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Journal

Current Addiction Reports, 4(2)

ISSN

2196-2952

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Publication Date

2017-06-01

DOI

10.1007/s40429-017-0133-3

Peer reviewed

HHS Public Access

Author manuscript

Curr Addict Rep. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Curr Addict Rep. 2017 June ; 4(2): 43–52. doi:10.1007/s40429-017-0133-3.

Longitudinal Studies on the Etiology of Cannabis Use Disorder: A Review

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Abstract

Purpose of review—This review summarizes the literature to date that has capitalized on the longitudinal research study framework in order to elucidate the etiology of cannabis use disorders (CUDs).

Recent findings—The studies are mixed with respect to reliable predictors of CUD development. Of the studies outlined, the most consistently indicated risk factors for CUD development include: male sex, past cannabis and other substance use (especially tobacco), and the presence of pre/comorbid psychopathology (especially mood disorders). Social motives and peer involvement may also play a role in this transition. Many of these CUD risk factors appear to be distinct from other factors linked with overall cannabis use.

Summary—CUD development is likely the product of interactions between biological, psychological, social, and environmental factors. However, many more well-planned and developmentally sensitive prospective studies are needed to identify specific and reliable risk factors for CUD development.

Keywords

cannabis use; longitudinal studies; etiology of cannabis use disorder; CUD

Introduction

With recent changes in legislation across the United States, cannabis use is increasingly becoming socially accepted and prevalent across age groups (1, 2). While the majority of cannabis use remains non-problematic in nature, a notable number of individuals go on to develop a cannabis use disorder (CUD). A study published using the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) data in 2011 estimated an 8.9% cumulative probability of transitioning to cannabis dependence among individuals who reported any history of cannabis use (3). The present review attempts to summarize the available longitudinal research in order to highlight the factors that place an individual at greater risk for the development of a CUD. Longitudinal research involving repeated observations within the same individuals offers unique advantages as compared to cross-sectional studies, including the ability to control for time-invariant unobserved

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individual differences and the establishment of temporal precedence of events, necessary for causal hypotheses. Thus, longitudinal research on cannabis users is well-positioned to critically inform our understanding of the etiology of CUD and highlight avenues for intervention and treatment.

The review begins with a brief discussion on the current nature and scope of CUD, followed by a review of the research on the relationship between cannabis use and later CUD development, and then summaries of the remaining relevant prospective research studies are presented and organized within broad domains of risk previously identified by cross-sectional studies of CUD development: environmental and genetic factors, other substance use and substance use disorders, and pre/comorbid psychopathology. In order to identify studies for inclusion, PubMed and Google Scholar searches were conducted on the terms "cannabis use disorder" and "'cannabis use disorder' longitudinal". Article abstracts were reviewed for relevance (i.e., longitudinal design with CUD diagnosis measured at follow-up) and included as appropriate (see Table 1 for a full list and brief summary of included articles).

Nature and Scope of Cannabis Use Disorder

Although the precise clinical presentation of CUD and its diagnosis has engendered considerable controversy in the past (4, 5), CUD is recognized to consist of behavioral and interpersonal impairments as well as traditional physiological symptoms associated with other substance use disorders (DSM–5; 6). Substantial cross-sectional and longitudinal research suggests the disorder is associated with a variety of negative consequences (7), including diminished educational/occupational attainment (8, 9), intelligence quotient (IQ) decline (10), financial and social difficulties (11), impaired driving ability (12, 13), and reduced life satisfaction (8). A recent prospective report from the Dunedin Multidisciplinary Health and Development Study further suggests that longer history of CUD is associated with an increased likelihood of experiencing financial and interpersonal relationship difficulties (14). Importantly, the impact of persistent CUD on social and economic outcomes was found to be similar to that of alcohol use disorders, suggestive of the burden this disorder can have on individuals and society.

Comparisons between past year DSM-IV CUD rates from 2001–2002 and 2012–2013 show that despite an overall increase in CUD diagnoses between time periods (1.5% to 2.9%, respectively), which was likely due to population increases in cannabis use, overall CUD diagnosis decreased by approximately 5% among past year users (1). This is consistent with other reports of declining rates of CUDs despite increasing cannabis use (15). Interestingly, the lifetime cumulative probability estimate that an individual will transition from use to dependence on a substance was lowest for cannabis (8.9%), compared to cocaine (20.9%), alcohol (22.7%), and nicotine (67.5%) (3). Thus, the factors that contribute to increased risk for the development of a CUD are complex in nature and likely represent an interaction between biological and psychosocial attributes.

Individuals appear to be at greatest risk for CUD onset between the ages of 15 and 20 (16). Heavy cannabis use during this period may modulate neurodevelopment (17), potentially increasing vulnerability to CUD development. Data from three large studies conducted in

Australia and New Zealand demonstrated that daily use of cannabis before age 17 led to 18 times higher odds for the development of a CUD by age 25, as compared to non-daily adolescent users and non-users (18). Thus, adolescence appears to be the optimal time period of study to elucidate factors that increase risk of developing CUD.

Cannabis Use versus Cannabis Use Disorder

A number of predominately population based studies have investigated whether there are disparate factors for predicting cannabis use versus CUD, each with varying results. For example, a prospective study of adolescents and young adults conducted in Germany observed factors such as peers' drug use, availability of drugs, a 'positive' attitude towards future drug use, and regular previous use of licit drugs as predictive of cannabis use at 3.5 year follow-up; whereas cannabis dependence was predicted primarily by parental death before age 15, low socio-economic status (SES), and baseline use of other illicit drugs (19). A more recent report from the Monitoring the Future (MTF) study conducted in the US, found that being male, African American, more unmonitored social time at age 18, and past-year cannabis use at age 18, were associated with greater risk of CUD at age 35. Only parental college education and truancy at age 18 was associated with greater risk for both non-disordered cannabis use and CUD as compared to those who abstained from cannabis (15).

In contrast, a pre-birth cohort study conducted in Australia revealed 8 independent predictors associated with overall cannabis use *and* increased CUD risk by 21-year follow-up. These included: having a mother who changed her marital status when the child was between 5 and 14 years old, high levels of aggressive/delinquent behavior at age 14, below average school performance at age 14, experience of childhood sexual abuse, cigarette smoking or alcohol drinking at age 14, and maternal smoking at age 14. Male sex was the only predictor found to be uniquely associated with CUD development and not cannabis use in this study (20).

Conflicting reports exist as to the stability of cannabis use and CUD symptoms across time. Young adult Swiss men were assessed twice, approximately 15 months apart. Most participants remained non-users (61.9%) across time, and only 15.5% changed their use category. Despite stable CUD symptoms across time points, CUD symptoms at time 1 were found to predict health issues (mental health [primarily sadness, nervousness and depression], physical health, and health consequences) at time 2, while controlling for age of onset of CUD and frequency of cannabis use. Notably, frequency of cannabis use at time 1 was not found to predict health issues at time 2 and health issues at time 1 were not found to predict CUD symptoms at time 2, suggesting a differentiation between cannabis use- and CUD-related correlates (21). In contrast, among adult individuals diagnosed with CUD at wave 1 of the NESARC study, approximately 67% remitted 3 years later; however, 37% did so without ceasing cannabis use. Characteristics related to achieving remission at follow-up included being of Hispanic or Latino origin, having 2+ past-year medical conditions, daily or almost daily use of cannabis, and other drug use at time 1 (22).

In efforts to hone in on specific factors that predict the transition from cannabis use to CUD development, a Dutch young adult sample with frequent cannabis use yet no CUD at

baseline was followed for 36 months. The predictors of CUD transition at follow-up included: living alone, baseline number of lifetime CUD symptoms, number of negative life events experienced, and coping as a motive for cannabis use. Other factors often identified in the literature (e.g., sociodemographic factors, internalizing and externalizing mental disorders, childhood family adversity, and family history of substance use or mental health problems) were not found to be predictive of CUD transition, including measures of previous cannabis use; possibly suggesting that among frequent cannabis users, cannabis consumption motives are stronger predictors of future cannabis-related problems than exposure level itself (23).

The Oregon Adolescent Depression Project identified distinct cannabis use trajectories, namely persistent increasing risk over time, maturing-out class (increasing risk to approximately age 20 followed by declining risk), and non-abusing and non-dependent (consistent low risk over time). The persistent increasing class was more likely to be male, have an externalizing disorder and early psychotic experiences, and report later CUD onsets and greater cumulative CUD durations when compared to the maturing-out class (24). Similarly, frequent and persistent cannabis and tobacco use during adolescence, male sex, and persistent anxiety/depression from adolescence to young adulthood predicted greater risk of developing cannabis dependence by age 24 in a sample of Australian participants reporting adolescent cannabis use (25).

Possible neurobiological substrates of the transition from frequent cannabis use to CUD are beginning to be investigated. In a neuroimaging study of 23 young adult frequent cannabis users (using > 10 days per month for at least 2 years), the authors observed a positive relationship between cannabis picture cue-induced activation of the left putamen at baseline and cannabis problem severity at 3-year follow-up (26). The putamen and caudate nucleus form the dorsal striatum, a brain region critically involved in the shift from goal-directed, non-disordered drug use to habitual/compulsive disordered use (27, 28). Activation of this region was also found to differentiate CUD and non-disordered users at follow-up at a trend level; advancing dorsal striatum cue-reactivity as a potential predictor of cannabis use-related problems (26).

Age of study participants at baseline assessment also appears to contribute to the identification of disparate risk factors for CUD development. Data acquired from adult cannabis users assessed both at the first and second wave of the NESARC project identified similar CUD-related factors such as male sex and other substance use disorder (SUD), but also unique factors including American Indian or Alaskan Native ethnicity, comorbid mood, anxiety or personality disorder, and age less than 45 years old. Contrasting with other reports that early age of cannabis use is a substantial risk factor, individuals who retrospectively recalled using cannabis before age 14 were less likely to transition to dependence in this study, after controlling for SES, psychiatric comorbidity and drug-use covariates (3).

In summary, these primarily population based longitudinal studies have identified a host of disparate factors that may be related to cannabis use and/or CUD development. The wide range of risk factors and inconsistencies observed are likely related to differences in sample characteristics (e.g., participant age, cannabis use history at baseline) and socio-cultural

influences across study settings. Despite these inconsistencies, several factors stand out as probable indices of increased risk of transition from cannabis use to CUD, namely male sex, other substance use (including alcohol and tobacco), and the presence of pre/comorbid psychopathology (the latter two discussed in greater detail below). Consistent with the prevalence data, measures of previous cannabis use do not appear to be reliable predictors of later CUD suggesting that CUD liability may be largely driven by these non-specific psychosocial factors.

Environmental and Genetic Factors

The vulnerability to both initiation of cannabis use and CUD development appears markedly heritable. A meta-analysis on twin studies estimated that genes account for approximately 48%/40% (males/females) of the proportion of total variance of initiation of cannabis use (i.e., ever used cannabis) and 51%/59% (males/females) of the proportion of total variance of problematic cannabis use (i.e., one or more of the symptoms of CUD during lifetime). In contrast, shared environment accounted for 25%/39% (males/females) of initiation of use and 20%/15% (males/females) of problematic use variance (29). A retrospective analysis of parental history of CUD and other psychopathology revealed that maternal or paternal histories of CUD, paternal histories of both SUDs (not including alcohol) and antisocial personality disorder increased offspring risk of developing CUD. Further, female probands with a maternal CUD history were at higher risk for CUD onset, suggestive of a parent-offspring gender concordance effect (30).

A substantial amount of work has been conducted on the construct of “intergenerational risk” for substance use disorder liability, which includes environment and genetic components shared between parents and offspring (for a review see 31). A self-report based assessment named the Transmissible Liability Index (TLI; 32) was developed to index SUD liability using items pertaining to child characteristics (e.g., externalizing and internalizing behaviors) associated with parental SUDs. The assessment is conceptualized as a measure of behavioral undercontrol in the child (33–35).

Data from the Center for Education and Drug Abuse Research (CEDAR) study was used to investigate the predictive ability of the TLI in identification of children at-risk for CUD development. The CEDAR study recruited men with lifetime presence or absence of SUD consequent to use of an illicit drug and who had a 10–12 year old biological son or daughter at baseline. Initial analysis aimed to evaluate the accuracy of predicting CUD from transmissible (via the TLI) and non-transmissible (via the Non-Transmissible Liability Index; NTLI) factors in the children. The NTLI encompassed items that assessed peer, family, school, and neighborhood contexts that were significantly correlated with CUD. The authors found the TLI was a significant predictor of CUD by age 19 (70% sensitivity and 50% specificity) and 22 (75% sensitivity and 54% specificity). Further, they found the NTLI added little to the accuracy of the TLI measure and concluded that the TLI is a reasonable screening measure of CUD risk in youth (36). However, the low specificity of the measure suggests the TLI may be capturing a broader concept than CUD risk alone, such as an externalizing or general SUD liability (37).

More recently, boys of the CEDAR sample were categorized at age 22 into one of three groups: lifetime diagnosis of CUD; cannabis use without CUD; and no lifetime history of cannabis use. Prior to first exposure to cannabis, the boys who later developed CUD exhibited severe transmissible liability than boys who later used cannabis but did not develop to CUD. Further, for boys with high TLI scores, initiation of cannabis use was followed by a progressive increase in risk that culminated in CUD (35). When looking at participants of both sexes from the CEDAR dataset, age of cannabis use initiation fully mediated the association between TLI score and CUD, suggesting that initiation age is an indicator of increased vulnerability. The authors also observed a cross-relationship with alcohol initiation such that age of alcohol initiation predicted CUD and vice versa, highlighting a potential nonspecific risk factor for both alcohol use disorder and CUD (38).

An early report on the CEDAR data highlighted the importance of the adolescent peer environment. The authors observed that the Peer Milieu Index (PMI) assessed at age 16 predicted CUD and mediated neurobehavioral disinhibition and CUD. The authors concluded that boys with attention disturbances and low behavior control tend to socialize with peers who increase their risk of developing CUD (39). This was later reaffirmed with the TLI measurement (37). In another analysis of the CEDAR data, peer environment and normative social attitudes at age 16 were found to mediate the relationship between TLI scores at ages 10–12 and use of illegal drugs at age 19 which predicted CUD at age 22. Peer environment at age 16 was also found to mediate quality of parent-child relationship and cooperative behavior relationships with substance use and CUD, and normative social attitudes mediated the relationship between quality of parent-child relationship on substance use and CUD (40).

Specific social motives for use of cannabis are also associated with increased risk for the development of CUD. A longitudinal cohort study of undergraduates revealed that individuals with a CUD were significantly more likely to use cannabis in the contexts of social facilitation and emotional pain than non-problematic users, even after controlling for cannabis use frequency and alcohol use. Individuals who developed a CUD during the study were more likely to use cannabis for social facilitation, suggesting individuals with CUD have disparate social motives of use (41). In contrast, solitary cannabis use during adolescence has been shown to be a significant risk factor for lower physical health and increased substance-related problems in young adulthood (42). Creswell and colleagues (43) demonstrated a concurrent relationship between solitary cannabis use, more frequent cannabis use, and CUD symptoms during adolescence.

Psychological and biological factors, however, likely mediate environmental predictors of CUD development. CEDAR data found that neurobehavioral disinhibition at 10–12 years old mediated the paths from neighborhood quality and parental SUD to later cannabis use and development of a CUD by age 22 (44). Testosterone level at age 10–12 was shown to mediate the relationship between disadvantaged neighborhood, assaultive behavior, social dominance norm-violating motivation, and CUD (45).

The impact of prenatal factors on development of CUD in the offspring has also been considered and an indirect pathway between prenatal exposure, early age of cannabis use

initiation (<16 years old), and later CUD development has been reported. Further, prenatal cannabis and alcohol exposure was related to depression symptoms at age 10, which also predicted early age of cannabis use and subsequent CUD (45).

In summary, the heritability of CUD vulnerability appears to manifest, at least in part, through psycho-behavioral characteristics that then interact with the environment to confer risk to the individual. Replication studies which use the TLI to predict risk in independent samples are much needed. One such study conducted on the Minnesota Twin Family Study dataset indicated that TLI scores are indeed highly heritability (76% of the proportion of total variance), associated with adolescent substance use, and predictive of SUD risk in females at similar rates to males (46). Another study sought to cross validate the TLI in a sample of first-year college students (47). Although the authors found lower sensitivity and specificity of their college version of the TLI (TLI-CV) as compared to the report by Kirisci and colleagues (36), higher baseline scores on the measure were found to be associated with concurrent cannabis dependence and were significantly related to incident cannabis dependence during the 4 year follow-up period (47). Given that the greatest risk for CUD onset is before age 20 (16), consideration of the differences in sample ages across studies should be weighed when reviewing the predictive ability of these factors.

Other Substance Use and Disorders

There appears to be a strong relationship between use of cannabis and other substances, as well as higher rates of comorbidity across SUDs (48–50). Some suggest cannabis serves as a “gateway” drug, ultimately leading to problematic substance use (51), while others argue for the existence of a shared vulnerability factor across substance use/SUDs (37). Population studies have identified other licit and illicit substance use as a prospective risk factor for the development of CUD (3, 19, 20, 25). For example, the use of tobacco has been reported to predict the use of cannabis (and vice versa), and that the odds of co-use of these substances are greatly increased in heavy users of either substance alone (52).

Similarly, CUD development by age 19, was more likely in Dutch adolescents with early onset and consistent tobacco use (but not early alcohol use), while controlling for a number of potential covariates (i.e., externalizing behavior problems, peer cannabis use) (53). In contrast, a study of German adolescents and young adults found no relationship between younger age at first alcohol and nicotine use and increased risk of CUD for up to the 8-year follow-up. However, there was an observed predictive relationship between younger ages of first alcohol and/or nicotine use and cannabis use (54).

Of the studies outlined in this review, tobacco use appears to be the most consistently associated substance with later CUD development. Similar routes of administration (i.e., smoking), higher prevalence of tobacco smoking versus other substance use in the general population, more permissive cultural norms, and more frequent study measurement of tobacco smoking may subserve this observed association. However, the absence of a relationship between early alcohol use and CUD development adds support to the presence of a specific prospective relationship between tobacco smoking and CUD. Many more studies that incorporate early measurement of a range of substances are needed to fully capture the nature of these intricate relationships.

Pre/Comorbid Psychopathology

Early childhood factors may increase vulnerabilities towards externalizing and internalizing symptoms and substance use problems (e.g., 55, 56). CUD and cannabis use has been previously associated with a number of comorbid psychiatric diagnoses including mood disorders (57, 58) and psychosis (59); however, the strength and directionality of these relationships remains unclear (60). Some evidence suggests cannabis use during adolescence is predictive of anxiety disorders, but not major depressive disorder (61), while others observe a small association between frequent cannabis use and *concurrent* depressive symptoms (62). In contrast, little support was observed for a predictive relationship between cannabis use and later mood or anxiety disorders in the NESARC adult data (48).

Examination of the prospective relationships between psychopathology and later cannabis use/CUD revealed no clear homogenous patterns in a sample of German adolescents. However, endorsement of other SUDs or any other psychological disorder at baseline was associated with increased rates of cannabis use and CUD, and having three or more disorders further increased these rates. Unipolar and bipolar mood disorders increased rates of cannabis use and CUD at follow-up; and panic disorder was found to predict cannabis use (but not CUD) at follow-up. Conduct disorders, but not attention-deficit/hyperactivity disorder (ADHD) or oppositional defiant disorder (ODD), were also found to predict increased rates of cannabis use, but not CUD (63).

Similarly, other studies have reported mixed associations between externalizing psychopathology symptoms and later CUD. Proximal externalizing factors during adolescence (but not distal childhood factors) were found to be moderately strong predictors of time to CUD onset, when controlling for demographic variables, family characteristics, and internalizing psychopathology (64). A meta-analysis which assessed for CUD in prospective longitudinal cohorts of school-age children diagnosed with ADHD found an initial association between childhood ADHD and elevated CUD risk in young adulthood; however, the authors noted substantial heterogeneity and cautioned against inferring a strong relation between the constructs (65).

Taken together, the relationship between pre/comorbid psychopathology and CUD remains unclear. The extant data seems to point to stronger prospective associations between psychopathology and cannabis use, as opposed to CUD development. This relationship may reflect an individual’s attempt to cope with their psychological distress through cannabis use (i.e., “self-medication”); however, more carefully designed longitudinal work in this area is needed before any strong conclusions of causality can be drawn.

Conclusions

The need for greater understanding of the etiology of CUD is critical given the increasing rates of cannabis use across the US. Approximately 9% of cannabis users will develop a CUD in their lifetime (3); however, what determines whether one will transition to problematic use or not remains largely unknown. Longitudinal studies, particularly those beginning in adolescence, have begun to shed light on the pathways to increased risk for

transitioning from cannabis use to CUD; however, little consilience exists in the extant literature.

CUD development most likely depends on a range of factors spanning biological and psychosocial domains. CUD has shown to be markedly heritable (29); yet, the environmental and psychological contexts of cannabis use appears to significantly modulate the risk of transitioning to CUD. Of the studies outlined, the most consistently identified risk factors include: male sex, past substance use (especially tobacco), and the presence of pre/comorbid psychopathology (especially mood disorders). Social motives for cannabis use and peer involvement likely also play a role and should be considered in much greater detail in future studies of CUD development. Importantly, many risk factors appear to be unique pathways of disorder development beyond exposure to cannabis, suggesting that non-specific psychosocial factors such as general life and psychological distress may be driving disordered use behavior.

Despite these inconsistencies, the field shows commitment in elucidating the nature of this complex phenomenon. Large scale longitudinal studies (e.g., the Adolescent Brain Cognitive Development (ABCD) study) will hopefully shed light on the various pathways of CUD development with enhanced attention to developmental and neurologic mechanisms. The extant research strongly suggests the risk for CUD must be considered within a developmental framework as this transition from use to disorder is most common in late adolescence/early adulthood (16, 18). Adolescence is marked by changes in brain maturation, psychological functioning, and social role transitions/peer involvement. Thus, the pursuit of sensitive and specific risk factors and cannabis use trajectories originating during this time frame would greatly facilitate etiological theories of CUD development. This knowledge could then be used to inform targeted intervention approaches that would ultimately reduce the potential burden of CUD on the individual and society at large.

Acknowledgments

This review was partially supported by the National Institutes of Health Grants 1KL2TR001444 of CTSA funding and T32AA013525 from NIAAA.

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Table 1

Full list and brief summary of included articles.

Author, Year	Country	Baseline age	Follow-up	N	Predictors of cannabis use ("USE") or cannabis use disorder ("CUD") or general study findings
Cannabis Use versus Cannabis Use Disorder					
von Sydow, Lieb, Pfister, Hofler, & Wittchen, 2002 (4)	Germany	14–24	3.5 years	1,723	USE: peer drug use, availability of drugs, a more 'positive' attitude towards future drug use, and regular previous use of licit drugs CUD: parental death before age 15, low socio-economic status (SES), and baseline use of other illicit drugs
Schulenberg et al., 2015 (5)	USA	18	Age 35	25,536	USE & CUD: parental college education and truancy at age 18 CUD: male, African American ethnicity (vs. white), having more unmonitored social time at age 18, and past-year cannabis use at age 18
Hayatbakhsh, Najman, Bor, O'Callaghan, & Williams, 2009 (6)	Australia	Pre-birth	Age 21	2,493	USE & CUD: having a mother who changed their marital status when the child was between 5 and 14 years old, high levels of aggressive/delinquent behavior at age 14, below average school performance at age 14, experience of childhood sexual abuse, cigarette smoking or alcohol drinking at age 14, and maternal smoking at 14 CUD: Male sex
Baggio et al., 2014 (7)	Switzerland	20	1.25 years	5,084	Most remained non-users (61.9%) across time, and 15.5% changed their use category (8.3% transitioned to "late-onset" users and 7.2% to "matured-out" users)
Feingold, Fox, Rehm, & Lev-Ran, 2015 (8)	USA	18+ (CUD)	3 years	444	Approximately 67% remitted at follow-up, 37% of which did so without ceasing use of cannabis. Wave 1 characteristics that were related to achieving remission at follow-up: Hispanic or Latino origin, two or more past-year medical conditions, daily or almost daily use of cannabis, and other drug use at time 1
van der Pol et al., 2013 (9)	Netherlands	18–30 (frequent cannabis users)	3 years	269	CUD: living alone, baseline number of lifetime CUD symptoms, number of negative life events experienced, and coping as a motive for cannabis use
Vingerhoets et al., 2016 (10)	Netherlands	21	3 years	23	Picture cue-induced activation of the left putamen at baseline predicted cannabis problem severity
Lopez-Quintero et al., 2011 (3)	USA	18+	3 years	7,389	CUD: male sex, other SUD, American Indian or Alaskan Native ethnicity (vs. white), comorbid mood, anxiety or personality disorder, and age less than 45 years old
Kosty, Seeley, Farmer, Stevens, & Lewinsohn, 2016 (11)	USA	16.6 (mean)	Age 30.5 (mean)	816	Three trajectory classes identified: (1) persistent increasing risk over time (2) maturing-out class, (3) non-abusing and non-dependent class. Persistent increasing class was more likely to be male, have an externalizing disorder between ages 24 and 30, have psychotic experiences during early adulthood, have later initial CUD onsets, and greater cumulative CUD durations when compared to individuals in the maturing-out class
Swift, Coffey, Carlin, Degenhardt, & Patton, 2008 (12)	Australia	14–17 (cannabis users)	Age 24	515	CUD: frequent and persistent cannabis and tobacco use during adolescence (ages 14–17), male sex, and to some extent, persistent anxiety/depression from adolescence to young adulthood
Environmental and Genetic Factors					

Author, Year	Country	Baseline age	Follow-up	N	Predictors of cannabis use ("USE") or cannabis use disorder ("CUD") or general study findings
Kosty et al., 2015 (13)	USA	24 (retrospective report of parental history)	Age 30	719	CUD: maternal or paternal histories of CUD, paternal histories of illicit drug use disorders (not including alcohol), and paternal histories of antisocial personality disorder
Kirisci et al., 2009 (14)	USA	10–12	Age 22	216 (boys)	Transmissible liability was a significant predictor of CUD by age 19 (70% sensitivity and 50% specificity) and age 22 (75% sensitivity and 54% specificity
Kirisci, Tarter, Ridenour, Reynolds, & Vanyukov, 2013 (15)	USA	10–12	Age 22	1) CUD (n = 64) 2) use only (n = 178) 3) no use (n = 170); (boys)	The boys who later developed CUD exhibited more severe transmissible liability than boys who later used cannabis but did not develop to CUD
Kirisci, Tarter, Ridenour, Zhai, et al., 2013 (16)				339	Age of cannabis use initiation mediated the association between transmissible liability and CUD. Alcohol initiation predicted CUD and vice versa
Feske et al., 2008 (17)				216 (boys)	Non-normative socialization assessed at age 16 predicted CUD and mediated the association between neurobehavioral disinhibition and CUD
Tarter et al., 2012 (18)				171 (cannabis using boys)	Non-normative socialization at age 16 mediated the association between childhood transmissible risk and CUD
Tarter et al., 2011 (19)				254	Peer environment and normative social attitudes at age 16 mediated the relationship between childhood transmissible liability and drug use at age 19 which predicted CUD at age 22. Peer environment at age 16 also mediated quality of parent-child relationship and cooperative behavior relationships with substance use and CUD, and normative social attitudes mediated the relationship between quality of parent-child relationship on substance use and CUD
Ridenour et al., 2009 (20)				216 boys	Neurobehavioral disinhibition at 10–12 years old mediated the paths from neighborhood quality and parental SUD to cannabis use and CUD
Tarter et al., 2009 (21)				208 boys	Testosterone level at 10–12 years old mediated the relationship between disadvantaged neighborhood, assaultive behavior, social dominance norm-violating motivation, and later cannabis use and CUD
Beck et al., 2009 (22)	USA	17–19 (College students)	1 year	322	Individuals with a CUD were significantly more likely to use cannabis in the contexts of social facilitation and emotional pain than non-problematic users at follow-up. Individuals who developed a CUD during the study were more likely to use cannabis in a context of social facilitation than consistent non-problematic users
Tucker, Ellickson, Collins, & Klein, 2006 (23)	USA	8th grade	Age 23	3,303	Solitary substance use (including cannabis) during adolescence predicted lower physical health and increased substance-related problems
Creswell, Chung, Clark, & Martin, 2015 (24)	USA	12–19	Age 25	447	Solitary cannabis use associated with concurrent frequent cannabis use and CUD symptoms during adolescence
Arria, Vincent, & Caldeira, 2009 (25)	USA	17–19 (College students)	4 years	1,018	Transmissible liability associated with concurrent CUD and was transitioning to CUD during follow-up

Author, Year	Country	Baseline age	Follow-up	N	Predictors of cannabis use (“USE”) or cannabis use disorder (“CUD”) or general study findings
Sonon, Richardson, Cornelius, Kim, & Day, 2016 (26)	USA	Prenatal	Age 22	590	Indirect pathway found between prenatal exposure to cannabis, early age of cannabis use initiation (<16 years old), and CUD development at age 22. Prenatal cannabis and alcohol exposure was related to depression symptoms at age 10, which also predicted early age of cannabis use and subsequent CUD
Other Substance Use and Disorders					
Badiani et al., 2015 (27)	New Zealand	Birth	Age 35	962–1,025 (depending on f/u)	Use of tobacco or cannabis leads to the use the other substance, and that the odds of co-use are greatly increased in heavy users of either substance
Prince van Leeuwen et al., 2014 (28)	Netherlands	11	Age 19	1,328	CUD: early onset and consistent tobacco use (but not early alcohol use)
Behrendt et al., 2012 (29)	Germany	14–24	8 years	2,210	No relationship between younger age at first alcohol and nicotine use and increased risk of CUD
Pre/Comorbid Psychopathology					
Blanco et al., 2016 (30)	USA	18+	3 years	34,653	No predictive relationship between cannabis use and later mood or anxiety disorders observed
Wittchen et al., 2007 (31)	Germany	14–17	10 years	1,310	USE and CUD: endorsement of other SUDs or any other psychological disorder (particularly unipolar and bipolar mood disorders), having three or more disorders
Farmer et al., 2015 (32)	USA	16	Age 30	816	Time to CUD onset: Proximal externalizing factors (occurring during adolescence) but not distal (childhood) factors
Charach, Yeung, Climans, & Lillie, 2011 (33)	Meta-analysis	“school aged” (mean = 12)	Age 18+	2,783 (ADHD and controls from 6 studies)	CUD: childhood ADHD
Staff et al., 2010 (34)	USA	12th grade	Ages 19–28	40,423	USE: changes in family, and to a lesser extent, school and work roles