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Identifying Early Risk Factors for Addiction Later in Life: A Review of Prospective Longitudinal Studies

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Abstract

Purpose of Review: To review prospective longitudinal studies that have identified risk factors for the development of substance use disorders in adulthood from individual differences during childhood and adolescence.

Recent Findings: Risk factors during childhood and adolescence that have been consistently linked to increased risk for addiction include externalizing and internalizing symptoms, early substance use, and environmental influences, such as parental behavior and exposure to traumatic experiences.

Summary: Since the etiology of substance use disorders is complex and likely is attributable to many causal pathways, systematic examination of the associations between risk factors will be necessary to understand the mixed findings in the existing literature, to determine which individuals should be targeted for prevention efforts, and to design interventions that address risk factors that are most likely to improve outcomes.

Keywords

substance use disorders; predictors; developmental; psychiatric; drug use

Introduction

Substance use disorders are associated with many personal and societal costs. For example, alcohol and tobacco use alone were linked to 568,000 preventable deaths in the US every year from 2006–2010 [1, 2], and the financial costs of substance use (e.g. health care, crime)

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Human and Animal Rights and Informed Consent

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are estimated to be around \$740 billion per year [1, 3–7]. Furthermore, treatment for substance use disorders is challenging, with the majority of individuals requiring multiple interventions before achieving stable abstinence [8, 9]. One strategy to reduce the negative consequences associated with substance use is to identify risk factors for the development of substance use disorders that can inform prevention efforts. Prospective longitudinal studies have the potential to provide important information about the complex pathways that lead to the development of substance use disorders; unlike cross-sectional studies they can use temporal information to disentangle causes from consequences and are less likely to be biased by temporal delay, as is the case in many retrospective studies relying on self-report.

Although many studies have examined factors that predict quantity of substance use, most people engage in some alcohol and drug use during their lifetime without developing a substance use disorder. For example, it is estimated that 86.4% of Americans drink alcohol in their lifetime, while 68.7% use tobacco products, and 46.9% use marijuana [10]. However, 30% of adults in the US will suffer from an alcohol use disorder in their lifetime [11], and the lifetime prevalence of nicotine and other drug use disorders is 27.9% and 9.9%, respectively [12, 13]. These data suggest that there is considerable heterogeneity in the personal and environmental factors that impact the likelihood of developing addiction. While the negative consequences associated with substance use vary along a continuum, individuals with a substance use disorder, as opposed those who engage in substance use, are likely at highest risk of experiencing negative consequences. Therefore, this article reviews prospective longitudinal studies that assess individual differences in childhood and adolescence (< 18 years old) with the *goal of predicting substance use disorders* later in life (> 18 years old). Since meta-analysis improves the power of small or inconclusive studies, if available, we review meta-analyses of prospective longitudinal studies examining risk factors for substance use disorders instead of detailing individual findings. This review examines the evidence suggesting that personal and environmental factors such as psychopathology, personal substance use, parental and peer influence, socioeconomic status, negative life events, and neurobiology impact the likelihood of developing addiction (see Table 1 for a list of the articles included).

Psychopathology

Psychiatric Diagnoses

Diagnosis of a mental health disorder early in life is one of the most extensively studied predictors of future substance use disorders in adulthood. A recent meta-analytic review found that childhood/adolescent diagnosis of attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD) or oppositional defiant disorder (ODD), and depression, were associated with an increased risk for adult addiction [14••]. In this study, ADHD and CD/ODD were associated with increased risk of alcohol, nicotine, other drug use and any substance use disorder, while depression was associated with an increased risk for alcohol, nicotine, and any substance use disorder [14]. While not significant in the meta-analysis by Groenman and colleagues [14], anxiety disorders in adolescence have also been associated with adult addiction, but findings are limited. One study found that social anxiety disorder in adolescence was associated with alcohol and cannabis dependence in adulthood [15], with a

stronger effect in women than men [16]. Below, we review the evidence that externalizing and internalizing symptoms are also risk factors for addiction later in life.

Externalizing Behavior

Using parental and adolescent self-reports, studies have demonstrated that greater levels of externalizing behavior in childhood and adolescence are associated with increased risk for alcohol [17] and cannabis [18, 19, 20] use disorders, as well as symptoms nicotine use disorder [21] in adulthood. Furthermore, specific symptoms of CD in early adolescence, in the absence of a clinical diagnosis of CD or ODD, predicted alcohol dependence in young adult males [22], while greater ODD symptoms in childhood/early-adolescence predicted nicotine, cannabis, and cocaine abuse and/or dependence in young adulthood [23]. Similarly, in youth without an ADHD diagnosis, two studies have found that greater inattentive symptoms in childhood/early-adolescence predicted alcohol, nicotine, and cannabis abuse/dependence in young adulthood [23, 24].

Several studies have also demonstrated associations with more specific externalizing behaviors and addiction in adulthood. Greater misbehavior at school, greater delinquency, deviant behavior, being sexually active, antisocial behavior, and lower perceived consequences of antisocial behavior are all associated with alcohol abuse and dependence in adulthood [24–27]. Similarly, delinquency and aggression in adolescence also predicted cannabis, nicotine, and other drug abuse/dependence in adulthood [24]. Additionally, novelty seeking in adolescence has also been shown to be predictive of alcohol, nicotine, cannabis, and other illicit substance use disorders in adulthood [28, 29]. Lastly, studies using composite scores that include assessments of externalizing symptoms and cognitive functioning during adolescence have shown that neurobehavioral disinhibition is associated with increased risk for substance use disorders in adulthood [30, 31].

Internalizing Symptoms

Similar to externalizing behaviors, internalizing symptoms during adolescence have been linked to greater likelihood of addiction in adulthood, but perhaps to a lesser extent. Internalizing and more specifically, depressive symptoms in adolescence have been linked to both alcohol dependence and nicotine dependence later in life [32–34]. The associations between depressive symptoms and future substance use disorders may be related to the presence of other risk factors, as depressive symptoms in adolescent males only predicted alcohol dependence in individuals with CD [22]. In contrast, some work suggests that internalizing behavior is inversely associated with cannabis use disorders in adulthood [19].

Personal Substance Use

Several studies have determined that alcohol and drug use before adulthood is a risk factor for the development of substance use disorders later in life. Research has been conducted to examine whether initiating alcohol use at various age-cutoff points is associated with heightened risk for addiction [35], with one study determining that initiating alcohol use before 11 increased risk for chronicity of adult alcohol dependence [36]. However, no evidence has been found that later cutoffs are associated with increased risk for alcohol

dependence [35, 36]. More recent work suggests that age of first intoxication is better predictor of risk for substance use disorder in adulthood, as unlike age of first drink [37], earlier age of first intoxication is a significant predictor of alcohol use disorder, nicotine, cannabis, and other illicit drug dependence, when controlling for other potential risk factors [38]. Beyond age of alcohol use initiation, frequency [24] and heaviness [35, 36] of alcohol use during adolescence [25–27, 32, 39] has also been linked to increased risk for alcohol and other substance dependence during adulthood.

Although less well-studied than alcohol, similar effects have been observed with other drugs. For example, earlier onset of tobacco use and continued tobacco use during adolescence, were associated with higher risk of developing a cannabis [19, 40, 41], alcohol [32], and illicit drug use disorders [42, 43] in young adulthood. Furthermore, frequency of marijuana use during adolescence was also associated with higher rates of adult alcohol [36] and cannabis dependence [41]. It has also been demonstrated that youth who experiment with or regularly use alcohol and/or drugs are at higher risk for developing other substance use disorders in young adulthood than those who abstain during this time of life [19, 44].

Environmental Influences

Parental Substance Use and Behavior

The existing evidence suggests that having parents with a substance use disorder increases risk for personal addiction in adulthood [30, 31]. More specifically, parental alcoholism during adolescence has been linked to alcohol and drug dependence in offspring in adulthood [35, 45–47]. Similarly, Kosty and colleagues demonstrated that parental history of cannabis and other illicit drug disorder increased the risk of offspring cannabis use disorder. While having a parent that smoked cigarettes during adolescence was associated with greater risk of personal nicotine dependence in young adulthood, after controlling for internalizing and externalizing symptoms, only the association between maternal smoking and amount of personal cigarette use remained significant [33]. Furthermore, parental history of other illicit substance use disorders also increased personal risk for cannabis use disorder, but there was no significant association between presence of a parental alcohol use disorder and personal risk for cannabis use disorder. These effects are likely attributable to both genetic and environmental risk factors. It is estimated that 40–60% of the variability in risk for developing alcohol, nicotine or illicit substance use disorders is attributable to genetic factors and genome wide-association studies have been able to attribute some of that variability to specific genetic loci [48]. However, adoption studies suggest that the association between parental substance use disorders and personal risk for addiction is also attributable to environmental influences. For example, Nwelin and colleagues demonstrated that individuals with adoptive or step-parents with substance use disorders were also more likely to develop a substance abuse/dependence in adulthood [49], suggesting that these familial associations are not entirely genetic in nature.

There is also research suggesting that subclinical parental substance use and behavior can influence personal risk for addiction later in life. A recent meta-analysis of longitudinal studies examined which modifiable parenting factors measured in adolescence were associated with future alcohol misuse (including alcohol use disorders) in their children. The

study determined that subclinical levels of parental alcohol use, favorable attitudes toward alcohol use, and parental provision of alcohol use were associated future alcohol misuse by their children [50••]. Furthermore, lack of parental involvement, monitoring, support and parent-child relationship quality were associated with increased risk for alcohol misuse later in life.

Peer Influences

Evidence from longitudinal studies suggests that socializing with peers that are engaging in alcohol and other drug use increases risk for substance disorders later in life [20, 21, 25, 40, 51, 52], but the directionality of the relationships between peer affiliation and personal substance use remain unclear. For example, deviant peer affiliations in adolescence mediated the association between substance use in adolescence and substance dependence in young adulthood [52]. In contrast, another study found that the association between peer affiliations and future cannabis use disorder was mediated by increased cannabis use, but did not find evidence that cannabis use predicted affiliation with peers who used cannabis [20].

Socioeconomic Status

Studies linking economic disadvantage in childhood and adolescence to risk for adult substance use disorders have produced mixed results. While childhood economic disadvantage has been associated with increased risk for alcohol [53] and tobacco [21, 53] dependence in adulthood, one study found that economic disadvantage during childhood was *less likely* to result in harmful drinking in adulthood in female participants [54]. Some studies have also failed to detect a significant association between socioeconomic status during childhood and/or adolescence and adult substance use disorders [22, 32, 40].

Negative or Traumatic Life Events

Most studies examining the association between negative and traumatic life events in childhood and adolescence and risk for developing addiction in adulthood have relied on retrospective reports [55]. Studies examining prospectively-substantiated childhood maltreatment demonstrated that any childhood maltreatment, physical abuse, emotional abuse, and neglect predicted cannabis dependence in young adulthood [19, 56]. Given the evidence that retrospective self-reports of childhood maltreatment might be better predictors of substance use disorders than prospective substantiated-reports [57, 58], it is worth noting that longitudinal studies beginning in childhood or adolescence have found associations between retrospective self-report of childhood adversity [55] or physical abuse [59] before the age of 18 and substance use disorders in adulthood.

Neurobiology

Compared to the wealth of literature using neurobiological assessments during adolescence to predict future patterns of substance use [for review, see 60], there have been few prospective longitudinal studies that investigate neural predictors of risk for substance use disorders. Further, in contrast to the cohort studies described previously, most longitudinal neuroimaging studies to date have sampled across a large age range at baseline and followed subjects for a relatively short time frame and are unable to risk factors that predict adult

addiction. For example, the ratio of orbitofrontal cortex to amygdala volume during adolescence (ages 8–19) has been associated with substance use disorders several years later (ages 12–27) [61], and less orbitofrontal cortex volume at age 12 has been shown to predict diagnosis of a substance use disorder prior to age 18 [62]. Lastly, one study found that the amplitude of the P300 component of the event related-potential and postural sway (a marker of neurodevelopmental delay) during childhood, but not adolescence, predicted substance use disorders in adulthood [63]. Future studies in this domain are needed to isolate neurobiological predictors occurring specifically in childhood and adolescence (<18 years of age) that can be used to identify clinical diagnosis of a substance use disorder in adulthood (> 18 years of age).

Examining the Complex Relationships Between Risk Factors for Addiction

Systematic inclusion of risk factors in prospective studies and careful evaluation of the relationships between risk factors is necessary for understanding heterogeneous findings in the existing literature and identifying the optimal targets for intervention. Existing studies suggest that different risk factors explain unique and overlapping variance in the risk for addiction. For example, Fergusson and colleagues determined that conduct and attentional problems during childhood and adolescence predicted alcohol, cannabis, nicotine, and other drug abuse/dependence in young adulthood using univariate models; however, only the effects of conduct problems remained significant when both predictors were modeled concurrently along with childhood adversity, socioeconomic status, family instability and conflict, parental substance use, childhood abuse, anxiety, and cognitive ability [64]. These findings suggest that conduct problems independently predict future substance use disorders; however, the association between inattention and future substance may be best explained by the correlations between inattention and conduct problems or other relevant personal and environmental risk factors. Although this is a single example, this pattern of results is pervasive in the literature, with many studies reporting significant effects in univariate analysis that are no longer significant when other personal and environmental risk factors are modeled simultaneously [e.g. 32, 33, 37, 35, 38, 40]. To begin disentangling the complex relationships between variables, Kraemer and colleagues have proposed methodology for determining whether risk factors are working independently, have overlapping influence, or if one variable is only related to the outcome by proxy of another risk factor [65••]. In the existing literature, the examination of many variables at once, the heterogeneity of the variables selected for inclusion, and only reporting the effects associated with variables of interest, hampers our understanding of how different variables work together to influence outcomes. Working towards clarifying these relationships is important, because while proxy variables may be useful for identifying individuals who are at risk for addiction, interventions targeted at proxy risk factors are unlikely to improve outcomes.

Another important step in determining how risk factors work together, is to test for mediators that provide evidence for hypothesized relationships between chains of risk factors and for moderators that affect the relationship between other variables [65]. For example, it has been demonstrated that a latent variable of childhood socioeconomic disadvantage was a better predictor of cigarette use in young adulthood (another latent variable combining nicotine dependence and smoking frequency) than 5 observed variables

(e.g. parental education, parental income) [21]. This association was mediated by educational achievement, conduct problems, and exposure to parental and peer smoking in adolescence. Given the temporal precedence of risk factors, these findings are consistent with the hypothesis that early economic disadvantage leads to factors in adolescence that promote risk for addiction in adulthood; however, it is important to note that tests of mediation tests do not prove causation. Furthermore, although the meta-analysis by Groenman and colleagues did not find evidence for an association between anxiety disorders in adolescence and adult addiction [14], one study found this association was moderated by sex, such that social anxiety disorder in adolescence predicted adult alcohol and cannabis dependence in women but not men [16]. Identification of moderators is important because they highlight which interventions might be appropriate for different individuals.

An alternative technique for examining the complicated relationships between risk factors involves the use of more data-driven statistical machine learning methods approaches that can use a large number of predictor variables and include higher order interactions between predictors in statistical models (e.g. random forest, support vector machine learning). Although to our knowledge, statistical machine learning has not been utilized to predict *substance use disorders* in adulthood from childhood and adolescent risk factors, these approaches have been used to predict binge drinking [66] and moderate/heavy alcohol use during adolescence [67]. In both studies, a variety of demographic, behavior, personality, cognitive, and neurobiological factors predicted alcohol use. Although these findings suggest that more complex models may improve our ability to predict addiction in adulthood, translating these findings into policy and preventions may prove to be challenging due to the highly dimensional nature of the results.

Developing indices of risk for substance use disorder that are easy to calculate and rely on a limited number of features may facilitate the translation of findings from prospective longitudinal studies for use in public health initiatives. For example, Meier and colleagues created a cumulative risk index by summing the presence of 9 childhood and adolescent risk factors: being male, lower family socioeconomic status, family history of substance use disorders, childhood conduct disorder and depression, early exposure to substances, and adolescent frequent alcohol, tobacco, and cannabis use [68]. The composite score predicted persistent substance use disorder in adulthood with 80% accuracy. They determined that 3% of adolescents without risk factors, 27% of adolescents with 3 risk factors, and 74% of adolescents with 6+ risk factors had persistent substance use disorder as adults. Similar work predicted cannabis use disorder in young adulthood using two composite scores thought to reflect transmissible and nontransmissible risk factors for substance use disorders derived from assessments obtained in boys during childhood [69]. Although promising due to their ease of use, careful examination of the variables included in composite scores is helpful for ensuring that important relationships between variables are not being obscured by aggregation of risk factors into composite scores. Lastly, across all approaches employed, replication in independent datasets is necessary to validate the veracity of findings.

Conclusions and Future Directions

Although progress has been made in identifying risk factors for addiction, the complicated relationships between risk factors are less well-understood and may hamper accurate identification of those at greatest risk and the creation of interventions targeted at the risk factors that have the greatest impact on risk for substance use disorders. This review highlights several risk factors that have been most consistently linked to higher risk for addiction, such as the presence of externalizing and internalizing symptoms, early substance use, and environmental influences including different aspects of the parent-child relationship and exposure to trauma. Further research to identify how these variables interact and to identify novel risk factors will be important for understanding the complexity of the various mechanisms that lead to the development of substance use disorders.

Since rates of illicit substance use are relatively lower, prospective longitudinal studies have predominately focused on predicting variable patterns alcohol, nicotine and/or marijuana use. To the extent that some risk factors for addiction are drug specific, larger longitudinal studies or recruitment of samples at higher risk for illicit drug use would aid in determining the factors that predict illicit substance use disorders. For example, a recent study determined that adolescents who experienced chronic pain were more likely to misuse opioids than adolescents without chronic pain [70]. With rates of opioid overdoses increasing 12.9-fold from 2007 to 2017 [71], more research is needed to determine which individuals are at greatest risk for opioid misuse and addiction.

While several large cohort studies exist for examining environmental and neurocognitive predictors of adult addiction, studies using neurobiological predictors have been limited. Large-scale prospective longitudinal studies, such as the Adolescent Brain Cognitive Development Study (ABCD), will provide an unprecedented opportunity to examine how cognitive, behavioral, and environmental risk factors for addiction are related to neurobiology and risk for addiction. For example, based on a review of the existing literature, it has been hypothesized that the relationship between internalizing symptoms and substance use is partially attributable to individual differences in the development of frontostriatal circuitry that predict the onset and escalation of depression, anxiety, and substance use [72]. Studies, like ABCD, should have an adequate sample size to examine this and many other hypotheses about the development of psychopathology, including addiction. Identifying biomarkers that predict increased risk of developing a substance use disorder could inform interventions that target and strengthen relevant circuitry.

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Table 1.

Potential Risk Factors During Childhood and Adolescence for Substance Use Disorders in Adulthood

Potential Risk Factor	First Author	Year	Sample Size	Relationship Between Risk Factors in Childhood or Adolescence and Adult Substance Use Disorders
Psychopathology				
<i>Psychiatric Diagnoses</i>	Groenman [14] *	2017	22,029	attention-deficit/hyperactivity disorder ↑ AUD, NUD, other SUD (including cannabis) and any SUD
			434	oppositional defiant disorder or conduct disorder ↑ AUD, NUD, other SUD (including cannabis) and any SUD
			2,451	major depressive disorder ↑ AUD, NUD, and any substance use disorder (including alcohol, nicotine, and cannabis)
	Buckner [15]	2008	816	social anxiety disorder ↑ AUD and CUD
	Buckner [16]	2009	1,204	social anxiety disorder ↑ AUD in women
<i>Externalizing Behavior</i>	Englund [17]	2008	178	externalizing ↑ AUD
	Hayatbakhsh [18]	2008	2,225	externalizing ↑ CUD
	Mills [19]	2017	3,778	externalizing ↑ CUD
	Defoe [20]	2019	364	conduct problems ↑ CUD
	Fergusson [21]	2007	1,265	conduct problems ↑ cigarette smoking including NUD
	Pardini [22]	2006	506	conduct disorder symptoms and conduct disorder-by-depression interaction ↑ AUD
	Pingault [23]	2013	1,804	inattention ↑ NUD; opposition ↑ NUD, CUD, and cocaine use disorder
	Hayatbakhsh [24]	2008	2,429	attention problems, delinquency, and aggression ↑ AUD, CUD, NUD and other SUD
	Guo [25]	2001	808	misbehavior at school, delinquency, antisocial behavior, being sexually active ↑ AUD
	D'Amico [26]	2005	1,986	deviant behavior ↑ AUD
	Bonomo [27]	2004	1,601	antisocial behavior ↑ AUD
	Foulds [28]	2017	1,265	novelty seeking ↑ AUD, CUD, NUD, and other SUDs
	Palmer [29]	2013	2,361	novelty seeking ↑ AUD, NUD and other SUDs (including CUD)
	Mezzich [30]	2007	263	disinhibition ↑ SUD (not specified)
	Tarter [31]	2004	170	disinhibition ↑ any SUD (excluding nicotine)
Fergusson [64]	2007	1265	conduct problems ↑ AUD, NUD, CUD and other illicit SUD	
<i>Internalizing Symptoms</i>	Huurre [32]	2010	1,471	depressive symptoms ↑ AUD
	Jester [33]	2019	504	internalizing ↑ NUD
	Bardone [34]	1998	459	depressive symptoms ↑ NUD
Personal Substance Use				
	King [35]	2007	375	illegal drug use ↑ illicit SUDs
	Guttmanova [36]	2011	808	alcohol, marijuana, or other illicit drug use ↑ lifetime AUD or chronicity of AUD
	Newton-Howes [38]	2019	1,056	earlier age of first alcoholic intoxication ↑ AUD, NUD, and CUD
	D'Amico [26]	2005	1,986	heaviness of alcohol use ↑ AUD
	Bonomo [27]	2004	1,601	frequent alcohol use ↑ AUD

Potential Risk Factor	First Author	Year	Sample Size	Relationship Between Risk Factors in Childhood or Adolescence and Adult Substance Use Disorders
	Huurre [32]	2010	1,471	drunkenness oriented drinking and cigarette use ↑ AUD
	Guo [39]	2000	808	earlier and heavier alcohol use ↑ AUD
	Mills [19]	2017	3,778	alcohol and tobacco use ↑ CUD
	Prince van Leeuwen [40]	2014	1,108	earlier onset and continued tobacco use ↑ CUD
	Swift [41]	2008	1,520	cigarette smoking ↑ CUD
	Brook [42]	2007	475	early cigarette use ↑ AUD and other SUDs (illicit drugs)
	Strong [43]	2016	1,242	regular cigarette use ↑ SUD (illicit drugs)
	Gil [44]	2004	1,273	experimentation and regular use of substances ↑ any SUD (excluding nicotine)
Environmental Influences				
<i>Parental Influences</i>	Mezzich [30]	2007	263	parental SUD ↑ SUD (substances not specified)
	Tarter [31]	2004	170	parental SUD ↑ any SUD (excluding nicotine)
	King [35]	2007	375	parental AUD ↑ AUD and other illicit SUD
	Knop [45]	2007	202	paternal AUD ↑ AUD
	Kosty [46]	2015	719	parental CUD and other SUD (illicit drugs excluding cannabis) ↑ CUD
	Chassin [47]	1999	454	parental AUD ↑ AUD and other SUD (substances not specified)
	Newlin [49]	2000	2,301	stepfather AUD ↑ AUD and any other SUD (excluding alcohol or nicotine)
	Yap [50] *	2017	6,456	parental alcohol use ↑ alcohol misuse (may include AUD)
			5,911	favorable parental attitudes toward alcohol use ↑ alcohol misuse (may include AUD)
			3,048	parental provision of alcohol use ↑ alcohol misuse (may include AUD)
22,936			lack of parent-child relationship quality ↑ alcohol misuse (may include AUD)	
19,618			lack of parental involvement ↑ alcohol misuse (may include AUD)	
15,673	lack of parental monitoring ↑ alcohol misuse (may include AUD)			
7561	Lack of parental support ↑ alcohol misuse (may include AUD)			
<i>Peer Influences</i>	Defoe [20]	2019	364	peer cannabis use ↑ CUD
	Fergusson [21]	2007	1,265	peer smoking ↑ cigarette smoking including NUD
	Guo [25]	2001	808	best friends who use alcohol and antisocial peers ↑ AUD
	Prince van Leeuwen [40]	2014	1,108	peer cannabis use ↑ CUD
	Gil [51]	2002	643	peer substance use and approval of substance use ↑ CUD
	Van Ryzin [52]	2014	998	deviant peers ↑ AUD, NUD, CUD
<i>Socioeconomic Status</i>	Poulton [53]	2002	1,000	socioeconomic disadvantage ↑ AUD and NUD
	Fergusson [21]	200	1,265	socioeconomic disadvantage ↑ cigarette smoking including NUD
<i>Negative/Traumatic Events</i>	Abajobir [56]	2017	2,526	any childhood maltreatment (physical and emotional abuse, neglect) ↑ CUD

Potential Risk Factor	First Author	Year	Sample Size	Relationship Between Risk Factors in Childhood or Adolescence and Adult Substance Use Disorders
	Mills [19]	2017	3,778	childhood maltreatment ↑ CUD
	Newbury [57]	2017	2,232	childhood maltreatment ↑ AUD and CUD
Neurobiology				
	O'Brien [61]	2017	78	greater ratio of orbitofrontal-to-amygdala volume ↑ survival time to SUD (including alcohol, nicotine and cannabis)
	Cheetham [62]	2017	107	smaller orbitofrontal cortex volume ↑ AUD or CUD
	Hill [63]	2009	133	lower P300 amplitude ↑ SUD (including alcohol, nicotine and cannabis)

Abbreviations: ↑ = increased risk for; AUD = alcohol use disorder; NUD = nicotine use disorder, CUD = cannabis use disorder, SUD = substance use disorder

* denotes meta-analysis

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