than individuals without disorders. Furthermore, the study showed that generalized anxiety disorder increases the risk of CUD 3.28 times. The presence of panic disorder practically doubles the chance of CUD when compared to individuals who do not present the disease. Additionally, social phobia increases the chance of CUD 2.45 times compared to individuals who do not present social phobia.

Gao and colleagues, found in a longitudinal study, that individuals with bipolar disorder are 2.43 times more likely to present CUD than individuals who do not show this disorder. Farmer and colleagues(54) evaluated in a longitudinal study, the influence of psychiatric symptoms during adolescence and its impact on the risk of CUD. Furthermore, this study didn't found a significative association between mood disorders and the risk of CUD.

Gao and colleagues showed that individuals with generalized anxiety disorder present a risk of CUD 3.28 times greater than individuals who do not presents this disorder. Marel and colleagues found that hat individuals with generalized anxiety disorder present a risk of CUD three times greater than individuals who do not presents this disorder(46). However, Farmer and colleagues didn't found a significative association between anxiety disorder and the risk of CUD(54).

Farmer e colleagues showed that the presence of the symptoms of externalizing disorders increases the risk of CUD 3.15 times when compared to individuals who do not present symptoms of this disorder(54). Moreover, the presence of disruptive behavior disorder increases the chance of CUD 2.32 times when compared to individuals who do not present the behavior, according to this study(54). Behrendt and colleagues (37),

verified in a longitudinal study that the presence of externalizing disorders increases the chance of CUD 1.69 times when compared to individuals who do not present the disease (37).

Kosty and colleagues(43) reported that the presence of antisocial personality disorder increases the chance of CUD in 1.73 times when compared to individuals who do not present characteristics of the disease. Ottosen and colleagues(47) showed in a longitudinal study that the presence of ADHD in women is associated with a risk of CUD 7.15 times greater when compared to women who do not present the disorder. The author also demonstrated that the presence of ADHD in men increases the chances of CUD in 4.20 times when compared to men who do not present the disorder(47).

Studies showed that the presence of psychiatric comorbidities is associated with the presence of CUD. The presence of an association between substance use disorder (SUD) and psychiatric comorbidities is associated with worse prognosis from SUD as well as the comorbidities(Magura et al., 2009). Thus, the early diagnosis and treatment of psychiatric comorbidities become essential as a preventive strategy for CUD.

Factors associated to the use of substances

Twelve studies evaluated the influence of the presence of factors associated with the use of substances and in the risk of developing CUD. Of those, one is a cross-study and ten are longitudinal studies.

Marel and colleagues(46) reported in a cross-study that the use of psychostimulant, nicotine, alcohol, opioid and sedative substances, the presence any SUD is associated with an increased risk of CUD. Gao and colleagues(40) found in a longitudinal study involving 422 participants that a history of cocaine dependence is associated with an increase on the chance of CUD in 4.87 times when compared to individuals who do not present dependency of this substance. That study also showed that a history of cocaine abuse increases the chance of CUD in 2.39 times when compared to individuals without this disorder. Letendre and colleagues showed that Heavy consumption of alcohol is associated with a risk of CUD 1.08 times the chance of those who do not use alcohol(45). However, Brook and colleagues did not find a significant association between nicotine, alcohol and other substance use disorder and CUD(38).

Kaynak and colleagues (41) showed in a cohort of 1253 participants that cannabis use in high school increases in 13.13 times the risk of CUD. Behrendt and colleagues also evaluated the association between the age of initiation of cannabis and CUD and found

that, the lower the age in the years of experimentation, the higher the risk of CUD ($p < 0.001$), however, authors did not find a significant association between age at first alcohol and nicotine use and CUD (37). Kirisci and colleagues(42) also found that age (in years) of the primary consumption of cannabis and alcohol is associated with the chance of CUD, the risk of CUD is 0.85 times the higher the age of cannabis experimentation is. Van Ryzin and colleagues showed that early substance use increases the chance of CUD in 3.32 times(51).

Van der Pol(49) found, in a cohort of 600 members, that individuals who continuously use cannabis present a risk of CUD 2.04 times greater when compared to individuals who use less frequently. This study also showed that the higher the average number of CUD symptoms throughout their life, the higher the chance of CUD, and this risk increases 1.45 times for each symptom. Brook and colleagues (38) found that issues resulting from the use of cannabis increase the likelihood of CUD 2.69 times. Kosty and colleagues(43) found that the presence of any SUD increases the risk of CUD 1.96 times when compared to individuals who do not present the disorder. Furthermore, Lee and colleagues found that the increase of consumption of alcohol over time increases chances of CUD in 15.54 times(44).

The studies found to confirm the presence of an association between CUD and the use of other substances. It is possible that disorders due to the use of drugs share similar risk factors such as genetic and environmental characteristics(55).

Individual vulnerability and personality

Five longitudinal studies evaluated individual characteristics related to greater or less vulnerability to developing CUD. Two studies assessed the association between sensation seeking (39,41) and CUD. One study evaluated coping strategy(49) another assessed the frequency of violent behavior, frequent arguments with a partner and behavior deviation and found an association with CUD (38). Two studies evaluated religiosity and found a protective effect of this factor. Three longitudinal studies assessed the influence of family history data with the risk of CUD.

Kaynak and colleagues (41) found in a longitudinal study involving 1,253 participants that the presence of sensation seeking increases the risk of CUD in 1.16 times. Van der Pol and colleague(49) found that hyperactivity increases the risk of CUD in 1.15 times when compared to individuals who aren't hyperactive. In that study, it was also observed that cannabis use as a coping mechanism increases the risk of CUD in 1.18

times when compared to individuals who do not use the drug for that reason. Brook and colleagues(38) found that the presence of a different relationship (measured by frequent arguments with a partner) increases the risk of CUD in 1.84 times. The study also found that high levels of behavior deviation increases the chance of CUD in 1.81 times, whereas frequent acts of violence increase the risk of CUD in 1.19 times when compared to individuals who didn't commit violent acts. Brook and colleagues also found that individuals who frequent skipped work presented a risk of CUD 1.55 times the chance of frequent individuals (38).

Letendre and colleagues(45) found that individuals who reported religiosity present a chance of CUD 0.92 times the risk of those who do not report religiosity. Kaynak and colleagues (41) showed that religiosity is associated with a chance of CUD 0.45 times the chance of those who did not present religiosity.

Cornelius and colleagues (35) showed that family history for substance use increases the chance of CUD. Kosty and colleagues, in a cohort study which evaluated 693 individuals found that the history of CUD between parents is associated with a 1.93 times higher likelihood when compared to individuals whose parents didn't possess the disorder. This study found no significant association between parental history of alcohol use disorder (either parent), of depression and anxiety disorder and CUD (43). Behrendt and colleagues(37) found that individuals with paternal alcohol dependence present a risk of CUD 1.47 times the chance of those without a parental history of alcohol dependence. This study found no significant association between history of maternal alcohol dependence and familial history of illegal drug dependence and CUD.

The findings highlight the presence of characteristics which suggest impulsive behavior, like the presence of violent acts, the search for sensations and the use of cannabis as a strategy to cope with characteristics which influence the risk of CUD. The findings are consistent with results from the reading material which highlight that the emergence of SUD is measured by impulsiveness, dysfunctional strategies for solving problems and emotional imbalance(56,57).

Environmental Factors

Seven studies evaluated environmental factors which influence the risk of CUD (35,36,37,41,40,45,49) Four of them evaluated the number of adverse events throughout life and financial crisis (36,40,45,49) another evaluated pair deviation (35) neighborhood characteristics(38), parental monitoring(41) and living alone(49).

Gao and colleagues found that history of physical abuse increases in 3.47 times the risk of CUD when compared to individuals who do not suffer physical abuse (40). Van der pol and colleagues showed that the average number of adverse events throughout a person's life increases in 1.35 times the chance of CUD(49). LeTendre and colleagues found that adverse experiences at childhood increase the likelihood of CUD in 1.47 times when compared to individuals who do not suffer adverse experiences(45). Abajobir and colleagues showed that having suffered any childhood maltreatment is associated with a risk of CUD 1.79 times the chance of those who do not suffer childhood maltreatment (36).

Van der Pol and colleagues, found in a cohort study involving 600 individuals, that living alone increases the risk of CUD in 2.66 time(49) when compared to individuals who do not live alone. Having gone through a financial crisis increases 2.44 times the risk of CUD in this same study. Cornelius and colleagues found in a cohort study that the presence of pair deviation is associated with an increased risk of CUD ($p=0.001$) (35). Brook and colleagues found no significant association between increased drug availability in the neighbourhood and the chance of CUD (38).

The studies show a correlation between trauma and negative experiences and CUD. These factors seem to reflect the harmful effect of premature stress on the risk of CUD(58).

Discussion

In our review, we found 12 studies published between 2010 and 2018, which evaluated factors associated with CE and 19 articles which assessed the factors associated with CUD.

We found a more significant number of studies that list environmental factors (such as family structure and behavior in addition to drug use by partners) as factors associated with CE. In addition, we found a greater number of studies which point to the presence of psychiatric comorbidities and factors related to early exposure to stress (early cannabis use and childhood trauma) as factors associated with CUD. We found only one reviewed study previously published, which compared predictors of CE and CUD. The authors of that study found a higher tendency of shared environmental factors, when compared to genetic factors, influenced the chance of CE. However, the study found this difference only in women (11).

A systematic review study published in 2007 (12) evaluated only the factors associated with CE and highlighted the importance of environmental factors, like a family environment and use of drugs by partners, and individual elements in the risk of CE,

nevertheless in this review only cohort studies were included. A systematic review published in 2016(60) evaluated only the psychosocial determiners of cannabis dependence, excluding the cannabis abuse. This study found that mainly low income, the presence of psychiatric comorbidities, the early cannabis use and the negative experiences in infancy, including childhood trauma, are important risk factors in the development of cannabis dependence. Additionally, the authors of this review compared the findings with the data of the reading material regarding factors associated with the development of cannabis abuse and found little consistent differences.

Studies concerning the determinants of the psychoactive drugs experimentation and of the subsequent development of disorders from the use of drugs highlight the importance of the environmental factors such as facilitators of drug experimentation (such as the increase of) and that individual factors would be more associated with the development of disorders by the use of drugs(61). The reading material also highlights that environmental factors, like the characteristics of socio-familiar behavior, influence in the formation of individual attributes of coping capacities and problem solving of the individuals(58). These studies highlight that socio-familiar dysfunction may contribute to more significant incapacity of the individuals to cope and solve problems and consequently increases the risk of drug experimentation.

In our review of factors associated with developing CUD, we found a higher number of studies which highlight the importance of the presence of diverse comorbidities (mainly anxiety disorders, mood disorder, ADHD and conduct disorder) and early exposure to drugs and adverse events in childhood in the risk of developing CUD. On the other hand, we found in the reading material a higher number of studies which highlight not only the presence of comorbidities and premature stress (58,59), but also the presence of intrauterine drug exposure(62,63) and low income increases the risk of developing SUD.

Of the studies found, we found some limitation such as heterogeneity of the studies concerning the measure of risk factors as well as to the evaluation of the outcome. Furthermore, few studies reported results relative to elements whose correlation to the issue was not significant. Most of the studies come from countries with high income: United States (38,45,54); Australia(46); France(15); Canada(48); The Netherlands (49) a Denmark(47). Therefore, the development of a greater number of studies in countries of average and low income is necessary.

The present review presents some limitations, such as we did not evaluate studies in other languages besides English and Portuguese; thus, some studies that could be necessary for the discussion were not included, including studies in Spanish that could

show the reality for Latin America. In addition to this, we excluded studies with information relative to neuroimaging and genetic alterations, which could constitute essential factors associated with experimentation and disorders due to the use of cannabis.

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4.2 ARTIGO 2: Associated factors with cannabis use disorders in a large sample of a latino american large city: A cross-sectional study

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ARTIGO 2: Associated factors with cannabis use disorders in a large sample of a latino american large city: a cross-sectional study

Title:

Associated factors with cannabis use disorders in a large sample of a latino american large city: a cross-sectional study

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ABSTRACT

INTRODUCTION Attitudes towards marijuana changed in the last few decades and, the perception that cannabis use is harmless became more prevalent. Considering states are discussing the legalisation of medical and recreational cannabis, it becomes relevant knowledge about the psychosocial impacts of use such as increased risk of traffic accidents, increased risk of the disorder by the use of other substances, as well as cannabis use disorder. **OBJECTIVE:** To assess the prevalence and factors associated with TUC in a representative sample of the population of Belo Horizonte. **RESULTS:** Among 7,643 individuals, 11.9% experimented cannabis, and 22.9% of them developed CUD. Subjects performing an early use were 2.55 times more prone to develop CUD. Male subjects were 2.48 times more prone to develop a CUD. The chance to be diagnosed with CUD was 1.66 higher in non-whites; 6.48-fold higher in subjects with comorbid cocaine use disorder; 1.95-fold higher in subjects with a comorbid alcohol use disorder and 1.24-fold higher in subjects without religious practice. Younger subjects were more prone to development CUD, and the chance increased 0.05-fold for each year of age, and each point of increase in the CTQ score for emotional abuse was associated with 1.05 times more chance of CUD. **DISCUSSION:** Our main findings are that that domains of socio-demographic characteristics (male gender, age and race), early stressful experiences (early drug use, childhood trauma), social support (married and religiosity) and comorbid drug addictions (cocaine and alcohol) are significative in subjects living in the middle-income country to delimit more CUD vulnerable groups. **CONCLUSION:** Changing cannabis policies related to its therapeutic and recreational use may produce reserved prognosis when we approach experimentation and CUD prevalence increase.

Introduction

Cannabis is the most commonly used illicit substance (Lipari et al., 2014). The United Nations Office on Drugs and Crime (UNODC) report that 3.8% of the global adult population consumed cannabis in 2016 (Unodc, 2018). Recently, there is a growing social acceptance of cannabis use (Lynskey e Hall, 2016). In parallel, there is a lower perception of the population that the use of cannabis represents an increase in the chance of negative psychiatric consequences, including dependence (Salloum et al., 2018), beyond cannabis is becoming legal in an increasing number of states, such as Uruguay and many states of the USA.

In Brazil, marijuana is the most commonly illicit substance used in recent years. Of the total adult population, 5.8% have experimented cannabis, and 2.5% of adults and 3.4% of adolescents reported having experimented cannabis in the last 12 months. In addition, there is an intense debate about legality of medical and recreational cannabis in the country (Castaldelli-Maia et al., 2018).

Associated with an increase in the prevalence of cannabis use in the world, there is a growth of the consequences for the use of marijuana, including increased demand in emergency services by the use of this substance. An observational study of 2016, conducted by Zhu and Wu, found that, between 2004 and 2011, the emergency department visit rate increased from 51 to 73 visits per 100,000 population aged ≥ 12 years for cannabis-only use (Zhu & Wu, 2016). Besides, we also have evidences that

unusual concentration of cannabinoids recently found in cannabis submitted to the forensic laboratory for chemical analysis. These findings prompted an investigation into whether genetic modifications occurred to the DNA of *Cannabis sativa* L. to increase its potency (Cascini et al., 2012).

Since states discuss the legalization of medical and recreational cannabis, it becomes relevant knowledge about the psychosocial impacts of use such as increased risk of traffic accidents, increased risk of disorder by the use of other substances, as well as cannabis use disorder (Radhakrishnan et al., 2014). Therefore, clinicians require accurate information to guide practice development and government to guide preventive politics and evaluation about new laws. Thus, the objective of this article is to evaluate the prevalence and factors associated with the development of CUD in a representative population of a capital city of a state in a developing country.

METHODS

Participants

We used the data yield by the cross-sectional study “Conhecer e Cuidar 2015” (Garcia, 2016) a populational health survey, conducted between November 2015 and March 2015 in the city of Belo Horizonte. Belo Horizonte has the sixth largest population in Brazil with 2,5 million inhabitants.

“Conhecer e Cuidar 2015” Study is a health survey that collected data regarding a broad range of health topics. Respondents were aged 15 to 65 years old and were recruited after the randomization process considering their health district, their household and from a list of eligible inhabitants in the selected household. Trained interviewers visited each household chosen and contacted the interviewed according to a protocol. Further information regarding the “Conhecer e Cuidar 2015” survey are described in Garcia, 2016 and could be obtained in the internet address <https://crr.medicina.ufmg.br/artigos/77/vulnerabilidade-e-o-uso-de-drogas>.

Sample

Conhecer e Cuidar sample was designed to be representative of the entire city regarding age, gender, health vulnerability and health district. At endpoint, the interviewers

visited 9,680 houses and included 8,080 subjects. The total refusal rate was of 12%. During data collection 123 (1.5%) questionnaires were excluded due to the incompleteness of the data obtained.

Measures

In addition to questions regarding sociodemographic and epidemiological characteristics, the questionnaire included the instruments below:

Mini-International Neuropsychiatric Interview (MINI): It is a short structured diagnostic interview that performs of accurate psychiatric diagnosis for epidemiological studies (Sheehan et al., 1998). A group of psychiatrists and researchers in the United States and Europe developed the MINI based on DSM-IV and ICD-10 (Sheehan et al., 1998). The application of the MINI requires a short period and brief training. Amorin et al. validated MINI for use in the Brazilian population in 2000 (Amorim, 2000). In our study, we used the MINI to diagnose use disorders of alcohol, cannabis, cocaine/crack, inhalants/solvents, hallucinogens, stimulants; and current depressive episode.

3 The Portuguese version of the abbreviated World Health Organization Quality of Life (WHOQOL-brief): it is an instrument for the evaluation of the quality of life developed by the World Health Organization in 1998 (Group, 1998). It is composed of 26 questions divided into four domains (physical, psychological, social and environment). It was validated and culturally adapted for the Brazilian population in 2000 and presented good psychometric characteristics (Fleck et al., 2000). In 2014, Silva and colleagues (Silva et al., 2014) determined a cutoff point of 60 for each subscale. Therefore, a score lower than 60 indicates poor quality of life in each subdomain, while a score equal to or greater than 60 indicates good quality of life.

4 Childhood Trauma Questionnaire (CTQ): it is an instrument that has 28 self-report items that provides a screening for history of sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect in childhood and adolescence, defined as prior to the age of 18 (Bernstein et al., 2003)

Statistical analysis

Statistical analysis was performed using SPSS® (IBM Corporation, CA). The level of statistical significance for all analyses was set at $p < 0.05$.

In the descriptive analysis, we calculated mean, standard deviation, median, quartiles, minimum and maximum for continuous variables. For categorical variables, we calculated frequencies and proportions. The Kolmogoroff-Smirnoff test assessed data normality.

For univariate analysis, we used the chi-square test for categorical variables and Mann-Whitney test for continuous variables. We conducted a multiple logistic regression with stepwise backward selection to determine which factors presented a more significant association with positive screening for CUD in our sample. We included in the model the variables with $p\text{-value} \leq 0.2$ and calculated the odds ratios (OR) considering a 95% confidence interval and significance of $p < 0.05$.

Monthly household income was categorised according to the recommendations of the Brazilian Institute of Geography and Statistics (Estatística, 2017) in low (less than \$ 794), average (from \$ 794 to \$ 3969) and high (greater or equal to \$ 3970).

Ethics

All participants were informed about the voluntary nature of the study and its implications and signed a consent form. This study was approved by the Research Ethics Committees of the Federal University of Minas Gerais (UFMG) with the following protocol number: CAAE 21727513.5.0000.5149. The study was carried out according to the latest version of the Declaration of Helsinki.

Results

Sample description

At endpoint, 7,598 subjects were included, 56,5% females and 43,5% males, mean age 37.17 ± 13.9 years old, 62.6% employed.

Table 1: Cannabis users and non-users demographic characteristics.

Qui-square test for categorical variables and Mann-Whitney test for continuous variables

Nine hundred (11.9%) subjects reported a use of cannabis (Table 1), 70,6% ($n = 635$) were male; 76.1% ($n = 625$) single and 626 ($n = 626$) were employed, with a mean

age of 30.9±11 years old. Users differed from non-users by having a lower mean age, a higher average of school years and higher average income. Individuals who experimented cannabis had a lower average score in the WHOQOL quality of life score (U = 2815395,500; p = 0.002), compared to individuals who did not.

Regarding subjects who experimented cannabis 401 (44%) reported an early use (i.e. before 16 years old), with a mean age of experimentation of 17.48±4 years old, and 26.3% reported smoking more than 400 cigarettes before 25 years old. The average time of regular use of cannabis was 4.24 years. Only 7.2% (n = 65) of cannabis users treated for CUD. Of those who received a treatment, 282 (31.3%) subjects were addressed for the treatment of a comorbid psychiatric disorder and not for the CUD.

Cannabis use disorder

In Table 2 we report the demographics, quality of life and trauma scores of subjects with and without CUD. Of the experimenters, 206 (22,8%) subjects developed a CUD. Subjects with a CUD presented a reduced average year of schooling (U=61,661, p = 0.003) and the reduced average income (U=28,603, p < 0.001) compared to individuals who did not develop CUD. The mean age of first marijuana use was lower in the group that developed CUD than in those who did not develop (U = 44,824, p <0.001), and had a higher mean of years of regular use of the substance (U = 102,303, 0. p <0.001). In addition, individuals who developed CUD had lower mean environmental satisfaction scores by WHOQOL (U = 59,275, p <0.001).

Table 3: Cannabis users with and without cannabis use disorder (CUD) demographic characteristics.

Characteristic		Total	No-CUD		CUD		p
			n	%	n	%	
Sex	Male	635	465	73.2%	170	26.8%	≥0,001
	Female	265	229	86.4%	36	13.6%	
Race	White	352	292	83%	60	17%	≥0,001
	Non-white	544	399	73.3	145	26.7%	

Marital status	Single	683	500	73.2%	183	26.8%	≥0,001
	Not-single	216	193	89.4%	23	10.6%	
Employment status	Employed	626	489	78,10%	137	21.9%	
	Not-employed	270	201	74.4%	69	25.6%	0.26
Current depression	Yes	82	58	70.7%	24	29.3%	0.167
	No	818	636	77.8%	182	22.2%	
Previous treatment for drug use	Yes	65	40	61.7%	25	38.5%	0.002
	No	835	654	78.3%	181	21.7%	
Religiosity	Yes	373	304	81.5%	69	18.5%	0.005
	No	527	390	74%	137	26%	
Lifetime Suicide ideation	Yes	283	203	71.7%	80	28.3%	0.006
	No	617	491	79.6%	126	20.4%	
ADHD	Yes	366	298	81.4%	68	18.6%	0.012
	No	534	396	74.5%	138	25.8%	
Alcohol use before 18 years old	Yes	805	611	75.9%	194	24.1%	0.001
	No	60	56	93.3%	4	6.7%	
Lifetime Halucinations	Yes	220	143	65%	77	35%	≥0,001
	No	668	545	81.6%	123	18.4%	
Early use of cannabis (<18 years old)	Yes	525	364	69.3%	161	30.7%	≥0,001
	No	374	329	88%	45	12%	
			Mean±S.D.	Mean±S.D.		95% C.I.	
Age (years)			32.3±11.3	26.51±8.8	≥0,001	-7.2 to -4.3	
Scholarity (years)			12.2±4.2	11.5±3.7	0.022	-1.3 to -0.1	
Average income (US\$)			863±1333	841±2818	0.9	-493 to 450	
First alcohol use age (years)			15.3±3.3	14.5±2.5	≥0,001	-1.5 to 0.6	

First cannabis use age (years)	18.2±5.9	15.6±3.2	≥0,001	-2.9 to -1.9
First cocaine use age (years)	20.1±5.7	18.1±5.8	0.002	-3.2 to -0.7
WHOQOL - Quality of life perception	78.2±15.7	76.6±17	0.224	-4.25 to 1.0
WHOQOL - Health satisfaction	76.5±18.9	77.1±18.7	0.69	-2.35 to 3.5
WHOQOL - Physical domain	56.3±10.3	55.2±11.8	0.23	-2.9 to 0.72
WHOQOL - Psychological domain	66.2±12.7	65±14	0.38	-3.2 to 1.2
WHOQOL - Social relationships	74.3±18.6	71.1±20.3	0.43	-6.35 to -0.09
WHOQOL - Environmental satisfaction	64.5±16.3	59.9±18.4	0.01	-7.4 to -1.8
QUESI - Emotional abuse	8.7±4.1	9.6±4.3	0.01	0.192 to 1.545
QUESI - Physical abuse	7.8±3.7	8±3.7	0.54	-0.402 to -0.761
QUESI - Sexual abuse	5.79±2.5	5.9±2.7	0.72	-334 to 0.5
QUESI - Emotional negligence	9.3±4.5	10.1±4.8	0.06	-0.17 to 1.45
QUESI - Physical negligence	7.84±3.5	8.3±3.8	0.15	-0.15 to 1.0
ASRS total score	22.5±11.7	26.2±14.4	0.001	1.5 to 5.8

Factors associated with cannabis use disorder

Seven factors remained statistically associated with positive diagnosis of CUD: (1) male gender, (2) race, (3) marital status, (4) religiosity, (5) early use (6) substance use disorders (i.e. alcohol or cocaine use disorders) and (7) emotional abuse.

Subjects performing an early use were 2.55 times more prone to develop CUD. Male subjects were 2.48 times more prone to develop a CUD. In our sample, the chance to be diagnosed with CUD was 1.66 higher in non-whites; 6.48-fold higher in subjects with comorbid cocaine use disorder; 1.95-fold higher in subjects with a comorbid alcohol use disorder and 1.24-fold higher in subjects without religious practice. Younger subjects were more prone to development CUD, and the chance increased 0.05-fold for each year of age, and each point of increase in the CTQ score for emotional abuse was associated with 1.05 times more chance of CUD (Table 3).

The logistic model indicated that the seven factors together distinguished between subjects with and without CUD and correctly classified 32,3% of individuals in the sample (χ^2 : 188,616; $p < 0.001$, $DF = 1$; Nagelkerke R^2 :0.323).

Table 4 - Associated factors with cannabis use disorders in the logistic regression.

Variable	Sig.	O.R.	95% C.I. para EXP(B)	
			Inferior	Superior
Male gender	<0.001	2.483	1.606	3.841
Race (Not-white)	0.009	1.658	1.133	2.426
Single	0.008	2.12	0.290	0.862
Without a religious practice	0.031	1.238	0.439	0.941
Age (years)	<0.001	0.951	0.931	0.971
Alcohol use disorder	<0.001	1.945	1.357	2.788
Cocaine use disorder	<0,021	6.48	5.13	7.95
Early cannabis use	<0.001	2.55	1.754	3.70
Emotional abuse	0.023	1.05	1.007	1.094
Constant	0.031	6.404		

Discussion

This study evaluated the prevalence and factors associated with the development of CUD in a representative sample of a large city in a developing country. Our main findings are that (1) male gender, (2) race, (3) marital status, (4) religious practice; (5) early use (6) substance use disorders (i.e. alcohol or cocaine use disorders) and (7) emotional abuse were highly associated with a diagnosis of CUD.

In our sample, the prevalence of lifetime cannabis use was 11,9% (n=900), and the prevalence of CUD was 2.69%, corresponding to a rate of 22,9% of CUD in subjects who used cannabis during the lifespan. Our prevalences are superior from those found in the

Brazilian National Alcohol Survey that found a use prevalence of 7% of lifetime cannabis use and a CUD prevalence of 0.72% in general Brazilian population (Jungerman et al., 2010; Laranjeira R, 2014). The UNODC reports that from 1999 to 2015, cannabis experimentation prevalence remained relatively constant at approximately 4%(Unodc, 2018). Although, other studies indicate an increase in both prevalences. North American surveys performed in 2016, estimated past-year cannabis use prevalence of 14.1% among those 18 years old and older. This reflects an increase from that observed in 2002, when lifetime and past-year use was 10.4% and 6.0%, respectively(Hasin et al., 2015)

Moreover, the prevalence of CUD parallels with experimentation of cannabis as it would be expected. The National Epidemiologic Survey of Alcohol and Related Conditions (NAESARC) stated that CUD prevalence was 0.2% in 2010 and increased to 3% in 2013 (Hasin et al., 2016).The increase in the prevalence of CUD motivated the World Health Organization to state that the prevalence of CUD is high enough to consider it a public health problem, at least in higher-income nations, and its prevalence appears to have increased since 2000.(WHO, 2016).

Moreover, in our sample, 44% of the subjects with lifetime use of cannabis had an early use, suggesting not an increase in the prevalence of experimentation but also a decrease in the experimentation age. Early use of cannabis is a significant predictor of subsequent misuse. (Hawkins et al., 1997) reported that misusers of alcohol appear to begin drinking at an earlier age than do users. Some authors suggest that the earlier the onset of any drug use, the higher the involvement in other drug use(Kandel, 1982) and the higher the frequency of use(Anthony e Petronis, 1995) . Earlier initiation into drug use also increases the probability of extensive and persistent involvement in the use of more dangerous drugs(Kandel, 1982) and the likelihood of the participation in deviant activities such as crime and selling drugs (Kaplan, 1995). (Robins e Przybeck, 1985) found that the onset of drug use before the age of 16 was a consistent predictor of drug abuse. Conversely, later age of onset of drug use has been shown to predict lower drug involvement and a higher probability of discontinuation of use(Kandel et al., 1976).

Consistently with previous data, males and younger adults (i.e., aged between 18 and 29 years old) demonstrate higher rates of CUDs than females and older adults(Coffey et al., 2003; Compton et al., 2004; Stinson et al., 2006). The use of drugs remains much lower among women than among men. Given the global population, men are three times more prone than women to use illicit drugs, as reported by the 2017 World Drug Report(UNODC, 2017) (Crime, 2017)

In our sample, the most prevalent psychiatric comorbidity associated with CUD was cocaine and alcohol addiction. This corroborates with previous findings that found a high risk of comorbid addictions in subjects with CUD(Wilson e Cadet, 2009). A possible explanation for the occurrence of both disorders is a common set of risk factors shared by both addictions and a common liability addiction model, such that described in the gateway model of addiction(Castaldelli-Maia et al., 2018).

The adverse childhood experiences (ACE) also associated with SUD diagnosis in our sample. ACE refers to stressful or traumatic events that children may suffer during early life, producing stress (Cdc, 2016). Repeated stress in children may influence their neurodevelopment and results in impaired cognitive functioning(Scientific Council, 2014). An ACE that affected child tends to resort to negative coping mechanisms such as substance use disorder and self-harm(Becker-Weidman, 2009; Jonson-Reid et al., 2012). Previous studies demonstrated a strong association between ACE and substance use disorders and that the presence of ACE influence on the management and prognosis of substance use disorders (Othieno et al., 2000; Douglas et al., 2010). Our results corroborate with the previous results found in the literature.

Being single and not having a religious practice associated with the diagnosis of CUD, in this study. Both factors are a proxy of social support, which is a well-known CUD preventive factor(Haug et al., 2014). Our results highlight the possible preventive action of religiosity, as the absence of this practice increased the risk of CUD.

Conclusion

Given the harmful effects of cannabis and CUD, a clear public health strategy for prevention of experimentation and addictive disorders are warranted. CUD can be associated with a constellation of biological, psychological and social factors. Our results from a large city in a developing country parallels with those reported in recent studies in different countries. Our research found that domains of socio-demographic characteristics (male gender, age and race), early stressful experiences (early drug use, childhood trauma), social support (married and religiosity) and comorbid drug addictions (cocaine and alcohol) are sigificative in subjects living in the middle-income country to delimit more CUD vulnerable groups.

Changing cannabis policies related to its therapeutic and recreational use may produce reserved prognosis when we approach experimentation and CUD prevalence increase. Policymakers should consider the already available large body of scientific

literature on substance use disorders to foster empirically-guided, common sense approaches to cannabis policy that produces prevention of addiction.

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5 DISCUSSÃO

Este trabalho é apresentado em dois tempos. No primeiro artigo, revisou-se a literatura sobre os fatores de risco para EM e para TUC. No segundo, relataram-se dados de um estudo epidemiológico transversal realizado na população de Belo Horizonte e avaliaram-se os fatores associados ao desenvolvimento de TUC.

Apurou-se que domínios sociodemográficos (sexo masculino, renda alta, idade jovem), características individuais (desvio de conduta, busca de sensações, desempenho escolar abaixo da média) e comorbidades como depressão, fatores familiares (pais com TUS e TUC), ambientais (uso de drogas por pares, baixo controle por parte dos pais) e aqueles relacionados ao uso de outras substâncias (transtorno pelo uso de álcool e pelo uso de tabaco) são riscos para EM. Fatores individuais como religiosidade e os ambientais (bom relacionamento familiar e viver em um ambiente que valoriza importância da escola) constituem proteção para EM. Fatores como sociodemográficos (sexo masculino e idade jovem), ambientais estressores (trauma infantil e crise financeira), individuais (busca de sensações, desvio de comportamento), comorbidades (transtornos de humor, transtornos ansiosos, TDAH, pais com TUS), aqueles relacionados ao uso de substâncias (transtorno pelo uso de álcool e pelo uso de tabaco) e o uso precoce de maconha acarretam risco para TUC. Religiosidade é um fator de proteção para TUC.

Observou-se elevado número de estudos que revelam que fatores ambientais, como viver em ambiente em que os indivíduos usam drogas e baixo suporte familiar, aumentaram a chance de experimentação de maconha. Identificou-se também alto número maior de fatores de proteção registrados nos estudos para EM, tais como suporte familiar e viver em um ambiente que valoriza a importância da escola e religiosidade. Por outro lado, encontrou-se expressivo número de pesquisas que evidenciaram a influência de comorbidades no transtorno pelo uso de maconha constataram-se poucos fatores de proteção para TUC, apenas religiosidade e sexo feminino, além de renda alta, que em um dos estudos era fator de proteção para TUC. No entanto, outros autores referiram este seria um fator de risco. A maioria dos estudos foi desenvolvida por países de renda alta, como Bélgica, França, Estados Unidos e Nova Zelândia.

Levando em consideração o crescente debate sobre a legalização da maconha no Brasil e a necessidade do conhecimento dos fatores associados ao TUC em países de renda média, no segundo artigo foram avaliados a prevalência e os fatores associados ao TUC em uma amostra representativa da população de Belo Horizonte. Entre 7.643 participantes, 11,9% declararam ter experimentado maconha e 22,9% apresentaram o diagnóstico de TUC no momento da entrevista. Indivíduos que fizeram uso precoce de maconha tiveram chance de desenvolver TUC 2,55 vezes. Em pessoas do sexo masculino acusou-se chance de desenvolver TUC 2,48 vezes maior do que mulheres. A chance de os indivíduos serem diagnosticados com TUC foi 1,66 maior naqueles que se declararam não brancos; 6,48 vezes maior nos com transtorno pelo uso de cocaína e 1,95 vez maior em caso transtorno pelo uso de álcool. Jovens e pessoas que sofreram abuso emocional exibiram mais chances de desenvolver TUC.

Obteve-se também a religiosidade é um fator de proteção contra TUC. Os presentes achados são semelhantes aos referenciados pelos estudos que fizeram parte desta revisão. No entanto, não se encontrou na população avaliada associação significativa entre comorbidades como a depressão e a ansiedade e TUC, assim como não houve associação significativa entre história familiar para uso de drogas e TUC, como reportado no artigo de revisão.

Considerando que comorbidades e história familiar para TUC podem representar vulnerabilidade biológica para doenças psiquiátricas (JUNG, KWANG-MOOK; PIOMELLI, 2016) e que estudos prévios demonstram que fatores sociais como pobreza, urbanismo, imigração interna e mudanças no estilo de vida são os principais moderadores de doença mental em países considerados de renda média e baixa (RATHOD et al., 2017), isso sugere que fatores biológicos podem influenciar com menos intensidade o risco desenvolvimento de TUC em países de renda média e baixa do que em países de renda alta.

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6 PERSPECTIVAS

Os resultados sugerem que os fatores de risco para TUC na população de Belo Horizonte se assemelham aos dos estudos encontrados na literatura, com mais evidência de que fatores psicossociais como estressores do tipo trauma infantil e uso precoce de drogas representam um risco para TUC. Dessa forma, estratégias de prevenção devem levar em consideração a importância da prevenção em indivíduos com mais fragilidade psicossocial.

O presente estudo de revisão permitiu concluir que fatores relativos a estrutura familiar e importância da escola constituem proteção contra a experimentação de maconha.

Futuras pesquisas poderão avaliar dados do funcionamento e estrutura familiar e a sua relação com o risco de experimentação de maconha na população de Belo Horizonte, com o objetivo de identificar alvos para estratégias de prevenção.

7 CONCLUSÕES

A conclusão a que chegou esta investigação é de que os fatores associados ao TUC na população de Belo Horizonte se assemelham aos da literatura. No entanto, comorbidades como depressão e ansiedade não foram fatores de risco para TUC na população avaliada, como demonstrado pelos autores consultados. Em função dos efeitos danosos da maconha e do TUC, é necessária a criação de estratégias que previnam a experimentação, principalmente a experimentação precoce de maconha.

Este estudo de revisão encontrou fatores de proteção contra EM como estrutura e funcionamento familiar, além da importância da escola. Estes podem ser alvos de prevenção primária da EM, principalmente em indivíduos jovens.

Nosso estudo epidemiológico transversal encontrou prevalência de experimentação e TUC superior à encontrada no Brasil até hoje. Além disso, os indivíduos fazem uso da maconha em idades cada vez mais jovens. Esse resultado leva a refletir sobre a importância de criação de estratégias de prevenção nessa população.

Apurou-se também que características sociodemográficas como sexo masculino, idade jovem, etnia não branca, uso precoce de maconha e trauma infantil, além de transtorno pelo uso de álcool e de cocaína, são significativamente associados ao desenvolvimento de TUC em pessoas que moram em países de renda média. No entanto, depressão e ansiedade não se mostraram significativamente associados a TUC. Os achados confirmam dados da literatura que propõem que fatores psicossociais são os principais moderadores do adoecimento mental em países de renda média e baixa.

O resultado permite inferir a importância da formulação de estratégias preventivas direcionadas para indivíduos jovens, de renda mais baixa e com estrutura e funcionamento familiar frágeis.

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