PREDICTORS OF SUBSTANCE USE/MISUSE IN YOUTH

PREDICTORS OF SUBSTANCE USE/MISUSE IN YOUTH

By CORAL RAKOVSKI, H.B.Sc.

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy

McMaster University, November 2024

McMaster University DOCTOR OF PHILOSOPHY (2024) Hamilton, Ontario

(Neuroscience)

TITLE: Predictors of Substance Use/Misuse in Youth

AUTHOR: Coral Rakovski, H.B.Sc. (McMaster University).

SUPERVISOR: Dr. Benicio N. Frey, M.D., M.Sc., Ph.D.

COMMITTEE: Dr. Flavio Kapczinski M.D., M.Sc., Ph.D., FRCPC; Dr. Luciano Minuzzi, M.D., Ph.D.

NUMBER OF PAGES: 210

Lay Abstract

Since youth are still developing, they are especially likely to engage in risky behaviours such as using or misusing substances and to experience severe consequences because of this behaviour. Identifying risk factors or other factors associated with youth substance use or misuse can help to improve efforts that are directed at preventing or reducing this problem. Previous research on the topic of youth substance use or misuse has focused on this issue in high-income countries, however, most of the world's youth live in low to middle-income countries such as Brazil. Therefore, this thesis aimed to identify risk factors or other associated factors of substance use or misuse among youth in Brazil and across the globe. We also determined the prevalence of underage drinking among Brazilian youth. Several different types of sociodemographic or clinical risk factors of youth substance use or misuse were found including tobacco use or misuse, depression, other or no religion, living in rural areas, and childhood maltreatment. The identification of these risk factors or other associated factors of youth substance use or misuse may help to improve efforts to prevent this problem and the associated negative outcomes.

Abstract

Introduction: Substance use/misuse is highly prevalent among youth, which is concerning given the associated adverse outcomes such as psychiatric conditions, interpersonal problems, as well as deficits in brain structure, function and cognition. Considering the rising global burden of disease due to substance use disorders, especially for youth in low- to middle-income countries, it is crucial for strategies enabling the prompt detection and early implementation of effective intervention measures for youth at the highest risk of substance use/misuse to be developed. The identification of predictors or other associated factors of youth substance use/misuse may facilitate the development of such strategies and inform policy or intervention efforts. Thus, this thesis aimed to identify predictors or other associated factors of substance use/misuse among youth in Brazil and across the globe. We also sought to determine the prevalence of underage alcohol use among youth in Brazil, since prior studies on similar topics have predominately been conducted in high-income countries.

Results: Various predictors or other associated factors of youth substance use/misuse including sociodemographic and clinical characteristics were identified. Risk factors for underage drinking in a nationally representative population of Brazilian adolescents were having other/no religion, residing in rural areas, depression, tobacco use, and illicit drug use. Alcohol abuse/dependence, tobacco abuse/dependence, manic episode history, suicide risk, and male sex were identified as important predictors of illicit substance abuse/dependence among young adults in Brazil using machine learning techniques. A relatively high prevalence of current underage alcohol use in Brazil of 22.2% was also

found. Our comprehensive systematic review and meta-analysis indicated that several different types of childhood maltreatment were predictive of various types of youth substance use/misuse, with the included studies conducted in 22 countries across the globe.

Conclusion: Several important sociodemographic and clinical predictors or associated factors of substance use/misuse among youth in Brazil and across the globe were found. The identification of significant predictors can facilitate the prompt detection of youth at the highest risk of substance use/misuse and enhance intervention efforts through the implementation of measures to also prevent these predictors. Therefore, these findings highlight the severity of substance use/misuse among youth and indicate the promising potential of identifying predictors or other associated factors in informing early intervention efforts to prevent or mitigate youth substance use/misuse.

Keywords: substance use; underage drinking; illicit substance use; predictors; youth

Acknowledgements

First, I would like to express my sincere gratitude to my former and current supervisors, Dr. Flavio Kapczinski and Dr. Benicio Frey. Thank you to Dr. Flavio Kapczinski for giving me the opportunity to join the McMaster Neuroscience Graduate Program and to work with your wonderful lab group. Your continual encouragement and guidance throughout my years as a graduate student was incredibly helpful in enabling me to learn crucial research skills and giving me the confidence to pursue important research and career-related opportunities. Thank you to Dr. Benicio Frey for welcoming me into your lab and for providing me with unwavering support and constructive feedback during my ongoing research projects. Your insight has undoubtedly improved the quality of my research and has helped to sharpen my research abilities. I am forever grateful for the invaluable opportunities, skills, and connections that you both have provided me with by supervising my Ph.D. work over the last several years, thank you again.

I would also like to express my sincerest gratitude to Dr. Taiane de Azevedo Cardoso for being an incredible mentor from the start to end of my graduate school journey. Your patience, constant support, and dedication allowed me to learn so much about clinical research. I can not thank you enough for your eagerness to teach me important research skills and to provide invaluable assistance along every step of the way.

Next, I would like to thank Dr. Minuzzi for providing constructive feedback and support as one of my supervisory committee members. My research and knowledge have certainly improved by incorporating your suggestions and through taking your

comprehensive statistics course. Thank you for taking the time to meet with me to further discuss concepts and questions that came up along the way, your support and encouragement were greatly appreciated.

A huge thank you to Dr. Bianca Wollenhaupt de Aguiar for your support, kindness, and willingness to help me address any questions or concerns that came up throughout the process of working on my research projects. I thoroughly enjoyed working with you over the last several years and wish you all the best in your research and career aspirations.

A special thanks to Dr. Raquel Brandini de Boni and the rest of her group from Brazil for collaborating on some of the papers that were included for my thesis. It has been a pleasure to work with you and I am very thankful that I had the opportunity to incorporate these relevant and important research studies from Brazil to further expand the existing literature related to the topic of predictors or associated factors of substance use/misuse among youth.

To my dear friends and family, thank you for your endless support and encouragement especially through the times when I needed it the most. A huge thank you to my parents for teaching me the importance of working hard to accomplish your goals and for motivating me with your love and support during the stressful moments. To my partner Michael Szmudrowski, I am deeply thankful to have had you by my side for these past two years to keep me grounded. I could not have asked for a more patient, empathetic, and loving partner to support me through the final stretch of my graduate studies. To my dear friends, thank you for reminding me to take much needed breaks from

work, for your words of encouragement, and for the fun memories along the way. I feel very fortunate to have such an uplifting support system, thank you all.

Finally, thank you to all the participants that took the time to complete these studies and therefore made this research possible.

Table of Contents

List of Figures

B) Physical abuse with alcohol use/misuse.

C) Sexual abuse with alcohol use.

D) Unspecified childhood maltreatment with cannabis use.

E) Physical abuse with cannabis use/misuse.

F) Sexual abuse with cannabis use.

G) Sexual abuse with unspecified substance use.

H) Sexual abuse with hallucinogen or LSD use.

I) Sexual abuse with cocaine use.

J) Sexual abuse with inhalant use.

List of Tables

CHAPTER 2

CHAPTER 3

CHAPTER 4

List of Abbreviations

AOR	Adjusted Odds Ratio
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AUC	Area Under the Curve
AUD	Alcohol Use Disorder
CI	Confidence Interval
HPA	Hypothalamic-Pituitary-Adrenal
LSD	Lysergic acid diethylamide
PICOS	Population, Intervention, Comparison, Outcome, Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	Prospective Register of Systematic Reviews
NSDUH	National Survey on Drug Use and Health
OR	Odds Ratio
RR	Relative Risk
SE	Standard Error
SUD	Substance Use Disorder

Declaration of Academic Achievement

Chapter 2

C. Rakovski interpreted the data and composed the manuscript. T. de Azevedo Cardoso aided in data interpretation and composing the manuscript. J.C. Mota conceptualized the study, performed the data analysis, and contributed to the composition of the manuscript. F.I. Bastos conceptualized the study, oversaw the data analysis, and revised the final version of the manuscript. F. Kapczinski provided significant intellectual contribution and revised the final version of the manuscript. R.B. De Boni conceptualized the study, oversaw the data analysis, and contributed to the composition of the manuscript.

This chapter in its entirety has been ***published*** in the **Brazilian Journal of Psychiatry**. The final accepted manuscript version of this article is presented within this thesis.

Rakovski C, de Azevedo Cardoso T, da Mota JC, Bastos FI, Kapczinski F, De Boni RB. Underage drinking in Brazil: findings from a community household survey. *Brazilian Journal of Psychiatry*. 2022;44(3):257-63. Copyright © 2022 The Author(s). DOI: 10.1590/1516-4446-2021-2103

Chapter 3

C. Rakovski aided in the conceptualization/design of the study, interpreted the data, and composed the manuscript. P.L. Ballester and T. de Azevedo Cardoso conceptualized/designed the study, conducted the statistical analyses, as well as

contributed to the interpretation and composition of the manuscript. Additionally, T. Azevedo Cardoso provided supervision. K. Jansen, B.B. Montezano, and L.D. Souza were responsible for data acquisition or analysis, as well as the conceptualization/design of the study. K. Jansen and L.D. Souza also contributed to the composition of the manuscript. F.P. Moreira aided in data acquisition/analysis. R.B. De Boni provided critical revisions to the manuscript for important intellectual content. B.N. Frey, and F. Kapczinski provided supervision and critical revisions to the manuscript for important intellectual content.

This chapter in its entirety has been ***published*** in the **Journal of Psychiatric Research.** The final accepted manuscript version of this article is presented within this thesis.

Rakovski, C., Ballester, P.L., Montezano, B.B., de Mattos Souza, L.D., Jansen, K., da Silva, R.A., Mondin, T.C., Moreira, F.P., De Boni, R.B., Frey, B.N., Kapczinski, F., de Azevedo Cardoso, T., 2023. Predictors of illicit substance abuse/dependence during young adulthood: A machine learning approach. *Journal of Psychiatric Research*, 157, 168-173. Copyright © 2022 Elsevier Ltd. DOI: 10.1016/j.jpsychires.2022.11.030

Chapter 4

C. Rakovski formulated the research question, conceptualized the study, conducted the literature search, performed the screening, conducted the data extraction, and composed the manuscript. M. Lalli assisted with the screening and the data extraction. J. Gu and M.

Hobson assisted with the data extraction and the composition of the introduction section. B. Wollenhaupt-Aguiar acted as third reviewer for a portion of the articles during the screening process and aided with supervision. T. de Azevedo Cardoso contributed to the conceptualization of the study, performed the meta-analyses, acted as third reviewer during the screening process, aided with the composition of the manuscript, provided supervision, and provided critical revisions to the manuscript for important intellectual content. L. Minuzzi, F. Kapczinski, and B.N. Frey provided supervision and critical revisions to the manuscript for important intellectual content.

This chapter in its entirety has been ***published*** in **Neuroscience and Biobehavioural Reviews.** The final accepted manuscript version of this article is presented within this thesis.

Rakovski, C., Lalli, M., Gu, J., Hobson, M., Wollenhaupt-Aguiar, B., Minuzzi, L., Kapczinski, F., de Azevedo Cardoso, T. and Frey, B.N., 2024. Childhood maltreatment as a predictor of substance use/misuse among youth: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, p.105873. Copyright © 2024 The Authors. DOI: https://doi.org/10.1016/j.neubiorev.2024.105873

Chapter 1: Introduction

1.1 Epidemiology of Youth Substance Use/Misuse

Youth are particularly vulnerable to mental disorder onset, such as substance use disorders (Degenhardt et al., 2016; Kieling et al., 2024; MacKillop & Ray, 2017; World Drug Report, 2020). This is alarming considering that the global burden of disease due to substance use disorders, including alcohol and illicit drugs (e.g., cannabis, cocaine, opioids, amphetamines, etc.), has been increasing over time (Degenhardt et al., 2019; IHME, 2024c). The total burden of disease is often estimated using disability-adjusted life years, consisting of the years of life lost due to premature mortality and the years of life lived with disability (Degenhardt et al., 2018; IHME, 2024c). It is estimated that in 1990 the share of total global disease burden attributable to substance use disorders was 0.8%, while in 2021 it was 1.1%, indicating a 33% increase in the disease burden due to substance use disorders over this time period (IHME, 2024c). According to the 2019 Global Burden of Disease study, drug use disorders ranked 6th while alcohol use disorders ranked 12th based on all leading causes for years lived with disability in youth aged 20 to 24 years (Kieling et al., 2024). Furthermore, as the disease burden among youth due to infectious diseases or neonatal disorders has been decreasing over time, especially in low- to middle-income countries, the burden due to mental disorders including substance use disorders is expected to increase since more children will survive these childhood health conditions (Erskine et al., 2015). Considering that about 90% of youth globally reside in low- to middle-income countries (Bauer et al., 2021; Erskine et al., 2015), it is of utmost

importance for strategies to be developed that enable the prompt detection and implementation of effective preventive or intervention-based measures among youth at the highest risk of substance use/misuse. For the purposes of this thesis, substance use/misuse refers to the use, risky use, or meeting the criteria for a substance use disorder involving alcohol or illicit substances. The specific substances investigated and the assessment criteria used to determine substance use/misuse are described in each individual thesis chapter (Chapters 2-4).

Of all substance use disorders worldwide, alcohol use disorders are the most prevalent, while the most prevalent drug use disorders tend to involve cannabis or opioids (Degenhardt et al., 2018; UNODC, 2022, 2023). A study using data from the Global School-based Student Health Survey on 22 different countries estimated that the mean past 30-day alcohol use prevalence among adolescents aged 12 to 15 years was approximately 14%, (Smith et al., 2024). It has also been previously estimated that the past 30-day prevalence of underage alcohol consumption among Brazilian adolescents aged 12 to 17 years is particularly high at about 21% (Coutinho et al., 2016). Importantly, the use of alcohol during adolescence has been consistently associated with an increased risk of alcohol use disorder and other substance use disorders (Boden et al., 2020; Kirsch & Lippard, 2022; Richmond-Rakerd et al., 2017; Yuen et al., 2020). It was estimated that in 2018 the global 12-month prevalence of illicit drug use, including cannabis, was approximately 5.4% for individuals between the ages of 15 to 64 years (World Drug Report, 2020). Furthermore, the prevalence of illicit drug use among youth is especially high, with peak drug use levels found among young adults between the ages of 18 to 25

years (UNODC, 2022; World Drug Report, 2020). In 2021, the global 12-month prevalence of cannabis use was approximately 5.3% among adolescents aged 15 to 16 years (UNODC, 2023). Notably, the initiation of drug use during adolescence, is associated with the subsequent development of drug use disorders (Briones et al., 2006; Kirsch & Lippard, 2022; Richmond-Rakerd et al., 2017; UNODC, 2023).

The global age-standardized 12-month prevalence of alcohol use disorders has decreased over time from 1.7% in 1990 to 1.3% in 2021 (IHME, 2024a). Among adolescents, levels of drinking have decreased over time in Europe, North America and Australia, while levels of drinking have been stable or increased over time in other areas (Glantz et al., 2020; Livingston, 2024). The 2022 National Survey on Drug Use and Health found that youth between the ages of 18 to 25 years in the United States had a particularly high 12-month alcohol use disorder prevalence of 16.4% (SAMHSA, n.d.). High-income countries have a higher prevalence of alcohol use disorders than low-income countries, as indicated by an age-standardized 12-month prevalence of 1.9% in 2021 for high-income countries in comparison to 1.1% for low-income countries (Glantz et al., 2020; IHME, 2024a). For Brazil, which is classified as an upper-middle-income country, the age-standardized 12-month prevalence of alcohol use disorder in 2021 was 2.5% which is considerably higher than the prevalence of 1.5% for upper-middle-income countries overall (Degenhardt et al., 2019; IHME, 2024a). The prevalence of alcohol use disorders globally and in high-income countries has decreased from 1990 to 2021, while this prevalence has been stable over time in low-income countries (IHME, 2024a).

Regarding global trends from 1990 to 2021, the 12-month prevalence of drug use disorders has remained relatively stable over the years at approximately 0.7% for all ages and 2.0% for youth between the ages of 20 to 24 years which is the age group with the highest prevalence (Degenhardt et al., 2019; IHME, 2024b; Shen et al., 2023). High-income countries tend to have a higher prevalence of drug use disorders than low-income countries, especially among youth (Degenhardt et al., 2019; IHME, 2024b; Shen et al., 2023). For instance, in 2021 the 12-month prevalence of drug use disorders in youth from 20 to 24 years was 5.3% among high-income countries and 0.9% among low-income countries (IHME, 2024b). For Brazil, the 12-month prevalence of drug use disorders among youth of the same age group in 2021 was 2.7% (Degenhardt et al., 2019; IHME, 2024b). Considering that the 12-month prevalence of drug use disorders for youth aged 20 to 24 years in 2021 was about 2.0% for upper-middle-income countries overall, it is important to note that this prevalence is particularly high among Brazilian youth (IHME, 2024b). The prevalence of drug use disorders globally and in low-income countries has been generally stable over time, while high-income countries have shown an overall increase from 1990 to 2021 (IHME, 2024b; Shen et al., 2023).

1.2 Biopsychosocial Model of Youth Substance Use/Misuse

Due to the complex etiology of substance use/misuse, the biopsychosocial model considers biological determinants, psychological determinants, and social determinants in an integrative manner (Briones et al., 2006; MacKillop & Ray, 2017; Rampa et al., 2021). Altogether, maladaptive substance use/misuse behaviours that are influenced by a

combination of biological, psychological, and social factors, tend to follow a cyclical pattern thus reinforcing the use/misuse of substances and making it especially challenging to successfully overcome this cycle (MacKillop & Ray, 2017; Rampa et al., 2021). Since adolescence and young adulthood are critical developmental periods from a biological, psychological, and social perspective, youth are especially vulnerable to the various factors that may influence substance use/misuse behaviours (Briones et al., 2006; Debenham et al., 2021; Jacobus, Squeglia, Meruelo, et al., 2015; Kaligis et al., 2021; MacKillop & Ray, 2017; Rampa et al., 2021).

1.2.1 Biological Factors Associated with Youth Substance Use/Misuse

It has been theorized that dysfunction or dysregulation in systems of the brain that have a primary role in reward and motivation as well as executive control, such as the mesolimbic dopaminergic system and the prefrontal/parietal networks respectively, may lead to the use/misuse of substances (Briones et al., 2006; Khurana et al., 2015; MacKillop & Ray, 2017; Rampa et al., 2021). Since youth experience maturation in reward-related limbic brain regions prior to maturation in the prefrontal cortex, which is important for executive functioning, they are susceptible to initiating risky behaviours including substance use (Briones et al., 2006; Debenham et al., 2021; Lees et al., 2020; Prencipe et al., 2011). A recent systematic review of longitudinal studies found evidence of neural predictors and consequences of youth substance use/misuse, including cannabis and other illicit drugs (Debenham et al., 2021). The following predictors of youth substance use were reported by Debenham et al., 2021: macrostructural predictors of

escalating young adult amphetamine-type stimulant use (e.g., smaller volumes of the medial prefrontal cortex, amygdala, and basal ganglia) (Becker et al., 2015); microstructural predictors of heavy cannabis use in youth (e.g., decreased white matter integrity among the fornix and superior corona radiata) (Jacobus, Thayer, et al., 2013); functional predictors of early adolescent cannabis use onset (e.g., reduced activation of the visuospatial posterior parietal cortex in executive functioning tasks) (Tervo-Clemmens et al., 2018); and cognitive predictors of youth cannabis use initiation (e.g., deficits in emotional perception) (Fishbein et al., 2016). Similarly, neural predictors of adolescent alcohol use have been identified and also include structural predictors (e.g., thinner cortices in various brain regions such as the left/right superior parietal, right superior frontal, and right precuneus regions), functional predictors (reduced activation in various brain regions such as the left middle temporal, right posterior cingulate, and left/right precuneus regions during a visual working memory task), and cognitive predictors (e.g., deficits in executive functioning) (Squeglia et al., 2017).

Substance use/misuse among youth can impact brain development and potentially lead to deficits in brain structure, function, and cognition (Debenham et al., 2021; Jacobus, Squeglia, Meruelo, et al., 2015; MacKillop & Ray, 2017; UNODC, 2023). The systematic review by Debenham et al., 2021 reported the following consequences of youth illicit substance use/misuse: macrostructural consequences of heavy adolescent cannabis use over three years (e.g., increased cortical thickness) (Jacobus, Squeglia, Meruelo, et al., 2015); microstructural consequences of heavy cannabis use in adolescents and occasional ecstasy use in young adults (e.g., reduced white matter integrity among

fronto-limbic association and projection fibre tracts) (De Win et al., 2008; Jacobus, Squeglia, et al., 2013); functional consequences of youth cannabis use or amphetamine-type stimulant use initiation (e.g., decreased activity among regions of the basal ganglia, parahippocampus, and occipital lobe during tasks related to associative memory and executive functioning) (Becker et al., 2013; De Win et al., 2008; Tervo-Clemmens et al., 2018); as well as residual and sustained cognitive consequences of youth cannabis use or amphetamine-type stimulant use (e.g., deficits in working memory, visuospatial abilities, and attention) (De Sola et al., 2008; Jacobus, Squeglia, Infante, et al., 2015; Tapert et al., 2002). Previous research has also identified neural consequences of alcohol use/misuse among youth including structural consequences (e.g., decreased frontal and temporal grey matter volume, decreased white matter growth among the corpus callosum and pons, as well as reduced white matter integrity among the right superior longitudinal fasciculus) (Bava et al., 2013; Lees et al., 2020; Pfefferbaum et al., 2018; Squeglia et al., 2015), functional consequences (e.g., increased activation in frontal and parietal brain regions during tasks related to executive functioning, and reduced activation in the cerebellum and dorsal striatum during tasks related to reward processing) (Cservenka et al., 2015; Jones et al., 2016; Lees et al., 2020; Squeglia et al., 2012; Wetherill et al., 2013), and cognitive consequences (e.g., deficits in learning, memory, and visuospatial functioning) (Hanson, Cummins, et al., 2011; Hanson, Medina, et al., 2011; Lees et al., 2020; Mota et al., 2013). Notably, it has been shown that weak executive control combined with heightened reward sensitivity during adolescence is predictive of adolescent experimental substance use progression toward the development of substance use disorders (Khurana et

al., 2015; Peeters et al., 2017). Altogether, the aforementioned adverse neural outcomes associated with substance use/misuse among youth indicate the complex biological processes underlying the reinforcement and potential progression of substance use/misuse behaviours among youth (Briones et al., 2006).

Genetic factors also influence an individual's likelihood to use/misuse substances (Briones et al., 2006; MacKillop & Ray, 2017; Rampa et al., 2021). There is substantial evidence from family and twin comparison studies to suggest that substance use disorders have a heritability of about 50% (MacKillop & Ray, 2017; Rampa et al., 2021). For instance, research has shown that children of parents with substance use disorders are more likely to develop a substance use disorder than children of parents without substance addiction, even when they are adopted into new homes early in life (Briones et al., 2006). Environmental factors encountered during development can modify gene expression, often referred to as epigenetics, which may also affect an individual's risk to misuse substances (Cánepa & Berardino, 2024; Hari Gopal et al., 2024; Rampa et al., 2021). Various characteristics, including exposure to early life adversity and stress, are known risk factors for substance use/misuse that have been associated with epigenetic changes (Cánepa & Berardino, 2024; Kaplan et al., 2022; Rampa et al., 2021; Winter et al., 2023). For example, maternal alcohol use during pregnancy may cause subsequent brain circuitry deficits among offspring in brain regions that are related to reward including the nucleus accumbens and the ventral tegmental area (e.g., dendritic morphology alterations to dopamine receptor-expressing medium spiny neurons in the nucleus accumbens and increased excitability of dopamine neurons in the ventral

tegmental area) (Kaplan et al., 2022). There is also evidence to suggest that DNA methylation changes in specific brain regions are associated with substance misuse (e.g., increased DNA methylation at cytosine-guanine sites in the prefrontal cortex among alcoholics compared to non-alcoholic controls) (Kaplan et al., 2022). Additionally, the use/misuse of substances among youth can in turn alter gene expression in the brain through epigenetic mechanisms including DNA methylation, leading to heightened reward sensitivity and further reinforcement of addictive behaviours (Kaplan et al., 2022; MacKillop & Ray, 2017; Salmanzadeh et al., 2021).

1.2.2 Psychological Factors Associated with Youth Substance Use/Misuse

There is evidence that psychological factors including personality, motivation, and psychiatric conditions influence the risk and maintenance of substance use/misuse behaviours among youth (Briones et al., 2006; MacKillop & Ray, 2017; Rampa et al., 2021). Personality traits such as impulsivity, sensation-seeking, depression, and extraversion are associated with youth substance use/misuse (Briones et al., 2006; Hamdan-Mansour et al., 2018; MacKillop & Ray, 2017; Rampa et al., 2021; Walther et al., 2012). However, the direction of the association between various personality traits and substance use/misuse has not yet been elucidated (Rampa et al., 2021; Walther et al., 2012).

Motivation is another psychological factor that is believed to reinforce substance use/misuse behaviours through associated learned outcomes (MacKillop & Ray, 2017; Rampa et al., 2021). Following substance use, individuals often experience positive

reinforcement such as feeling high or social enhancement, as well as negative reinforcement such as relief from anxiety, depression, or stress (MacKillop & Ray, 2017; Rampa et al., 2021). Withdrawal symptoms, and a desire to avoid them, may also provide motivation for individuals to continue to use substances (MacKillop & Ray, 2017; Rampa et al., 2021).

Bidirectional associations have been found between several types of other psychiatric conditions and substance use/misuse (Briones et al., 2006; Rampa et al., 2021; Roberts et al., 2007). Prior studies have found that youth with conduct disorder, attention-deficit hyperactivity disorder, depression, and bipolar disorder are at a higher risk of subsequently using/misusing substances than youth without such psychiatric conditions (Briones et al., 2006; Gau et al., 2007; Roberts et al., 2007). Substance use/misuse among youth has also been identified as a risk factor for the development of other psychiatric conditions including depression, bipolar disorder, manic/hypomanic symptoms, and suicide (Alinsky & Hipp, 2024; Briones et al., 2006; Fergusson et al., 2009; Lalli et al., 2021; Rampa et al., 2021; Roberts et al., 2007). This is problematic considering that youth with substance use disorders and other comorbid psychiatric conditions are more likely to have other adverse clinical outcomes, such as functional impairment (Roberts et al., 2007). Thus, various psychological factors have a significant role in the risk and maintenance of substance use/misuse among youth (MacKillop & Ray, 2017; Rampa et al., 2021).

1.2.3 Social Factors Associated with Youth Substance Use/Misuse

Social factors, such as those related to social networks and culture, impact the risk of youth to use/misuse substances and also reinforce these behaviours (Briones et al., 2006; MacKillop & Ray, 2017; Rampa et al., 2021). There is substantial evidence to support that social networks including relationships with family members and peers have a significant influence on an individual's substance use/misuse behaviours (Briones et al., 2006; MacKillop & Ray, 2017; Steinberg et al., 1994; Trucco, 2020). For instance, previous research has demonstrated that youth with family members that use substances are at a higher risk of using/misusing substances than youth from families without substance use (Briones et al., 2006; MacKillop & Ray, 2017; Rampa et al., 2021; Trucco, 2020). Adverse childhood experiences which are often faced by youth living in dysfunctional households such as maltreatment, witnessing abuse, or caregiver incarceration are known risk factors for youth substance use/misuse (Afifi et al., 2020; Briones et al., 2006; Kirsch & Lippard, 2022; Rampa et al., 2021). An authoritative parenting style characterized by parental control and warmth is a protective factor against youth substance use/misuse, while harsh or hostile parenting are risk factors (MacKillop & Ray, 2017; Trucco, 2020). Adolescents with peers who use substances are more likely to engage in such behaviours since they are influenced by their peers (MacKillop & Ray, 2017; Steinberg et al., 1994; Trucco, 2020). It has also been shown that individuals tend to select social networks of others that engage in similar substance use/misuse behaviours, which perpetuates this cycle of using/misusing substances (MacKillop & Ray, 2017; Steinberg et al., 1994; Trucco, 2020). Parental monitoring of adolescents is a

protective factor against youth substance use/misuse and these effects even seem to extend to the youth's friendship groups (Steinberg et al., 1994; Trucco, 2020). Additionally, school disengagement as well as truancy among youth are associated with an increased likelihood of substance use/misuse (Briones et al., 2006). In contrast, adolescent involvement in groups that tend to have a positive influence and provide a sense of belonging, such as religious or academic-related programs, is a protective factor against youth substance use/misuse (MacKillop & Ray, 2017; Trucco, 2020). While various sociodemographic characteristics such as socioeconomic status, sex, or race may also have an influence on youth substance use/misuse behaviours, previous research has found mixed results overall, thus this warrants further investigation (MacKillop & Ray, 2017; Trucco, 2020). Notably, substance use among youth is associated with social consequences (e.g., worsening of interpersonal problems, difficulties fulfilling duties, or reduced participation in recreational activities) which may contribute to the maintenance or escalation of substance-related behaviours (Alinsky & Hipp, 2024; Trucco, 2020).

The identification of strong predictors or other associated factors of youth substance use/misuse may facilitate the prompt detection of youth at the highest risk and inform early intervention approaches or policy efforts aimed at preventing or reducing youth substance use/misuse and its adverse outcomes. While substantial progress has been made with regards to identifying numerous different types of biopsychosocial factors that may contribute to or result from substance use/misuse among youth, further research is critical especially in the areas of clinical and sociodemographic characteristics. Furthermore, the identification of strong predictors of youth substance use/misuse holds

the potential to significantly improve prevention and early intervention efforts by implementing measures to mitigate or prevent these predictors as well.

1.3 Aims and Objectives

Given previous findings of high youth substance use/misuse prevalences and associations with numerous adverse outcomes, as predominately investigated in high-income countries, the general aim of this thesis was to 1) identify predictors or other associated factors of substance use/misuse among youth in Brazil and across the globe as well as 2) determine the prevalence of underage alcohol use among youth in Brazil. The specific objectives are as follows:

1. Chapter 2 consists of a study that aimed to determine the lifetime and 12-month prevalence of underage drinking, as well as its associated factors, among adolescents (between 12-17 years) in Brazil.
2. Chapter 3 presents a prospective, population-based cohort study of young adults (between 18-24 years at baseline) from Pelotas, Brazil that aimed to identify predictors of illicit substance abuse/dependence using machine learning techniques.
3. Chapter 4 includes a comprehensive systematic review and meta-analysis of the existing literature on childhood maltreatment as a predictor of substance use/misuse among youth (24 years or younger).

1.4 Hypotheses

The hypotheses for the aforementioned objectives are as follows:

1. Previous research using school-based samples has estimated the past 30-day prevalence of underage alcohol consumption among adolescents in Brazil, thus, we expected the 12-month prevalence to be slightly higher and the lifetime prevalence to be considerably higher than the past 30-day prevalence estimates. Based on other findings, we also expected to find associations between underage drinking and various factors related to sociodemographic characteristics, medical conditions, other types of substance use, and alcohol-related problems.
2. As recent research has indicated the potential of machine learning techniques in the context of substance use, we hypothesized that the use of machine learning techniques would enable the identification of sociodemographic and clinical predictors of illicit substance abuse/dependence among young adults in Pelotas, Brazil.
3. A few prior systematic reviews found evidence to support that childhood physical abuse and sexual abuse predicted adolescent cannabis use/misuse. Considering this and other relevant previous research, we hypothesized that a wider variety of maltreatment types (including physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect) would predict a variety of types of substance use/misuse (including alcohol, cannabis, and other illicit drugs) in youth.

1.5 References

Afifi, T. O., Taillieu, T., Salmon, S., Davila, I. G., Stewart-Tufescu, A., Fortier, J., Struck, S., Asmundson, G. J. G., Sareen, J., & MacMillan, H. L. (2020). Adverse childhood experiences (ACEs), peer victimization, and substance use among adolescents. *Child Abuse & Neglect*, *106*. https://doi.org/10.1016/J.CHIABU.2020.104504

Alinsky, R. H., & Hipp, J. (2024). Adolescent Alcohol Use and Alcohol Use Disorders. *Pediatrics in Review*, *45*(4), 244–246. https://doi.org/10.1542/PIR.2022-005896

Bauer, A., Baltra, R. A., Pabon, M. A., Díaz, Y., Garman, E., Hessel, P., Lund, C., Malvasi, P., Matijasevich, A., McDaid, D., Park, A. La, Paula, C. S., Zimmerman, A., & Evans-Lacko, S. (2021). Examining the dynamics between young people's mental health, poverty and life chances in six low- and middle-income countries: protocol for the CHANCES-6 study. *Social Psychiatry and Psychiatric Epidemiology*, *56*(9), 1687–1703. https://doi.org/10.1007/S00127-021-02043-7

Bava, S., Jacobus, J., Thayer, R. E., & Tapert, S. F. (2013). Longitudinal changes in white matter integrity among adolescent substance users. *Alcoholism, Clinical and Experimental Research*, *37 Suppl 1*(Suppl 1). https://doi.org/10.1111/J.1530-0277.2012.01920.X

Becker, B., Wagner, D., Koester, P., Bender, K., Kabbasch, C., Gouzoulis-Mayfrank, E., & Daumann, J. (2013). Memory-related hippocampal functioning in ecstasy and amphetamine users: A prospective fMRI study. *Psychopharmacology*, *225*(4), 923–934. https://doi.org/10.1007/S00213-012-2873-Z

Becker, B., Wagner, D., Koester, P., Tittgemeyer, M., Mercer-Chalmers-Bender, K., Hurlemann, R., Zhang, J., Gouzoulis-Mayfrank, E., Kendrick, K. M., & Daumann, J. (2015). Smaller amygdala and medial prefrontal cortex predict escalating stimulant use. *Brain : A Journal of Neurology*, *138*(Pt 7), 2074–2086. https://doi.org/10.1093/BRAIN/AWV113

Boden, J., Blair, S., & Newton-Howes, G. (2020). Alcohol use in adolescents and adult psychopathology and social outcomes: Findings from a 35-year cohort study. *Australian and New Zealand Journal of Psychiatry*, *54*(9), 909–918. https://doi.org/10.1177/0004867420924091

Briones, D. F., Wilcox, J. A., Mateus, B., & Boudjenah, D. (2006). Risk factors and prevention in adolescent substance abuse: a biopsychosocial approach. *Adolescent Medicine Clinics*, *17*(2), 335–352. https://doi.org/10.1016/J.ADMECLI.2006.03.005

Cánepa, E. T., & Berardino, B. G. (2024). Epigenetic mechanisms linking early-life adversities and mental health. *The Biochemical Journal*, *481*(10), 615–642. https://doi.org/10.1042/BCJ20230306

Coutinho, E. S. F., França-Santos, D., Da Silva Magliano, E., Bloch, K. V., Barufaldi, L. A., De Freitas Cunha, C., De Vasconcellos, M. T. L., & Szklo, M. (2016). ERICA: Patterns of alcohol consumption in Brazilian adolescents. *Revista de Saude Publica*, *50*(Suppl 1), 1s-9s. https://doi.org/10.1590/S01518-8787.2016050006684

Cservenka, A., Jones, S. A., & Nagel, B. J. (2015). Reduced cerebellar brain activity during reward processing in adolescent binge drinkers. *Developmental Cognitive Neuroscience*, *16*, 110–120. https://doi.org/10.1016/J.DCN.2015.06.004

De Sola, S., Tarancón, T., Peña-Casanova, J., Espadaler, J. M., Langohr, K., Poudevida, S., Farré, M., Verdejo-García, A., & De La Torre, R. (2008). Auditory event-related potentials (P3) and cognitive performance in recreational ecstasy polydrug users: evidence from a 12-month longitudinal study. *Psychopharmacology*, *200*(3), 425–437. https://doi.org/10.1007/S00213-008-1217-5

De Win, M. M. L., Jager, G., Booij, J., Reneman, L., Schilt, T., Lavini, C., Olabarriaga, S. D., Den Heeten, G. J., & Van Den Brink, W. (2008). Sustained effects of ecstasy on the human brain: a prospective neuroimaging study in novel users. *Brain : A Journal of Neurology*, *131*(Pt 11), 2936–2945. https://doi.org/10.1093/BRAIN/AWN255

Debenham, J., Birrell, L., Champion, K., Lees, B., Yücel, M., & Newton, N. (2021). Neuropsychological and neurophysiological predictors and consequences of cannabis and illicit substance use during neurodevelopment: A systematic review of longitudinal studies. *The Lancet. Child & Adolescent Health*, *5*(8), 589–604. https://doi.org/10.1016/S2352-4642(21)00051-1

Degenhardt, L., Bharat, C., Glantz, M. D., Sampson, N. A., Scott, K., Lim, C. C. W., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Andrade, L. H., Bromet, E. J., Bruffaerts, R., Bunting, B., de Girolamo, G., Gureje, O., Haro, J. M., Harris, M. G., He, Y., de Jonge, P., … Kessler, R. C. (2019). The epidemiology of drug use disorders cross-nationally: Findings from the WHO's World Mental Health Surveys. *The International Journal on Drug Policy*, *71*, 103–112. https://doi.org/10.1016/J.DRUGPO.2019.03.002

Degenhardt, L., Charlson, F., Ferrari, A., Santomauro, D., Erskine, H., Mantilla-Herrara,

A., Whiteford, H., Leung, J., Naghavi, M., Griswold, M., Rehm, J., Hall, W., Sartorius, B., Scott, J., Vollset, S. E., Knudsen, A. K., Haro, J. M., Patton, G., Kopec, J., … Vos, T. (2018). The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet. Psychiatry*, *5*(12), 987–1012. https://doi.org/10.1016/S2215-0366(18)30337-7

Degenhardt, L., Stockings, E., Patton, G., Hall, W. D., & Lynskey, M. (2016). The increasing global health priority of substance use in young people. *The Lancet. Psychiatry*, *3*(3), 251–264. https://doi.org/10.1016/S2215-0366(15)00508-8

Erskine, H. E., Moffitt, T. E., Copeland, W. E., Costello, E. J., Ferrari, A. J., Patton, G., Degenhardt, L., Vos, T., Whiteford, H. A., & Scott, J. G. (2015). A heavy burden on young minds: the global burden of mental and substance use disorders in children and youth. *Psychological Medicine*, *45*(7), 1561–1563. https://doi.org/10.1017/S0033291714002888

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2009). Tests of causal links between alcohol abuse or dependence and major depression. *Archives of General Psychiatry*, *66*(3), 260–266. https://doi.org/10.1001/ARCHGENPSYCHIATRY.2008.543

Fishbein, D. H., Novak, S. P., Ridenour, T. A., Thornburg, V., Hammond, J., & Brown, J. (2016). Neurocognitive Characteristics of Early Marijuana Use Initiation in Adolescents: A Signature Mapping Analysis. *Https://Doi.Org/10.15288/Jsad.2016.77.431*, *77*(3), 431–440. https://doi.org/10.15288/JSAD.2016.77.431

Gau, S. S. F., Chong, M. Y., Yang, P., Yen, C. F., Liang, K. Y., & Cheng, A. T. A. (2007). Psychiatric and psychosocial predictors of substance use disorders among adolescents: Longitudinal study. *The British Journal of Psychiatry*, *190*(1), 42–48. https://doi.org/10.1192/BJP.BP.106.022871

Glantz, M. D., Bharat, C., Degenhardt, L., Sampson, N. A., Scott, K. M., Lim, C. C. W., Al-Hamzawi, A., Alonso, J., Andrade, L. H., Cardoso, G., De Girolamo, G., Gureje, O., He, Y., Hinkov, H., Karam, E. G., Karam, G., Kovess-Masfety, V., Lasebikan, V., Lee, S., … Kessler, R. C. (2020). The epidemiology of alcohol use disorders cross-nationally: Findings from the World Mental Health Surveys. *Addictive Behaviors*, *102*, 106128. https://doi.org/10.1016/j.addbeh.2019.106128

Hamdan-Mansour, A. M., Mahmoud, K. F., Al Shibi, A. N., & Arabiat, D. H. (2018). Impulsivity and Sensation-Seeking Personality Traits as Predictors of Substance Use Among University Students. *Journal of Psychosocial Nursing and Mental Health Services*, *56*(1), 57–63. https://doi.org/10.3928/02793695-20170905-04

Hanson, K. L., Cummins, K., Tapert, S. F., & Brown, S. A. (2011). Changes in neuropsychological functioning over 10 years following adolescent substance abuse treatment. *Psychology of Addictive Behaviors : Journal of the Society of Psychologists in Addictive Behaviors*, *25*(1), 127–142. https://doi.org/10.1037/A0022350

Hanson, K. L., Medina, K. L., Padula, C. B., Tapert, S. F., & Brown, S. A. (2011). Impact of Adolescent Alcohol and Drug Use on Neuropsychological Functioning in Young Adulthood: 10-Year Outcomes. *Journal of Child & Adolescent Substance Abuse*,

20(2), 135–154. https://doi.org/10.1080/1067828X.2011.555272

Hari Gopal, S., Alenghat, T., & Pammi, M. (2024). Early life epigenetics and childhood outcomes: a scoping review. *Pediatric Research*. https://doi.org/10.1038/S41390-024-03585-7

IHME. (2024a). *Global Burden of Disease (2024) – with major processing by Our World in Data. "Age-standardized current cases of individuals with alcohol use disorders, per 100 people" [dataset]*. IHME, Global Burden of Disease, "Global Burden of Disease - Mental Health Prevalence" [Original Data]. https://ourworldindata.org/alcohol-consumption#:~:text=Prevalence of alcohol use disorders&text=At the country level%2C as,15 and 49 years old.

IHME. (2024b). *Global Burden of Disease (2024) – with major processing by Our World in Data*. IHME, Global Burden of Disease, "Global Burden of Disease - Mental Health Prevalence" [Original Data]. https://ourworldindata.org/grapher/prevalence-of-drug-use-disorders-by-age?tab=table&time=latest

IHME. (2024c). *Global Burden of Disease (2024) – with minor processing by Our World in Data. "Substance use disorders" [dataset]*. IHME, Global Burden of Disease, "Global Burden of Disease - Deaths and DALYs" [Original Data]. https://ourworldindata.org/grapher/alcohol-drug-use-disorders-share-total-disease

Jacobus, J., Squeglia, L. M., Bava, S., & Tapert, S. F. (2013). White matter characterization of adolescent binge drinking with and without co-occurring marijuana use: a 3-year investigation. *Psychiatry Research*, *214*(3), 374–381. https://doi.org/10.1016/J.PSCYCHRESNS.2013.07.014

Jacobus, J., Squeglia, L. M., Infante, M. A., Castro, N., Brumback, T., Meruelo, A. D., & Tapert, S. F. (2015). Neuropsychological Performance in Adolescent Marijuana Users with Co-Occurring Alcohol Use: A Three-Year Longitudinal Study. *Neuropsychology*, *29*(6), 829. https://doi.org/10.1037/NEU0000203

Jacobus, J., Squeglia, L. M., Meruelo, A. D., Castro, N., Brumback, T., Giedd, J. N., & Tapert, S. F. (2015). Cortical thickness in adolescent marijuana and alcohol users: A three-year prospective study from adolescence to young adulthood. *Developmental Cognitive Neuroscience*, *16*, 101–109. https://doi.org/10.1016/J.DCN.2015.04.006

Jacobus, J., Thayer, R. E., Trim, R. S., Bava, S., Frank, L. R., & Tapert, S. F. (2013). White matter integrity, substance use, and risk taking in adolescence. *Psychology of Addictive Behaviors : Journal of the Society of Psychologists in Addictive Behaviors*, *27*(2), 431–442. https://doi.org/10.1037/A0028235

Jones, S. A., Cservenka, A., & Nagel, B. J. (2016). Binge drinking impacts dorsal striatal response during decision making in adolescents. *NeuroImage*, *129*, 378–388. https://doi.org/10.1016/J.NEUROIMAGE.2016.01.044

Kaligis, F., Ismail, R. I., Wiguna, T., Prasetyo, S., Indriatmi, W., Gunardi, H., Pandia, V., & Magdalena, C. C. (2021). Mental health problems and needs among transitional-age youth in Indonesia. *International Journal of Environmental Research and Public Health 2021, Vol. 18, Page 4046*, *18*(8), 4046. https://doi.org/10.3390/IJERPH18084046

Kaplan, G., Xu, H., Abreu, K., & Feng, J. (2022). DNA Epigenetics in Addiction Susceptibility. *Frontiers in Genetics*, *13*.

https://doi.org/10.3389/FGENE.2022.806685

Khurana, A., Romer, D., Betancourt, L. M., Brodsky, N. L., Giannetta, J. M., & Hurt, H. (2015). Experimentation versus progression in adolescent drug use: A test of an emerging neurobehavioral imbalance model. *Development and Psychopathology*, *27*(3), 901–913. https://doi.org/10.1017/S0954579414000765

Kieling, C., Buchweitz, C., Caye, A., Silvani, J., Ameis, S. H., Brunoni, A. R., Cost, K. T., Courtney, D. B., Georgiades, K., Merikangas, K. R., Henderson, J. L., Polanczyk, G. V., Rohde, L. A., Salum, G. A., & Szatmari, P. (2024). Worldwide Prevalence and Disability From Mental Disorders Across Childhood and Adolescence: Evidence From the Global Burden of Disease Study. *JAMA Psychiatry*, *81*(4), 347–356. https://doi.org/10.1001/JAMAPSYCHIATRY.2023.5051

Kirsch, D. E., & Lippard, E. T. C. (2022). Early life stress and substance use disorders: The critical role of adolescent substance use. *Pharmacology, Biochemistry, and Behavior*, *215*. https://doi.org/10.1016/J.PBB.2022.173360

Lalli, M., Brouillette, K., Kapczinski, F., & de Azevedo Cardoso, T. (2021). Substance use as a risk factor for bipolar disorder: A systematic review. *Journal of Psychiatric Research*, *144*, 285–295. https://doi.org/10.1016/J.JPSYCHIRES.2021.10.012

Lees, B., Meredith, L. R., Kirkland, A. E., Bryant, B. E., & Squeglia, L. M. (2020). Effect of alcohol use on the adolescent brain and behavior. *Pharmacology, Biochemistry, and Behavior*, *192*. https://doi.org/10.1016/J.PBB.2020.172906

Livingston, M. (2024). Declining Teenage Drinking: A Global Phenomenon? *Journal of Adolescent Health*, *74*(3), 395–396.

https://doi.org/10.1016/J.JADOHEALTH.2023.12.009

MacKillop, J., & Ray, L. A. (2017). The Etiology of Addiction : A Contemporary Biopsychosocial Approach. *Integrating Psychological and Pharmacological Treatments for Addictive Disorders*, 32–53. https://doi.org/10.4324/9781315683331-2

Mota, N., Parada, M., Crego, A., Doallo, S., Caamaño-Isorna, F., Rodríguez Holguín, S., Cadaveira, F., & Corral, M. (2013). Binge drinking trajectory and neuropsychological functioning among university students: a longitudinal study. *Drug and Alcohol Dependence*, *133*(1), 108–114. https://doi.org/10.1016/J.DRUGALCDEP.2013.05.024

Peeters, M., Oldehinkel, T., & Vollebergh, W. (2017). Behavioral Control and Reward Sensitivity in Adolescents' Risk Taking Behavior: A Longitudinal TRAILS Study. *Frontiers in Psychology*, *8*(FEB). https://doi.org/10.3389/FPSYG.2017.00231

Pfefferbaum, A., Kwon, D., Brumback, T., Thompson, W. K., Cummins, K., Tapert, S. F., Brown, S. A., Colrain, I. M., Baker, F. C., Prouty, D., De Bellis, M. D., Clark, D. B., Nagel, B. J., Chu, W., Park, S. H., Pohl, K. M., & Sullivan, E. V. (2018). Altered Brain Developmental Trajectories in Adolescents After Initiating Drinking. *The American Journal of Psychiatry*, *175*(4), 370–380. https://doi.org/10.1176/APPI.AJP.2017.17040469

Prencipe, A., Kesek, A., Cohen, J., Lamm, C., Lewis, M. D., & Zelazo, P. D. (2011). Development of hot and cool executive function during the transition to adolescence. *Journal of Experimental Child Psychology*, *108*(3), 621–637.

https://doi.org/10.1016/J.JECP.2010.09.008

Rampa, S., Molebatsi, K., & January, J. (2021). Aetiology and Early Developmental Influences on Substance Use Disorders. *Substance Use and Misuse in Sub-Saharan Africa: Trends, Intervention, and Policy*, 17–30. https://doi.org/10.1007/978-3-030-85732-5_2

Richmond-Rakerd, L. S., Slutske, W. S., & Wood, P. K. (2017). Age of initiation and substance use progression: A multivariate latent growth analysis. *Psychology of Addictive Behaviors : Journal of the Society of Psychologists in Addictive Behaviors*, *31*(6), 664–675. https://doi.org/10.1037/ADB0000304

Roberts, R. E., Roberts, C. R., & Xing, Y. (2007). Comorbidity of substance use disorders and other psychiatric disorders among adolescents: evidence from an epidemiologic survey. *Drug and Alcohol Dependence*, *88 Suppl 1*(Suppl 1). https://doi.org/10.1016/J.DRUGALCDEP.2006.12.010

SAMHSA. (n.d.). *Center for Behavioral Health Statistics and Quality. 2022 National Survey on Drug Use and Health. Table 5.9B—Alcohol use disorder in past year: among people aged 12 or older; by age group and demographic characteristics, percentages, 2021 and 2022*. SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2021 and 2022. Retrieved July 10, 2024, from https://www.samhsa.gov/data/sites/default/files/reports/rpt42728/NSDUHDetailedTabs2022/NSDUHDetailedTabs2022/NSDUHDetTabsSect5pe2022.htm#tab5.9b

Shen, J., Hua, G., Li, C., Liu, S., Liu, L., & Jiao, J. (2023). Prevalence, incidence, deaths,

and disability-adjusted life-years of drug use disorders for 204 countries and territories during the past 30 years. *Asian Journal of Psychiatry*, *86*. https://doi.org/10.1016/J.AJP.2023.103677

Smith, L., López Sánchez, G. F., Pizzol, D., Oh, H., Barnett, Y., Schuch, F., Butler, L., McDermott, D. T., Ball, G., Chandola-Saklani, A., Shin, J. Il, & Koyanagi, A. (2024). Global Trends in the Prevalence of Alcohol Consumption Among School-Going Adolescents Aged 12-15 Years. *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine*, *74*(3), 441–448. https://doi.org/10.1016/J.JADOHEALTH.2023.10.007

Squeglia, L. M., Ball, T. M., Jacobus, J., Brumback, T., McKenna, B. S., Nguyen-Louie, T. T., Sorg, S. F., Paulus, M. P., & Tapert, S. F. (2017). Neural predictors of initiating alcohol use during adolescence. *American Journal of Psychiatry*, *174*(2), 172–185. https://doi.org/10.1176/APPI.AJP.2016.15121587/SUPPL_FILE/APPI.AJP.2016.15121587.PREVIOUSLY.PUBLISHED.PDF

Squeglia, L. M., Pulido, C., Wetherill, R. R., Jacobus, J., Brown, G. G., & Tapert, S. F. (2012). Brain response to working memory over three years of adolescence: influence of initiating heavy drinking. *Journal of Studies on Alcohol and Drugs*, *73*(5), 749–760. https://doi.org/10.15288/JSAD.2012.73.749

Squeglia, L. M., Tapert, S. F., Sullivan, E. V., Jacobus, J., Meloy, M. J., Rohlfing, T., & Pfefferbaum, A. (2015). Brain Development in Heavy Drinking Adolescents. *The American Journal of Psychiatry*, *172*(6), 531.

https://doi.org/10.1176/APPI.AJP.2015.14101249

Steinberg, L., Fletcher, A., & Darling, N. (1994). Parental Monitoring and Peer Influences on Adolescent Substance Use. *Pediatrics*, *93*(6), 1060–1064. https://doi.org/10.1542/PEDS.93.6.1060

Tapert, S. F., Granholm, E., Leedy, N. G., & Brown, S. A. (2002). Substance use and withdrawal: neuropsychological functioning over 8 years in youth. *Journal of the International Neuropsychological Society : JINS*, *8*(7), 873–883. https://doi.org/10.1017/S1355617702870011

Tervo-Clemmens, B., Simmonds, D., Calabro, F. J., Day, N. L., Richardson, G. A., & Luna, B. (2018). Adolescent cannabis use and brain systems supporting adult working memory encoding, maintenance, and retrieval. *NeuroImage*, *169*, 496–509. https://doi.org/10.1016/J.NEUROIMAGE.2017.12.041

Trucco, E. M. (2020). A review of psychosocial factors linked to adolescent substance use. *Pharmacology, Biochemistry, and Behavior*, *196*. https://doi.org/10.1016/J.PBB.2020.172969

UNODC. (2022). *UNODC World Drug Report 2022 highlights trends on cannabis post-legalization, environmental impacts of illicit drugs, and drug use among women and youth*. UNODC. https://www.unodc.org/unodc/en/press/releases/2022/June/unodc-world-drug-report-2022-highlights-trends-on-cannabis-post-legalization--environmental-impacts-of-illicit-drugs--and-drug-use-among-women-and-youth.html

UNODC. (2023). *United Nations Office on Drugs and Crime World Drug Report 2023*.

United Nations. https://www.unodc.org/res/WDR-2023/WDR23_Exsum_fin_DP.pdf

Walther, B., Morgenstern, M., & Hanewinkel, R. (2012). Co-Occurrence of Addictive Behaviours: Personality Factors Related to Substance Use, Gambling and Computer Gaming. *European Addiction Research*, *18*(4), 167–174. https://doi.org/10.1159/000335662

Wetherill, R. R., Squeglia, L. M., Yang, T. T., & Tapert, S. F. (2013). A longitudinal examination of adolescent response inhibition: Neural differences before and after the initiation of heavy drinking. *Psychopharmacology*, *230*(4), 663–671. https://doi.org/10.1007/S00213-013-3198-2/METRICS

Winter, J. J., Rodríguez-Acevedo, K. L., Dittrich, M., & Heller, E. A. (2023). Early life adversity: Epigenetic regulation underlying drug addiction susceptibility. *Molecular and Cellular Neurosciences*, *125*. https://doi.org/10.1016/J.MCN.2023.103825

World Drug Report. (2020). *Drug use and health consequences*. United Nations. https://wdr.unodc.org/wdr2020/en/drug-use-health.html

Yuen, W. S., Chan, G., Bruno, R., Clare, P., Mattick, R., Aiken, A., Boland, V., McBride, N., McCambridge, J., Slade, T., Kypri, K., Horwood, J., Hutchinson, D., Najman, J., De Torres, C., & Peacock, A. (2020). Adolescent Alcohol Use Trajectories: Risk Factors and Adult Outcomes. *Pediatrics*, *146*(4), e20200440. https://doi.org/10.1542/peds.2020-0440

Chapter 2: Underage drinking in Brazil: findings from a community household survey

Coral Rakovski,[1] Taiane de Azevedo Cardoso,[2] Jurema Corrêa da Mota,[3] Francisco I. Bastos,[3] Flavio Kapczinski,[1,2,4,5,6] Raquel Brandini De Boni[3]

1. Neuroscience Graduate Program, McMaster University, Hamilton, ON, Canada
2. Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada
3. Instituto de Comunicação e Informação Cientifica e Tecnológica em Saúde, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil
4. Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento, Departamento de Psiquiatria, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
5. Centro de Pesquisa Experimental, Laboratório de Psiquiatria Molecular, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil
6. Centro de Pesquisa Clínica, Laboratório de Psiquiatria Molecular, HCPA, Porto Alegre, RS, Brazil

This chapter in its entirety has been ***published*** in the **Brazilian Journal of Psychiatry**. The final accepted manuscript version of this article is presented within this thesis.

Rakovski C, de Azevedo Cardoso T, da Mota JC, Bastos FI, Kapczinski F, De Boni RB. Underage drinking in Brazil: findings from a community household survey. *Brazilian Journal of Psychiatry*. 2022;44(3):257-63. DOI: 10.1590/1516-4446-2021-2103

Abstract

Objectives: Previous studies have estimated the 30-day prevalence of alcohol use to be approximately 21% among youth in Brazil, despite the legal drinking age of 18 years. The present study aimed to determine the prevalence of underage drinking and its associated factors among adolescents in Brazil.

Methods: The 3rd National Survey on Drug Use by the Brazilian Population (III Levantamento Nacional sobre o Uso de Drogas pela População Brasileira) is a nationwide, multi-stage, probability-sample household survey. Herein, youth between the ages of 12-17 years were included. Lifetime and 12-month alcohol use prevalence were estimated. Factors associated with 12-month alcohol use were evaluated through multivariate analysis considering survey weights and design.

Results: Overall, 628 youth were interviewed. Estimated lifetime and 12-month alcohol use were 34.3 (standard error [SE] = 1.9) and 22.2% (SE = 1.7), respectively. Factors associated with 12-month drinking were: other/no religion vs. Christianity; living in rural vs. urban areas; self-reported diagnosis of depression vs. no self-reported depression; lifetime tobacco use vs. no history of tobacco use; and any illicit drug use vs. no history of illicit drug use.

Conclusion: Considering that alcohol use is a major risk factor for early death among Brazilian youth, our findings highlight the importance of preventative measures to reduce underage drinking.

Keywords: Alcohol; underage drinking; population-based surveys; mental health; Brazil

2.1 Introduction

Underage alcohol use is a public health concern, resulting in several adverse consequences among adolescents.[1] According to data from the United States, the lifetime prevalence of alcohol use is about 60% for adolescents by the end of high school,[2] despite a legal drinking age of 21 years or older. Interestingly, the past-30-day prevalence of underage drinking in the United States decreased significantly from 2002 to 2019 (percent decrease by age group: 41.1% for individuals aged 16-17; 54.7% for individuals aged 14-15; and 61.9% for individuals aged 12-13) based on the 2019 National Survey on Drug Use and Health (NSDUH).[3] Additionally, a systematic review found that the mean prevalence of current alcohol use is approximately 35% among Brazilian adolescents between the ages of 10 to 19 years.[4] Alcohol consumption by adolescents has been associated with negative outcomes including deficits in cognition and brain development, poor relationships with others, poor academic achievement, criminality, as well as death.[1,5-8] Evidence also suggests that components of social context, such as peer influences and parenting factors, especially during early adolescence, have an influence on later drinking behaviors and on alcohol-related problems.[9] Importantly, prior findings have also indicated that alcohol use during adolescence is a predictor of alcohol use disorder (AUD) and substance use disorder.[9,10]

It is well known that, during adolescence, the brain undergoes numerous neurodevelopmental changes and continues to develop until young adulthood, causing the brain to be especially vulnerable throughout this period.[5,11] Adolescents are particularly susceptible to engagement in high-risk behaviors, such as underage drinking, because the prefrontal cortex, which has a primary role in decision making, is still undergoing

maturation at this stage.[12] Alcohol use during adolescence has been associated with changes in brain structure and function, as well as cognitive deficits.[5] Furthermore, adolescents commonly engage in binge drinking, which is associated with a greater likelihood of being diagnosed with an AUD and additional neurobiological changes (e.g., decreased cortical thickness in the frontal lobe and cingulate; decreased grey-matter volume in the frontal lobe, temporal lobe, and cerebellum; various changes in task activation across specific regions of the brain).[13] Binge drinking refers to the consumption of approximately five or more alcohol beverages for males and four or more alcohol beverages for females during a 2-hour period.[13,14] Together, these findings reinforce the importance of studying this population to prevent the negative outcomes that arise from alcohol consumption during adolescence.

Notably, a study in Brazil that analyzed data from almost 75,000 adolescents between the ages of 12 and 17 found that 21% consumed alcohol within the past 30 days, despite the current legal drinking age of 18 years or older in the country.[15] While these results are concerning, there are a lack of studies assessing the lifetime and 12-month prevalence of alcohol use among Brazilian adolescents, as well as potential contributing factors.

Thus, the aim of the present study was to determine the prevalence of underage drinking and its associated factors among a nationally representative population of adolescents in Brazil.

2.2 Methods

The 3rd National Survey on Drug Use by the Brazilian Population (III Levantamento Nacional sobre o Uso de Drogas pela População Brasileira) is a nationwide, multi-stage, probability-sample household survey. The sample included 16,273 Brazilians aged 12 to 65 years, living in urban and/or rural areas who were interviewed between 2015 and 2016. Native individuals living in indigenous villages, persons deprived of liberty, and individuals with physical or mental disabilities that precluded answering the interview questions were not eligible.[16-19] Details regarding sampling, questionnaires, data collection, data entry, and handling of non-response are fully available elsewhere.[20]

2.2.1 Participants

In the present analysis, 628 youth between the ages of 12 and 17 years were included, representing 20 million individuals of this age after proper weighting, as briefly described elsewhere.[17]

2.2.2 Outcome

The main outcome was underage drinking, assessed by self-reported alcohol use in the preceding 12 months. In Brazil, since 2015, it is a crime to "sell, provide, serve, minister, or deliver" alcoholic beverages to youth under the age of 18 years.[21]

2.2.3 Variables

Demographic variables were collected using questions from the Brazilian Demographic census,[22] and included: sex at birth (male vs. female); sexual orientation (heterosexual, homosexual, other/do not want to answer); color/race (white, black, mixed, other); school attendance (yes, not anymore); religion (Catholic, Christian, none, other);

having a steady partner (yes, no); number of children (none, one or more); geographic macro-region of residence (North/Northeast, Southeast/South, and Center-West); and living in urban vs. rural areas.

General health variables included: self-rated health (very good/good, fair/do not know, and very poor/poor)[23]; and reporting 12-month treatment and/or diagnosis for diabetes, heart disease, hypertension, asthma, renal disease, depression, anxiety, or bipolar disorder.

Lifetime substance use was aggregated as prescription medication used to "feel high" (benzodiazepines, anticholinergics, barbiturates, and opioids), tobacco use, and illicit drug use (inhalants, marijuana, cocaine/crack, ecstasy).

Alcohol-related problems included binge drinking in the previous 30 days (defined as the consumption of approximately five or more alcohol beverages for males and four or more for females within a 2-hour period),[14] and 12-month report of the following: having used alcohol in situations representing physical risk (such as driving, swimming, piloting motorcycles, operating machines, etc.); and having personal problems due to alcohol use. In addition, individuals were asked whether, in the previous 12 months, they had done any of the following after using alcohol: driven, had an argument, destroyed something, hurt themselves, been beaten, hurt someone, been threatened, had difficulties fulfilling obligations at school/work, left school, or stolen something.

2.2.4 Statistical analysis

Prevalence, standard error (SE), and estimated population were calculated for selected demographic variables, general health (self-rated and selected medical conditions), lifetime substance use, and alcohol-related problems. Prevalence and SE were estimated for all variables stratified by underage drinking and compared using Pearson's chi-square test with Rao-Scott adjustment.[24] Variables presenting a p-value < 0.20 at the bivariate test were considered for the multivariable regression model. The final model was fitted considering the backward method, maintaining those variables with a significance level of 5%, with the exception of sex, age, and self-rated health, which were kept in the model by epidemiological criteria. All the analyses considered sample weights, design effect, and weight calibration. Analyses were performed in R version 3.5.0 using the "survey" and "surveyer" packages.[25]

2.2.5 Ethics statement

The 3rd National Survey on Drug Use by the Brazilian Population was approved by an ethics committee of Fundação Oswaldo Cruz (Fiocruz; CAAE # 35283814.4.0000.5241).

2.3 Results

This study included 628 youth between the ages of 12-17 years, representing 20 million individuals of this age in Brazil. The sample characteristics are described in Table 1. Briefly, 56% of the study participants were male, 90% attended school, and 86% reported their overall health as very good/good. Anxiety and asthma were the most common self-reported diagnoses, with a prevalence of 8 and 10% respectively. Alcohol,

tobacco, and marijuana were the substances most frequently reported for lifetime use, by 34.3 (SE = 1.9), 6.3 (SE = 1.1), and 3.3% (SE = 0.8) of the participants, respectively.

Underage drinking was estimated at 22.2% (SE = 1.7). Of those who reported underage drinking, 22.7% (SE = 4.1) reported binge drinking and 9.4% (SE = 2.6) had an argument after consuming alcohol. Factors associated with underage drinking in the bivariate analysis were: not attending school ($p = 0.01$); not being Christian ($p < 0.001$); living in a rural area ($p < 0.001$); poor self-rated health ($p < 0.001$); depression ($p < 0.001$); bipolar disorder ($p < 0.001$); lifetime tobacco use ($p < 0.001$); and lifetime use of any illicit drug ($p < 0.001$) (Table 1).

Table 2 shows the final adjusted model. Specifically, the main risk factors for 12-month alcohol use were: residing in rural areas compared to urban areas (adjusted odds ratio [AOR] 2.29, 95% confidence interval [95%CI] 1.30-4.04); self-reporting a diagnosis of depression (AOR 8.79, 95%CI 1.03-74.72); lifetime tobacco use (AOR 13.27, 95%CI 5.14-34.27); and any illicit drug use (AOR 3.40, 95%CI 1.03-11.18). Importantly, being Christian was a protective factor in comparison to other/no religion (AOR 2.55, 95%CI 1.52-4.29).

Figure 1 shows that those with 12-month alcohol use had a greater prevalence of alcohol-related problems in comparison to the general adolescent population, as follows: binge drinking (22.7 vs. 5%, respectively); risk of physical injury (3.5 vs. 0.8%, respectively); relationship problems (7.1 vs. 1.6%, respectively); driving under the influence of alcohol (2.1 vs. 0.5%, respectively); having an argument (9.4 vs. 2.1%, respectively); destruction of objects (1.2 vs. 0.3%, respectively); self-harm (2.2 vs. 0.5%,

respectively); being beaten (1.7 vs. 0.4%, respectively); hurting someone else (2.8 vs. 0.6%, respectively); and difficulty fulfilling one's obligations (2.2 vs. 0.5%, respectively).

2.4 Discussion

The present study found a lifetime prevalence of 34.3% and a 12-month prevalence of 22.2% for alcohol use among youth between the ages of 12 and 17 years in Brazil. The prevalence of underage drinking was greater among individuals residing in rural areas as compared to urban areas, individuals self-reporting depression as compared to those that did not self-report depression, individuals with lifetime tobacco use as compared to those with no history of tobacco use, and individuals with any illicit drug use as compared to those with no history of illicit drug use. Interestingly, being Christian was associated with a lower prevalence of underage drinking as compared to individuals who self-reported other/no religion. Furthermore, those who consumed alcohol within the last 12 months had a higher prevalence of binge drinking, physical injury, relationship problems, driving under the influence of alcohol, having an argument, destruction of objects, self-harm, being beaten, hurting someone else, and difficulty fulfilling one's obligations as compared to the overall population.

According to the 2019 NSDUH, the 12-month prevalence of alcohol use among adolescents aged 12-17 years in the United States was 21.2%.[26] These findings are similar to those of the current study, which found a 12-month prevalence of 22.2% for alcohol use by youth of the same age range in Brazil. A previous systematic review found a mean prevalence of 35% (23 to 67%) for current alcohol use among Brazilian adolescents, which is also similar to the findings of the current study.[4] In contrast, Canadian survey

results from 2018-2019 found a 12-month prevalence of 44% for alcohol use among adolescents from grades 7-12.[27]

Prior studies have demonstrated significant associations between specific sociodemographic characteristics and an increased prevalence of alcohol use among adolescents, including residing in rural areas as well as non-religiosity.[28,29] A longitudinal study also found that adolescent alcohol use was a predictor of subsequent illicit drug abuse.[30] Interestingly, a meta-analysis showed that AUD was a predictor of depression.[31] A previous study in Brazil found a significant relationship between alcohol use and physical violence for adolescent males between the ages of 13 and 15 years.[32] Underage alcohol consumption is also linked to binge drinking, which has concerning associations with alcohol-related injury, alcohol-related physical/sexual assault, and road traffic collisions.[33] Lastly, the current study indicated that being Christian is a protective factor against underage drinking, which has been supported by other studies showing that religiosity protects against alcohol use in adolescents.[29] Unfortunately, the small sample size precludes the assessment of the putative protective effect of other religions and denominations on underage drinking and harmful/dependent use of alcohol in a broader sense. Overall, the findings of prior studies are consistent with the main results of our present study, indicating that various sociodemographic characteristics, illicit substance use, and medical conditions are factors associated with adolescent alcohol consumption as well as its related problems.

The high prevalence of alcohol use and alcohol-related problems among Brazilian adolescents that we found in the present study highlights the importance of implementing

preventative measures against underage drinking in this population. This is particularly urgent considering that alcohol consumption among adolescents has been linked to functional and cognitive impairments such as deficits in learning, executive functioning, attention, and memory.[5,6] Notably, underage drinking can impact the development of the adolescent brain, resulting in the aforementioned functional and cognitive deficits.[5,6] Several risk factors for underage drinking have been identified, such as childhood physical abuse, parenting factors, peer influences, conduct problems, and depression.[9,34,35] Fortunately, there is some evidence suggesting that the implementation of interventions including family-based prevention programs, mentoring, mHealth technology (e.g., mobile applications, social networking websites, text messages, etc.), and public health measures (e.g., restrictions on alcohol availability, taxation to increase prices, etc.) can prevent or reduce alcohol use among adolescents.[36-39] A recent study of adolescents of 11-17 years in the United Kingdom demonstrated that positive reactions to alcohol advertisements were associated with an increased susceptibility to underage drinking for those with no history of alcohol use, and with high-risk drinking for current alcohol users.[40] This indicates that regulation of alcohol advertisements may also help to inhibit underage drinking. A Brazilian study found, through the use of machine-learning algorithms, that driving under the influence of alcohol was associated with male sex, binge drinking, and past-year drug use.[41] This indicates the promising potential of machine-learning techniques to inform policymaking and the implementation of targeted interventions through the prompt identification of individuals that are at a particularly

high risk of facing the adverse outcomes associated with adolescent alcohol consumption in Brazil.

The findings of the present study should be considered in light of some limitations. One limitation was the cross-sectional design of this study, which precludes any inference of causality. Another limitation was the use of self-report assessments, which may be a source of social desirability bias. Furthermore, parenting style regarding alcohol use was not evaluated, which is a known contributing factor to adolescent alcohol use.[42] Despite these limitations, several strengths of this study are worth highlighting. First, this study used a probability sample, which allows generalizability of the findings to the entire Brazilian population at this age. Additionally, a wide variety of factors were examined, including sociodemographic characteristics, medical conditions, the use of illicit substances, and alcohol-related problems, enabling an extensive investigation of the factors associated with underage drinking.

Overall, the main findings of this study demonstrate the high prevalence of alcohol use among Brazilian youth, as well as the alarming alcohol-related problems (e.g., binge drinking, physical injury, relationship problems, driving under the influence of alcohol, etc.) associated with underage drinking in this population. Other known consequences of underage drinking include deficits in cognition and brain development, difficulties with interpersonal relationships, and academic issues. The present study found several risk factors for alcohol use among Brazilian adolescents, such as residing in rural areas, self-reporting a diagnosis of depression, tobacco use, any illicit drug use, and having no/other religion in comparison to Christianity. Identification of such risk factors

for adolescent alcohol use will enable the timely implementation of suitable interventions among those who are at the highest risk of underage drinking. The early implementation of interventions and public health measures focused on the prevention or reduction of adolescent alcohol consumption may be promising to limit the devastating consequences of underage drinking in Brazil.

2.5 Acknowledgements

The authors would like to thank the FIOCRUZ and the SCIENCE (Sociedade para o Desenvolvimento da Pesquisa Científica) teams, as well as all the respondents who participated in the surveys. This study was funded by different Brazilian government agencies: the original survey was funded by a contract with Secretaria Nacional de Políticas sobre Drogas (SENAD; Federal decree 7.179, May 10, 2010). New analyses were carried out in the context of the "Analysis/reanalysis of Brazilian major databases on substance use" component of Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) Health Network program grant (E-26/010.002428/2019), coordinated by FIB. TAC acknowledges her postdoctoral fellowship from the Canadian Institutes of Health Research (CIHR). FIB is a career scientist at Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). FK has received grants from Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (Fundação de Amparo à Pesquisa do Estado de São Paulo [FAPESP] 2014/50891-1 and CNPq 465458/2014-9), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS; 2012551-0000250.0), the Canada Foundation for Innovation (CFI), the Social Sciences and

Humanities Research Council (SSHRC), the CIHR, and the Natural Sciences and Engineering Research Council (NSERC). RBDB has received grants from CNPq (312543/2020-4) and FAPERJ (E-26/203.154/2017).

2.6 Disclosure

FK has received personal fees as a speaker/consultant from Janssen-Johnson & Johnson. The other authors report no conflicts of interest.

2.7 References

1. Ryan SA, Kokotailo P, Committee on Substance Use and Prevention. Alcohol use by youth. Pediatrics. 2019;144:e20191357.
2. Johnston LD, Miech RA, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. Monitoring the future national survey results on drug use, 1975-2018: overview, key findings on adolescent drug use [Internet]. 2019 [cited 2021 Sep 17]. eric.ed.gov/?id=ED604018
3. National Institute on Alcohol Abuse and Alcoholism (NIAAA). Alcohol facts and statistics [Internet]. [cited 2021 Apr 15]. www.niaaa.nih.gov/publications/brochures-and-fact-sheets/alcohol-facts-and-statistics
4. Barbosa Filho VC, de Campos W, da Silva Lopes A. Prevalence of alcohol and tobacco use among Brazilian adolescents: a systematic review. Rev Saude Publica. 2012;46:901-17.
5. Lees B, Meredith LR, Kirkland AE, Bryant BE, Squeglia LM. Effect of alcohol use on the adolescent brain and behavior. Pharmacol Biochem Behav. 2020;192:172906.
6. Spear LP. Effects of adolescent alcohol consumption on the brain and behaviour. Nat Rev Neurosci. 2018;19:197-214.
7. Guo L, Deng J, He Y, Deng X, Huang J, Huang G, et al. Alcohol use and alcohol-related problems among adolescents in China: a large-scale cross-sectional study. Medicine (Baltimore). 2016;95:e4533.

8. Popovici I, Homer JF, Fang H, French MT. Alcohol use and crime: findings from a longitudinal sample of U.S. adolescents and young adults. Alcohol Clin Exp Res. 2012;36:532-43.

9. Yuen WS, Chan G, Bruno R, Clare P, Mattick R, Aiken A, et al. Adolescent alcohol use trajectories: risk factors and adult outcomes. Pediatrics. 2020;146:e20200440.

10. Boden J, Blair S, Newton-Howes G. Alcohol use in adolescents and adult psychopathology and social outcomes: findings from a 35-year cohort study. Aust N Z J Psychiatry. 2020;54:909-18.

11. Blum RW, Bastos FI, Kabiru CW, Le LC. Adolescent health in the 21st century. Lancet. 2012;379:1567-8.

12. Jadhav KS, Boutrel B. Prefrontal cortex development and emergence of self-regulatory competence: the two cardinal features of adolescence disrupted in context of alcohol abuse. Eur J Neurosci. 2019;50:2274-81.

13. Jones SA, Lueras JM, Nagel BJ. Effects of binge drinking on the developing brain. Alcohol Res. 2018;39:87-96.

14. National Institute on Alcohol Abuse and Alcoholism (NIAAA). NIAAA council approves definition of binge drinking [Internet]. 2004 [cited 2021 Sep 17]. pubs.niaaa.nih.gov/publications/Newsletter/winter2004/Newsletter_Number3.pdf

15. Coutinho ES, França-Santos D, da Silva Magliano E, Bloch KV, Barufaldi LA, De Freitas Cunha C, et al. ERICA: patterns of alcohol consumption in Brazilian adolescents. Rev Saude Publica. 2016;50 Suppl:8s.

16. Krawczyk N, Silva PL, De Boni RB, Mota J, Vascncellos M, Bertoni N, et al. Non-medical use of opioid analgesics in contemporary Brazil: findings from the 2015 Brazilian National Household Survey on Substance Use. Global Public Health; 2019.

17. De Boni RB, de Vasconcellos MT, Silva PN, Coutinho C, Mota J, Peixoto JN, et al. Reproducibility on science: challenges and advances in Brazilian alcohol surveys. Int J Drug Policy. 2019;74:285-91.

18. Bertoni N, Szklo A, De Boni R, Coutinho C, Vasconcellos M, Nascimento Silva P, et al. Electronic cigarettes and narghile users in Brazil: do they differ from cigarettes smokers? Addict Behav. 2019;98:106007.

19. De Boni RB, de Vasconcellos MT, Pedro Luis NS, Silva KM, Bertoni N, Coutinho CF, et al. Substance use, self-rated health and HIV status in Brazil. Substance use, self-rated health and HIV status in Brazil. AIDS Care. 2021;33(10):1358-62

20. Instituto de Comunicação e Informação Científica e Tecnológica em Saúde (ICICT), Fundação Oswaldo Cruz (Fiocruz). 3rd national survey on drug use by the Brazilian population [Internet]. 2017 [cited 2021 Sep 21]. www.arca.fiocruz.br/bitstream/icict/34614/2/III%20LNUD_ENGLISH.pdf

21. Brasil, Presidencia da Republica. Lei 13.106. Diário Oficial da União, 17 março 2015. www.planalto.gov.br/ccivil_03/_ato2015-2018/2015/lei/l13106.htm

22. Instituto Brasileiro de Geografia e Estatística (IBGE). Censo demográfico 2010. censo2010.ibge.gov.br/resultados.html

23. Idler EL, Benyamini Y. Self-Rated health and mortality : a review of twenty-seven community studies. J Health Soc Behav. 1997;38:21-37.

24. Rao JN, Scott AJ. On chi-squared tests for multiway contingency tables with proportions estimated from survey data. Ann Statist. 1984;12:46-60.

25. Lumley T. Complex surveys: a guide to analysis using R. Wiley Series in Survey Methodology. Hoboken: John Wiley & Sons; 2010.

26. Substance Abuse and Mental Health Services Administration (SAMHSA). Results from the 2018 national survey on drug use and health: detailed tables [Internet]. [cited 2021 Apr 24]. www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2018R2/NSDUHDetailedTabs2018.pdf

27. Canada, Government of Canada. Summary of results for the Canadian student tobacco, alcohol and drugs survey 2018-19 [Internet]. [cited 2021 Apr 24]. www.canada.ca/en/health-canada/services/canadian-student-tobacco-alcohol-drugs-survey/2018-2019-summary.html

28. Donath C, Gräßel E, Baier D, Pfeiffer C, Karagülle D, Bleich S, et al. Alcohol consumption and binge drinking in adolescents: comparison of different migration backgrounds and rural vs. urban residence - a representative study. BMC Public Health. 2011;11:84.

29. Charro Baena B, Meneses C, Caperos JM, Prieto M, Uroz J. The role of religion and religiosity in alcohol consumption in adolescents in Spain. J Relig Health. 2019;58:1477-87.

30. Griffin KW, Lowe SR, Botvin C, Acevedo BP. Patterns of adolescent tobacco and alcohol use as predictors of illicit and prescription drug abuse in minority young adults. J Prev Interv Community. 2019;47:228-42.

31. Boden JM, Fergusson DM. Alcohol and depression. Addiction. 2011;106:906-14.

32. Andrade SS, Yokota RT, de Sá NN, da Silva MM, de Araújo WN, Mascarenhas MD, et al. [Association between physical violence, consumption of alcohol and other drugs, and bullying among Brazilian adolescents]. Cad Saude Publica. 2012;28:1725-36.

33. Chung T, Creswell KG, Bachrach R, Clark DB, Martin CS. Adolescent binge drinking. Alcohol Res. 2018;39:5-15.

34. de Moraes CL, de Freitas Ferreira M, Reichenheim ME, Gaudard E Silva A, Valéria da Veiga G. Pathways linking childhood physical abuse to alcohol misuse in adolescent boys and girls: a prospective cohort study from Rio de Janeiro, Brazil. J Stud Alcohol Drugs. 2020;81:362-71.

35. Isaksson J, Schwab-Stone M, Stickley A, Ruchkin V. Risk and protective factors for problematic drinking in early adolescence: a systematic approach. Child Psychiatry Hum Dev. 2020;51:231-8.

36. Byrnes HF, Miller BA, Grube JW, Bourdeau B, Buller DB, Wang-Schweig M, et al. Prevention of alcohol use in older teens: a randomized trial of an online family prevention program. Psychol Addict Behav. 2019;33:1-14.

37. Thomas RE, Lorenzetti DL, Spragins W. Systematic review of mentoring to prevent or reduce alcohol and drug use by adolescents. Acad Pediatr. 2013;13:292-9.

38. Hutton A, Prichard I, Whitehead D, Thomas S, Rubin M, Sloand E, et al. mHealth interventions to reduce alcohol use in young people: a systematic review of the literature. Compr Child Adolesc Nurs. 2020;43:171-202.

39. Alcohol and Public Policy Group. Alcohol: no ordinary commodity - a summary of the second edition. Addiction. 2010;105:769-79.

40. Boniface S, Critchlow N, Severi K, MacKintosh AM, Hooper L, Thomas C, et al. Underage adolescents' reactions to adverts for beer and spirit brands and associations with higher risk drinking and susceptibility to drink: a cross-sectional study in the UK. Alcohol Alcohol. 2021 Apr 23;agab018. doi: 10.1093/alcalc/agab018. Online ahead of print.

41. Rabelo-da-Ponte FD, Scherer JN, Roglio V, Borges EN, Galland F, Sousa T, et al. From phone use to speeding and driving under influence: identifying clusters of driving risk behaviors as an opportunity for targeted interventions. J Psychiatr Res. 2021;143:556-62.

42. Zuquetto CR, Opaleye ES, Feijó MR, Amato TC, Ferri CP, Noto AR. Contributions of parenting styles and parental drunkenness to adolescent drinking. Braz J Psychiatry. 2019;41:511-7.

2.8 Figures and Tables

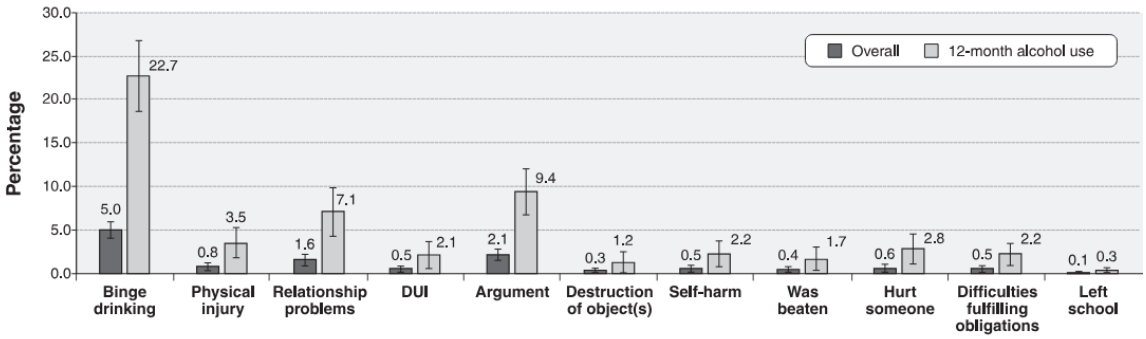


Figure 1 Alcohol-related problems among youth between the ages of 12-17 years, Brazil, 2015. DUI = driving under the influence.

Table 1 Sociodemographic and clinical characteristics and their association with underage drinking among youth between the ages of 12-17 years, Brazil, 2015

				Underage drinking				
	Overall			Yes		No		
Variables	Estimated population (N)	%	SE	%	SE	%	SE	p-value[†]
Sex								0.61
Male	11,436,244	56.4	2.7	58.7	4.8	55.7	3.2	
Female	8,840,14	43.6	2.7	41.3	4.8	44.3	3.2	
Sexual orientation								0.34
Heterosexual	19,599,154	96.7	0.9	95.2	1.6	97.1	1.0	
Homosexual (gay or lesbian)	99,640	0.5	0.2	1.1	0.8	0.3	0.2	
Other/do not know/do not want to answer	577,591	2.8	0.9	3.6	1.3	2.6	1.0	
Skin color								0.57
White	7,145,829	35.2	2.4	37.4	5.0	34.6	2.5	
Black	2,014,357	9.9	1.3	8.4	2.3	10.4	1.7	
Mixed	10,872,106	53.6	2.3	54.1	5.2	53.5	2.4	
Other	244,093	1.2	0.6	0.0	0.0	1.5	0.8	
Attends school								0.01
Yes	18,247,771	90.0	1.4	82.5	3.7	92.1	1.7	
Not anymore	2,028,614	10.0	1.4	17.5	3.7	7.9	1.7	
Religion								
Christian	6,609,932	32.6	2.7	18.0	3.7	36.8	3.1	0.00
Other	13,666,454	67.4	2.7	82.0	3.7	63.2	3.1	
Stable partner								0.55
Yes	361,130	1.8	0.8	2.6	1.3	1.5	1.1	
No	19,915,255	98.2	0.8	97.4	1.3	98.5	1.1	
Number of children								0.05
None	20,018,134	98.7	0.8	97.4	1.2	99.1	0.3	
One	258,251	1.3	0.4	2.6	1.2	0.9	0.3	
Region								0.56
North-Northeast	8,962,864	44.2	3.3	45.2	5.3	43.9	3.5	
South-Southeast	9,420,721	46.5	3.4	47.8	5.1	46.1	3.7	
Center-West	1,892,800	9.3	1.6	7.0	1.9	10.0	1.8	
Urban vs. rural								0.00
Urban	16,318,779	80.5	2.3	70.2	4.9	83.4	2.4	
Rural	3,957,606	19.5	2.3	29.8	4.9	16.6	2.4	
Self-rated health								0.11
Very good/good	17,468,645	86.1	1.9	90.8	2.7	84.4	2.3	
Fair/poor/very poor	2,807,740	13.85	1.9	9.2	2.7	15.2	2.3	
Self-reported diagnosis or treatment in last 12 months								
Diabetes	93,408	0.5	0.2	0.5	0.5	0.5	0.3	0.97
Heart disease	222,538	1.1	0.4	0.5	0.5	1.3	0.5	0.36
Hypertension	347,169	1.7	1.0	2.1	1.2	1.6	1.2	0.79
Asthma	2,002,763	9.9	1.8	11.5	3.2	9.4	2.0	0.57
Depression	136,807	0.7	0.3	2.2	1.1	0.2	0.2	0.00
Anxiety	1,543,697	7.6	1.5	9.3	2.5	7.1	1.8	0.47
Bipolar disorder	72,075	0.4	0.2	1.3	0.9	0.1	0.1	0.00
Renal disease	114,951	0.6	0.3	1.3	1.0	0.3	0.3	0.16
Substance use, lifetime								
Tobacco	1,267,767	6.3	1.1	22.0	4.0	1.7	0.6	0.00
Benzodiazepines	228,988	1.1	0.5	2.8	1.7	0.6	0.3	0.03
Amphetamines	118,612	0.6	0.5	2.2	2.0	0.1	0.1	0.00
Barbiturates	61,177	0.3	0.2	0.3	0.3	0.3	0.2	0.91
Opioids	418,148	2.1	1.0	1.5	0.8	2.2	1.3	0.59
Inhalants	222,550	1.1	0.4	2.9	1.3	0.6	0.3	0.01
Marijuana	677,601	3.3	0.8	12.5	3.1	0.7	0.4	0.00
Cocaine	234,275	1.2	0.4	4.9	1.7	0.1	0.1	0.00

				Underage drinking				
	Overall			Yes		No		
Variables	Estimated population (N)	%	SE	%	SE	%	SE	p-value[†]
Ecstasy	77,424	0.4	0.2	1.3	0.8	0.1	0.1	0.01
Injected drug use	59,482	0.3	0.2	1.0	0.8	0.1	0.1	0.02
Any medication	804,116	3.4	1.3	6.1	2.6	3.4	1.3	0.59
Any illicit drug	813,557	4.0	0.8	13.9	3.2	1.2	0.5	0.00
Was threatened in last 12 months	1,294,245	6.4	1.2	9.9	2.9	5.4	1.3	0.10
Was beaten in last 12 months	82,175	0.4	0.2	1.1	0.8	0.2	0.2	0.09

SE = standard error.
[†] χ^2 with Rao-Scott adjustment.

Table 2 AOR for past 12-month alcohol use among youth between the ages of 12-17 years, Brazil, 2015

		95%CI	
Variables	AOR	Lower	Higher
Sex			
Male	1.11	0.66	1.85
Female	Ref.	-	-
Religion			
Christian	Ref.	-	-
Other (none/Catholic/others)	2.55	1.52	4.29
Urban vs. rural			
Urban	Ref.	-	-
Rural	2.29	1.30	4.04
Self-rated health			
Very good/good	Ref.	-	-
Fair/poor/very poor	0.60	0.26	1.40
Tobacco use, lifetime			
Yes	13.27	5.14	34.27
No	Ref.	-	-
Any illicit drug use, lifetime			
Yes	3.40	1.03	11.18
No	Ref.	-	-
Self-reported diagnosis/treatment for depression in last 12 months			
Yes	8.79	1.03	74.72
No	Ref.	-	-

95%CI = 95% confidence interval; AOR = adjusted odds ratios; Ref. = reference category.
Hosmer-Lemeshow test p-value = 0.7925.

Chapter 3: Predictors of illicit substance abuse/dependence during young adulthood: A machine learning approach

Coral Rakovski[a], Pedro L. Ballester[a], Bruno Braga Montezano[b,c,d], Luciano Dias de Mattos Souza[b], Karen Jansen[b], Ricardo Azevedo da Silva[b], Thaise Campos Mondin[e], Fernanda Pedrotti Moreira[b], Raquel Brandini de Boni[f], Benicio N. Frey[g,h], Flavio Kapczinski[c,d,g,i], Taiane de Azevedo Cardoso[b,g]

a. Neuroscience Graduate Program, McMaster University, Hamilton, ON, Canada
b. Health and Behavior Department, Catholic University of Pelotas, Pelotas, RS, Brazil
c. Bipolar Disorder Program, Laboratory of Molecular Psychiatry, Hospital de Clínicas de Porto Alegre, Instituto Nacional de Ciência e Tecnologia Translacional em Medicina, Porto Alegre, RS, Brazil
d. Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
e. Department of Student Affairs, Federal University of Pelotas, Pelotas, RS, Brazil
f. Instituto de Comunicação e Informação Cientifica e Tecnológica em Saúde / Oswaldo Cruz Foundation, RJ, Brazil
g. Mood Disorders Program, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada
h. Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada
i. Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (INCT-TM), Porto Alegre, RS, Brazil

This chapter in its entirety has been ***published*** in the **Journal of Psychiatric Research.** The final accepted manuscript version of this article is presented within this thesis.

Rakovski, C., Ballester, P.L., Montezano, B.B., de Mattos Souza, L.D., Jansen, K., da Silva, R.A., Mondin, T.C., Moreira, F.P., De Boni, R.B., Frey, B.N., Kapczinski, F., de Azevedo Cardoso, T., 2023. Predictors of illicit substance abuse/dependence during young adulthood: A machine learning approach. *Journal of Psychiatric Research*, 157, 168-173. DOI: 10.1016/j.jpsychires.2022.11.030

Abstract

Prior studies have found an especially high prevalence of illicit substance use among adolescents and young adults in Brazil. The current study aimed to employ machine learning techniques to identify predictors of illicit substance abuse/dependence among a large community sample of young adults followed for 5 years. This prospective, population-based cohort study included a sample of young adults between the ages of 18 to 24 years from Pelotas, Brazil at baseline (T1). The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was used to assess illicit substance abuse/dependence. A clinical interview was conducted to collect data on sociodemographic characteristics and psychopathology. Elastic net was used to generate a regularized linear model for the machine learning component of this study, which followed standard machine learning protocols. A total of 1560 young adults were assessed at T1, while 1244 were reassessed at the 5-year follow-up period (T2). The strongest predictors of illicit substance abuse/dependence at baseline (AUC of 0.83) were alcohol abuse/dependence, tobacco abuse/dependence, being in a current major depressive episode, history of a lifetime manic episode, current suicide risk, and male sex. The strongest predictors for illicit substance abuse/dependence at the 5-year follow-up (AUC: 0.79) were tobacco abuse/dependence at T1, history of a lifetime manic episode at T1, male sex, alcohol abuse/dependence at T1, and current suicide risk at T1. Our findings indicate that machine learning techniques hold the potential to predict illicit substance abuse/dependence among young adults using sociodemographic/clinical characteristics, with relatively high accuracy.

Keywords: Illicit substance use; Young adults; Prospective cohort study; Mental health

3.1 Introduction

In 2018, the global 12-month prevalence for illicit substance use was estimated at approximately 5.4% for individuals between the ages of 15 to 64 years (World Drug Report, 2020). Global illicit substance use has increased by approximately 30% from 2000 to 2018, especially among developing countries in comparison to developed countries, with adolescents and young adults constituting the greatest proportion of illicit substance users (UNODC World Drug Report, 2020). Importantly, data from the World Health Organization's World Mental Health Surveys Initiative collected from 2001 to 2015 showed that the prevalence of past-year illicit drug use was 2.6% for low to lower middle income countries, 6.1% for upper to middle income countries, and 9.3% for high income countries (Degenhardt et al., 2019). According to the 2018 National Survey on Drug Use and Health from the United States, the 12-month prevalence of illicit substance use (including the misuse of prescription drugs) among young adults between the ages of 18 to 25 years was 38.5% (Lipari and Park-Lee, 2019). A population-based study in Brazil found a prevalence of 7.3% for illicit substance abuse/dependence among young adults from 18 to 24 years (de Matos et al., 2018). This study also found that post-traumatic stress disorder and generalized anxiety disorder were associated with illicit substance abuse/dependence in this population (de Matos et al., 2018). Taking into consideration that cannabis has been legalized in many countries (Nazif-Munoz et al., 2020; Steinberg et al., 2021; Wilkinson et al., 2016), it is important to note that all of the aforementioned studies included cannabis as an illicit substance.

A U.S. study investigating illicit substance use among college students found that the median age of illicit substance use onset was during young adulthood for various

types of substances, ranging from about 17 years for cannabis to 21 years for ecstasy (Arria et al., 2017). A more recent study found a peak age at onset of 19.5 years and a median age of 25 years for substance use or addictive behaviour disorders (Solmi et al., 2021). The 3rd National Survey on Drug Use by the Brazilian Population found a 12-month prevalence of 7.4% for illicit substance use, including cannabis, by young adults between the ages of 18 to 24 years (Bastos et al., 2017). Notably, based on data from the Global Burden of Diseases, Injuries and Risk Factors Study 2010, illicit substance use disorders accounted for almost 11% of disability-adjusted life years due to mental and substance use disorders (Whiteford et al., 2013). Additionally, this same study showed that men with substance use disorders experienced a greater burden in comparison to women with substance use disorders (Whiteford et al., 2013). Overall, these findings demonstrate the importance of studying predictors of illicit substance use among young adults to promptly detect illicit substance abuse/dependence and implement appropriate interventions.

Machine learning techniques, which are especially useful in the context of predictive applications, include the training of models based on previously established input and output pairs. These are used to generalize models and predict outputs for unseen data (Barenholtz et al., 2020). Machine learning models are well-equipped to handle multidimensional data involving several independent variables (Barenholtz et al., 2020). Thus, machine learning models hold the potential to provide predictions regarding diagnostic or prognostic outcomes that are especially relevant to clinical data, such as substance use data (Barenholtz et al., 2020). However, it is important to note that some

machine learning models have been limited by insufficient data or validation methods, resulting in models that perform at chance (Barenholtz et al., 2020). A recent systematic review showed that while some prior studies with machine learning models applied to substance use data had good to excellent predictive performance, only a few longitudinal studies on this topic have been conducted thus far (Barenholtz et al., 2020). Furthermore, most of these previous studies focused on physiological predictors (e.g., neurological, neurobehavioural and other biomarkers) (Barenholtz et al., 2020) which are more expensive and less feasible to assess in a clinical setting than other clinical/sociodemographic characteristics. To address these limitations, our current study employed a longitudinal design and included several sociodemographic and mental health features (e.g., tobacco abuse/dependence, alcohol abuse/dependence, current suicide risk, mood episodes, anxiety disorders, etc.).

Thus, the aim of the present study was to predict illicit substance abuse/dependence at baseline and at 5-years of follow-up, using sociodemographic and clinical characteristics coupled with machine learning techniques in a large and representative sample of young adults in Brazil.

3.2 Material and Methods

3.2.1 Participants

This prospective population-based cohort study included a community sample of 1560 young adults (ages 18 to 24 years) from Pelotas, Brazil at baseline. At the follow-up period, 5 years later, 1244 participants (79.7%) were reassessed. We used probabilistic sampling. The sample selection at baseline was performed by clusters considering the

population of 39,667 in the target age range (18-24 years) according to the current census of 448 sectors in the city (IBGE, 2008). In order to assure the necessary sample size, 89 census-based sectors were randomly selected. The home selection in the sectors was performed according to a systematic sampling, the first one being the house at the corner pre-established by the IBGE as the beginning of the sector, the interval of selection was determined by skipping two houses. After identifying the subjects, the trained interviewers explained the aims of the study for the potential participants. The inclusion criteria for this study were that 1) participants must be between the ages of 18 to 24 years at baseline and 2) participants must reside in Pelotas, Brazil. Participants that had a severe cognitive disability which would preclude their understanding of the study assessments were excluded. There were 1762 eligible individuals that were invited to participate, of which 1560 provided consent and agreed to participate. Interviews were conducted by trained undergraduate students in the area of health sciences at the homes of participants and paper questionnaires were used to collect data. The baseline interviews took place between 2007 and 2009. Follow-up assessments were conducted from 2012 to 2014, with a mean of 5 years after baseline. Of the 1560 participants invited to participate in the follow-up assessments, 1244 gave written informed consent. At follow-up, tablets were used to collect data through the Open Data Kit (ODK) software, and the interviews were conducted by trained clinical psychologists. This study was approved by the Research Ethics Committee of the Universidade Catolica de Pelotas under protocol number 2008/118. Additional information can be found in previously published papers (Duarte Faria et al., 2015; Jansen et al., 2011; Vieira et al., 2018).

3.2.2 Outcomes

The primary outcome of this study was illicit substance abuse/dependence, which was assessed using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (Henrique et al., 2004). The ASSIST is a self-reported questionnaire that has been validated for the Brazilian population (Henrique et al., 2004). Specifically, the ASSIST assesses an individual's current usage (past 3 months) of the following substances: tobacco, alcohol, cannabis, cocaine, inhalants, sedatives, hallucinogens, opioids and other drugs. Only the use of non-prescribed substances should be assessed. Cannabis, cocaine, inhalants, sedatives, hallucinogens, opioids, and other drugs were grouped together and included in the "illicit substances" variable. A cut-off score of 4 or greater was used as an indicator for abuse/dependence (or need for brief intervention to manage risky substance use) for all of the aforementioned substances, except for alcohol in which a cut-off score of 11 or greater was used, as recommended by the World Health Organization (Humeniuk and World Health Organization., 2010). The reliability of the instrument was good in the validation study (Cronbach's alpha of 0.80 to alcohol, 0.79 to cannabis and 0.81 to cocaine) (Henrique et al., 2004).

3.2.3 Predictors

After providing informed consent, each participant underwent a clinical interview that included the assessment of sociodemographic data (e.g., sex, age, current employment/study status, socioeconomic status), and psychopathology. Socioeconomic status was assessed with an instrument developed for the Brazilian population by the Associação Brasileira de Empresas de Pesquisa (ABEP, 2008). The Mini-International Neuropsychiatric Interview (MINI) (Amorim, 2000) was used to evaluate mood (current

major depressive episode and lifetime hypomanic or manic episode), anxiety disorders (panic disorder, agoraphobia, social phobia, and generalized anxiety disorder), OCD, PTSD, eating disorders (bulimia, anorexia), anti-social personality disorder, and suicide risk. This clinical interview was validated for the Brazilian population (Amorim, 2000), and showed great reliability, as the inter-rater and test-retest agreement was >0.75 for all diagnoses except current manic episode (0.35) (Amorim, 2000). Mental health treatment referrals were provided to any participants who were diagnosed with psychiatric conditions during the clinical interview. Quality of life was assessed using the 36-Item Short Form Health Survey (SF-36), a self-reported assessment validated for the Brazilian population, which consists of the following 8 domains: physical functioning (limitations on performing usual physical activities, including climbing flights of stairs, walking, etc), role physical (limitation of physical activity resulting from health problems), bodily pain (not only the intensity and discomfort caused by the pain but also the extent to which it interferes with usual activities), general health (general health perception), vitality (energy and fatigue levels), social functioning (limitation of social activities due to physical and/or emotional problems), role emotional (limitations due to emotional problems), and mental health (psychological distress and well-being) (Ciconelli et al., 1999). The greater the score in each domain, the better the quality of life of the individual in that domain. The reliability coefficients for the eight SF-36 domains ranged from 0.77 to 0.94, with an average value of 0.82, and the validity ranged from 0.51 to 0.85 (Ciconelli et al., 1999). The self-reporting questionnaire 20 (SRQ-20), an instrument validated for the Brazilian population, was used to evaluate mental health. The SRQ-20

has 20 questions which reflect various common mental disorders, such as anxiety and depression. This study analyzed the total SRQ-20 score, with higher scores indicating more mental health complaints (Gonçalves et al., 2008). The validation study found that the discriminant power of SRQ-20 for psychiatric screening was 0.9, and Cronbach's alpha was 0.86 (Gonçalves et al., 2008).

3.2.4 Statistical Analysis

The statistical analyses were conducted using the SPSS 21 and R 4.0.4. The sample characteristics were presented by absolute and relative frequencies. The sociodemographic characteristics between groups was compared using the chi squared test. For the machine learning component, elastic net was used to generate a regularized linear model (https://cran.r-project.org/web/packages/glmnet/index.html) (Zou and Hastie, 2005). The elastic net method linearly combines lasso and ridge regression regularizations, to generate models that can eliminate redundant variables while preserving low coefficients, leading to better generalization. The experiments followed a holdout testing protocol. Data was first separated between training (75%) and test (25%). The elastic net followed a grid search hyperparameter optimization using the caret package (https://cran.r-project.org/web/packages/caret/index.html) version 6.0-86 with α set to 0.2, 0.5, and 0.8 and λ set to 0.01, 0.1, and 0.2. From that, the best model was extracted and applied to the test data. Model training also involved a class imbalance correction by instance weighting. Each instance was weighted based on the frequency of the opposite class. Variables with missing data were removed from the analyses except for age. Variable importance was extracted based on the coefficient values of the final model.

A total of two models were generated following the aforementioned procedure: 1) T1 predictors for illicit substance abuse/dependence at T1, and 2) T1 predictors for illicit substance abuse/dependence at T2.

3.3 Results

This study included 1560 young adults. Table 1 shows the sociodemographic characteristics of the participants. The prevalence of illicit substance abuse/dependence at baseline (T1) was 11.7% (n = 182). For T1, the proportion of males was higher in individuals with current illicit substance abuse/dependence (55.5%) than in individuals without current illicit substance abuse/dependence (42%, p = 0.001). Furthermore, the proportion of individuals aged 21-24 was higher among those with current illicit substance abuse/dependence (56.9%) than in those without current illicit substance abuse or dependence (47.5%, p = 0.018) for T1 (Table 1).

At 5-years of follow-up (T2), we reassessed 1244 individuals, however, we excluded 5 individuals due to missing data in the substance abuse/dependence assessment, reaching a total sample size of 1239 individuals. The current prevalence of illicit substance abuse/dependence was 16.5% (n = 205). For T2, the proportion of males was higher among individuals with current illicit substance abuse/dependence (55.1%) than among individuals without current illicit substance abuse/dependence (39.4%, p < 0.001), the proportion of individuals who had a skin colour other than white was greater among individuals with current illicit substance abuse/dependence (34.5%) than among individuals without current illicit substance abuse/dependence (26.1%, p = 0.014), the proportion of individuals who were not currently studying at T1 was greater among

individuals with current illicit substance abuse/dependence (63.4%) compared to individuals without current illicit substance abuse/dependence (51.6%, $p = 0.002$). Finally, the proportion of lower socioeconomic status (D + E) at T1 was greater among individuals with current illicit substance abuse/dependence (24.9%) than among individuals without current illicit substance abuse/dependence (11.2%, $p < 0.001$).

Figure 1 shows the accuracy of the machine learning model. The model predicting illicit substance abuse/dependence at T1 showed an area under the receiver operating characteristics curve (AUC) of 0.83. The model's performance is also described by a balanced accuracy of 0.73, a sensitivity of 0.64, and a specificity of 0.82. Additionally, this model had a positive predictive value of 0.32 and a negative predictive value of 0.95. The most important variables to predict illicit substance abuse/dependence at T1 were alcohol abuse/dependence, tobacco abuse/dependence, being in a current major depressive episode, history of a lifetime manic episode, current suicide risk, and male sex (Figure 2). The model predicting illicit substance abuse/dependence at T2 showed an AUC of 0.79. The model's performance is also described by a balanced accuracy of 0.69, a sensitivity of 0.65, and a specificity of 0.74. The model had a positive predictive value of 0.33 and a negative predictive value of 0.91. The most important variables were tobacco abuse/dependence at T1, history of a lifetime manic episode at T1, male sex, alcohol abuse/dependence at T1 and current suicide risk at T1 (Figure 3). Finally, Figure 4 shows how the model is able to concentrate a large percentage of participants with substance abuse/dependence within the top predictions. For instance, 60% of participants with substance abuse/dependence in T1 were within the 20% highest T1 model

predictions. Similarly, about 47% of participants with substance abuse/dependence in T2 were within the 20% highest T2 model predictions.

3.4 Discussion

Our results showed that the model predicting illicit substance abuse/dependence at T1 had an AUC of 0.83, while the main predictors for this model were alcohol abuse/dependence, tobacco abuse/dependence, being in a current major depressive episode, history of a lifetime manic episode, current suicide risk, and male sex. The model predicting illicit substance abuse/dependence at T2 had an AUC of 0.79, while the main predictors for this model were tobacco abuse/dependence at T1, history of a lifetime manic episode at T1, male sex, alcohol abuse/dependence at T1, and current suicide risk at T1.

A recent systematic review found that some studies which applied machine learning models to predict substance use disorder (SUD) had a high predictive accuracy, however, other models demonstrated poor performance and there was a lack of robust, longitudinal studies (Barenholtz et al., 2020). Additionally, a prior machine learning study investigating predictors of SUD found about thirty strong predictors, primarily focused on behavioural characteristics, with an AUC of 0.74 for individuals between the ages of 10-12 years and an AUC of 0.86 for individuals aged 22 years (Jing et al., 2020). Swearing, poor behaviour while playing, and irritability were determined to be the most important predictors of SUD at ages 10 to 12 years (Jing et al., 2020). This prior study was limited in that it had a smaller sample size (n= 700) than our current study and included a non-probabilistic clinical sample. Notably, our present study which specifically aimed to find

sociodemographic and clinical predictors of illicit substance abuse/dependence in a large population-based sample had an AUC of 0.83 at T1 and of 0.79 at T2. Alcohol abuse/dependence, tobacco abuse/dependence, current major depressive episode, lifetime manic episode, sex, and current suicide risk were found to be the strongest predictors of illicit substance abuse/dependence in our present study. A previous longitudinal study showed that the use of non-illicit substances (e.g., tobacco and alcohol) among adolescents is a predictor of illicit and prescription drug abuse during young adulthood, which is consistent with our current findings (Griffin et al., 2019). These findings are especially important to be aware of since this indicates that finding appropriate interventions to prevent alcohol and tobacco use during adolescence or young adulthood may in turn prevent subsequent illicit substance use among young adults (Griffin et al., 2019). Another recent machine learning study that aimed to determine predictors of substance use (including alcohol, tobacco, cannabis, and inhalants) among a national sample of Mexican children between grades 5 to 6, reported that best friend illicit substance use, father illicit substance use and male sex had the strongest associations with substance initiation (Vázquez et al., 2020). Similarly, our present study also found male sex to be an important predictor of illicit substance abuse/dependence for a community sample of young adults.

Alarmingly, since young people between the ages of 10-24 years are still undergoing brain development, this makes them more vulnerable to both initiating substance use and to experiencing disruptions in cognitive or emotional development as a result of such substance use (Degenhardt et al., 2016; Kulak and Griswold, 2019). A

recent systematic review found strong evidence to suggest that substance use among young people is associated with deficits in brain structure, brain function, and cognition (Debenham et al., 2021). Thus, it is of utmost importance to determine characteristics that are significant predictors of illicit substance abuse/dependence among young adults to prevent the negative outcomes which are associated with early substance use. Interestingly, while the implementation of taxation, public bans, advertising restrictions, and a minimum legal age are useful in limiting alcohol consumption among young people, these measures are not relevant or feasible in the context of illicit substance use (Stockings et al., 2016). With regards to managing substance use among adolescents, prior findings suggest that interventions such as motivational interviewing, medication-assisted treatment, and school-/parent-based interventions are effective (Kulak and Griswold, 2019). Currently, there is a lack of research on interventions that are effective in preventing illicit substance use among young adults, indicating the importance of further investigating preventative measures that are suitable for this specific population (Stockings et al., 2016).

Our findings should be interpreted in light of some limitations. First, a screening test (ASSIST) was used to assess illicit substance abuse/dependence, instead of a structured clinical interview. Thus, future studies investigating predictors of illicit substance abuse/dependence among young adults should incorporate more robust procedures, such as structured clinical interviews, to assess clinical outcomes. Second, we grouped all the illicit substances together and we did not separate substance abuse from substance dependence due to limited sample size. Considering that the etiology and

development of substance abuse/dependence may vary across different substances, future studies should investigate the predictors for each illicit substance independently. Third, cannabis was included as an illicit substance because it is illicit in Brazil, however, it has been legalized in many countries (Nazif-Munoz et al., 2020; Steinberg et al., 2021; Wilkinson et al., 2016). Fourth, we can not claim that the predictors assessed at T1 are predictors for the development of illicit substance abuse/dependence at T2, because individuals who had reported illicit substance abuse/dependence were not excluded from this model. Fifth, social desirability bias is possible when assessing substance use, as indicated by Latkin et al., 2017, in a study showing that individuals with high levels of socially desirable responding report significantly lower frequency of recent drug use (Latkin et al., 2017). Finally, it is always important to consider that these findings may not be generalizable to other populations, due to the lack of an external dataset for testing, instead of using a holdout of the same sample. Despite these limitations, the present machine learning study was unique from previous studies that used similar approaches, since it determined several sociodemographic/clinical characteristics that were able to predict illicit substance abuse/dependence among young adults at a high accuracy. The sociodemographic/clinical predictors found in this present study, are more feasible to assess in clinical settings than the physiological/behavioural predictors that were the predominant focus of prior machine learning studies investigating similar topics. Other strengths of the present study include the use of sophisticated analytical strategies, the prospective cohort design, and the use of probabilistic sampling which ensured that our sample is representative of young adults from Pelotas, Brazil.

3.5 Conclusions

Importantly, the present study demonstrates that machine learning approaches can determine sociodemographic and clinical characteristics that predict illicit substance abuse/dependence among young adults. Machine learning techniques in the field of substance use have the potential to accurately predict diagnostic or prognostic outcomes (Barenholtz et al., 2020). These findings are especially promising from a clinical perspective, since they highlight the possibility of promptly detecting young adults that are at the highest risk of having illicit substance abuse/dependence, thus enabling the early implementation of interventions to prevent the associated adverse outcomes. Future studies should address current limitations of machine learning in the field of substance use, such as the lack of external datasets for testing and validation.

3.6 Authors Contributors

Dr. Ballester and Dr. Cardoso had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses, *Concept and design:* Dr. Cardoso, Dr. Ballester, Dr. Jansen, Mr. Montezano, Ms. Rakovski, and Dr. Souza, *Acquisition, analysis, or interpretation of data:* Dr. Cardoso, Mr. Montezano, Ms. Rakovski, Dr. Ballester, Dr. Jansen, Dr. Souza, Dr. Silva, Dr. Moreira, and Dr. Mondin, *Drafting of the manuscript:* Dr. Cardoso, Ms. Rakovski, Dr. Ballester, Dr. Jansen, and Dr. Souza, *Critical revision of the manuscript for important intellectual content:* Dr. De Boni, Dr. Kapczinski, and Dr. Frey, *Statistical analysis:* Dr. Cardoso and Dr. Ballester, *Supervision:* Dr. Cardoso, Dr. Frey and Dr. Kapczinski.

3.7 Declaration of Competing Interest

The authors declare no conflicts of interest.

3.8 Acknowledgements

This work was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (KJ, #422500/2016-0), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (RAS, #17/2551-0001433-2 and #19/2551-0000689-6), and Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (FK, Fundação de Amparo à Pesquisa do Estado de São Paulo [# 2014/50891-1] and Conselho Nacional de Desenvolvimento Científico e Tecnológico [# 465458/2014-9]). Dr. Cardoso acknowledges her postdoctoral fellowship from the Canadian Institutes of Health Research (CIHR).

3.9 References

ABEP — Associação Brasileira de Empresas de Pesquisa: Dados com base no Levantamento Sócio Econômico (IBOPE). Accessed May 2008 through the website: http://www.abep.org.br.

Amorim, P., 2000. Mini International Neuropsychiatric Interview (MINI): validação de entrevista breve para diagnóstico de transtornos mentais. Brazilian J. Psychiatr. 22, 106–115. https://doi.org/10.1590/S1516-44462000000300003.

Arria, A.M., Caldeira, K.M., Allen, H.K., Bugbee, B.A., Vincent, K.B., O'Grady, K.E., 2017. Prevalence and incidence of drug use among college students: an 8-year longitudinal analysis. Am. J. Drug Alcohol Abuse 43, 711–718. https://doi.org/10.1080/00952990.2017.1310219.

Barenholtz, E., Fitzgerald, N.D., Hahn, W.E., 2020. Machine-learning approaches to substance-abuse research: emerging trends and their implications. Curr. Opin. Psychiatr. 33, 334–342. https://doi.org/10.1097/YCO.0000000000000611.

Bastos, F.I., Vasconcellos, M.T.L., De Boni, R.B., Dos Reis, N.B., Coutinho, C.F., 2017. 3rd National Survey on Drug Use by the Brazilian Population.

Ciconelli, R.M., Ferraz, M.B., Santos, W., Meinão, I., Quaresma, M.R., 1999. Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36). Rev. Bras. Reumatol. 143–150.

de Matos, M.B., de Mola, C.L., Trettim, J.P., Jansen, K., da Silva, R.A., Souza, L.D.d.M., Ores, L. da C., Molina, M.L., Coelho, F.T., Pinheiro, R.T., Quevedo, L. de A., 2018. Psychoactive substance abuse and dependence and its association with anxiety disorders: a population-based study of young adults in Brazil. Rev. Bras.

Psiquiatr. 40, 349–353. https://doi.org/10.1590/1516-4446-2017-2258.

Debenham, J., Birrell, L., Champion, K., Lees, B., Yücel, M., Newton, N., 2021. Neuropsychological and neurophysiological predictors and consequences of cannabis and illicit substance use during neurodevelopment: a systematic review of longitudinal studies. Lancet. Child Adolesc. Heal. 5, 589–604. https://doi.org/ 10.1016/S2352-4642(21)00051-1.

Degenhardt, L., Bharat, C., Glantz, M.D., Sampson, N.A., Scott, K., Lim, C.C.W., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Andrade, L.H., Bromet, E.J., Bruffaerts, R., Bunting, B., de Girolamo, G., Gureje, O., Haro, J.M., Harris, M.G., He, Y., de Jonge, P., Karam, E.G., Karam, G.E., Kiejna, A., Lee, S., Lepine, J.P., Levinson, D., Makanjuola, V., Medina-Mora, M.E., Mneimneh, Z., Navarro-Mateu, F., Posada- Villa, J., Stein, D.J., Tachimori, H., Torres, Y., Zarkov, Z., Chatterji, S., Kessler, R.C., 2019. The epidemiology of drug use disorders cross-nationally: findings from the WHO's World Mental Health Surveys. Int. J. Drug Pol. 71, 103–112. https://doi.org/ 10.1016/J.DRUGPO.2019.03.002.

Degenhardt, L., Stockings, E., Patton, G., Hall, W.D., Lynskey, M., 2016. The increasing global health priority of substance use in young people. Lancet Psychiatr. 3, 251–264. https://doi.org/10.1016/S2215-0366(15)00508-8.

Duarte Faria, A., De Azevedo Cardoso, T., Campos Mondin, T., De Mattos Souza, L.D., Da Silva Magalhaes, P.V., Patrick Zeni, C., Da Silva, R.A., Kapczinski, F., Jansen, K., 2015. Biological rhythms in bipolar and depressive disorders: a community study with drug-naïve young adults. J. Affect. Disord. 186, 145–148.

https://doi.org/10.1016/J.JAD.2015.07.004.

Gonçalves, D.M., Stein, A.T., Kapczinski, F., 2008. Avaliação de desempenho do Self-Reporting Questionnaire como instrumento de rastreamento psiquiátrico: um estudo comparativo com o Structured Clinical Interview for DSM-IV-TR. Cad. Saude Publica 24, 380–390. https://doi.org/10.1590/S0102-311X2008000200017.

Griffin, K.W., Lowe, S.R., Botvin, C., Acevedo, B.P., 2019. Patterns of adolescent tobacco and alcohol use as predictors of illicit and prescription drug abuse in minority young adults. J. Prev. Interv. Community 47, 228. https://doi.org/10.1080/10852352.2019.1603672.

Henrique, I.F.S., De Micheli, D., Lacerda, R.B., Lacerda, de, de, L.A., Formigoni, M.L.O. de S, 2004. [Validation of the Brazilian version of alcohol, smoking and substance involvement screening test (ASSIST)]. Rev. Assoc. Med. Bras. 50, 199–206. https:// doi.org/10.1590/S0104-42302004000200039.

Humeniuk, R., World Health Organization, 2010. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) : Manual for Use in Primary Care 68.

IBGE — Instituto Brasileiro de Geografia e Estatistíca : Accessed May 2008 through the website: http://www.ibge.gov.br.

Jansen, K., Ores, L.D.C., Cardoso, T.D.A., Lima, R.D.C., Souza, L.D.D.M., Magalhães, P.V. D.S., Pinheiro, R.T., Da Silva, R.A., 2011. Prevalence of episodes of mania and hypomania and associated comorbidities among young adults. J. Affect. Disord. 130, 328–333. https://doi.org/10.1016/J.JAD.2010.10.007.

Jing, Y., Hu, Z., Fan, P., Xue, Y., Wang, L., Tarter, R.E., Kirisci, L., Wang, J., Vanyukov,

M., Xie, X.Q., 2020. Analysis of substance use and its outcomes by machine learning I. Childhood evaluation of liability to substance use disorder. Drug Alcohol Depend. 206 https://doi.org/10.1016/J.DRUGALCDEP.2019.107605.

Kulak, J.A., Griswold, K.S., 2019. Adolescent substance use and misuse: recognition and management. Am. Fam. Physician 99, 689–696.

Latkin, C.A., Edwards, C., Davey-Rothwell, M.A., Tobin, K.E., 2017. The relationship between social desirability bias and self-reports of health, substance use, and social network factors among urban substance users in Baltimore, Maryland. Addict. Beyond Behav. 73, 133. https://doi.org/10.1016/J.ADDBEH.2017.05.005.

Lipari, R.N., Park-Lee, E., 2019. Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health.

Nazif-Munoz, J.I., Oulhote, Y., Ouimet, M.C., 2020. The association between legalization of cannabis use and traffic deaths in Uruguay. Addiction 115, 1697–1706. https://doi.org/10.1111/ADD.14994.

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J.B., Jones, P., Kim, J.H., Kim, J.Y., Carvalho, A.F., Seeman, M.V., Correll, C.U., Fusar-Poli, P., 2021. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol. Psychiatr. https://doi.org/10.1038/S41380-021-01161-7.

Steinberg, S., Meng, Y., Kapanen, A.I., Reardon, J., Yuen, J., 2021. Impact of recreational

cannabis legalization on patient self-reporting of cannabis use at a pharmacist-led primary care clinic, 2003 J. Am. Pharmaceut. Assoc. 61, 813–818. https://doi.org/10.1016/J.JAPH.2021.06.023. e1.

Stockings, E., Hall, W.D., Lynskey, M., Morley, K.I., Reavley, N., Strang, J., Patton, G., Degenhardt, L., 2016. Prevention, early intervention, harm reduction, and treatment of substance use in young people. Lancet Psychiatr. 3, 280–296. https://doi.org/10.1016/S2215-0366(16)00002-X.

UNODC World Drug Report, 2020. Global drug use rising; while COVID-19 has far reaching impact on global drug markets [WWW Document], n.d. URL. https://www.unodc.org/unodc/press/releases/2020/June/media-advisory—global-launch-of- the-2020-world-drug-report.html. accessed 6.27.21.

Vázquez, A.L., Domenech Rodríguez, M.M., Barrett, T.S., Schwartz, S., Amador Buenabad, N.G., Bustos Gamiño, M.N., Gutiérrez López, M. de L., Villatoro Velázquez, J.A., 2020. Innovative identification of substance use predictors: machine learning in a national sample of Mexican children. Prev. Sci. 212 (21), 171–181. https://doi.org/10.1007/S11121-020-01089-4, 2020.

Vieira, D.C., de Azevedo Cardoso, T., Mondin, T.C., Jansen, K., da Silva, R.A., de Mattos Souza, L.D., Kapczinski, F., Magalhães, P.V.S., 2018. Mood disorders and prospective suicidality in young adults: a population-based cohort study. Acta Psychiatr. Scand. 137, 109–115. https://doi.org/10.1111/ACPS.12846.

Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E.,

Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., Burstein, R., Murray, C.J.L., Vos, T., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382, 1575–1586. https://doi.org/10.1016/S0140-6736(13)61611-6.

Wilkinson, S.T., Yarnell, S., Radhakrishnan, R., Ball, S.A., D'souza, D.C., 2016. Marijuana legalization: impact on physicians and public health. Annu. Rev. Med. 67, 453–466. https://doi.org/10.1146/ANNUREV-MED-050214-013454.

World Drug Report, 2020 [WWW Document], 2020. United Nations. URL. https://wdr.unodc.org/wdr2020/en/drug-use-health.html. accessed 6.23.21.

Zou, H., Hastie, T., 2005. Regularization and variable selection via the elastic net. J. R. Stat. Soc. Ser. B Stat. Methodol. 67, 301–320. https://doi.org/10.1111/J.1467-9868.2005.00503.X.

3.10 Figures and Tables

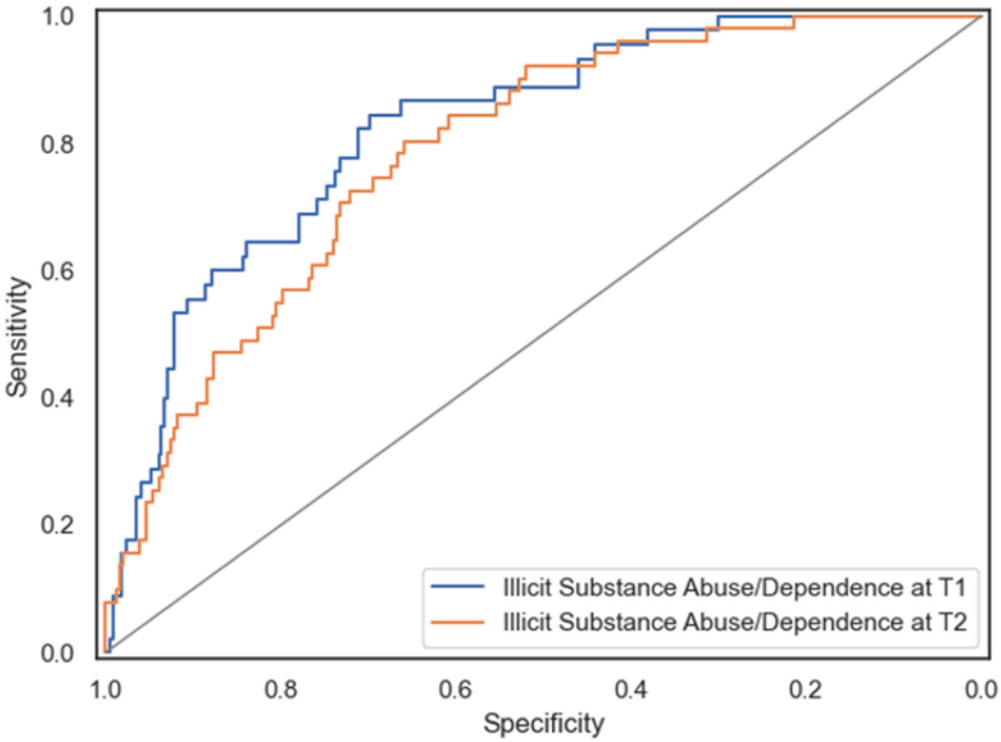


Figure 1. Receiver operating characteristic (ROC) curve for both models. The model for T1 has an area under the ROC curve (AUC) of 0.83 and the model for T2 has an AUC of 0.79.

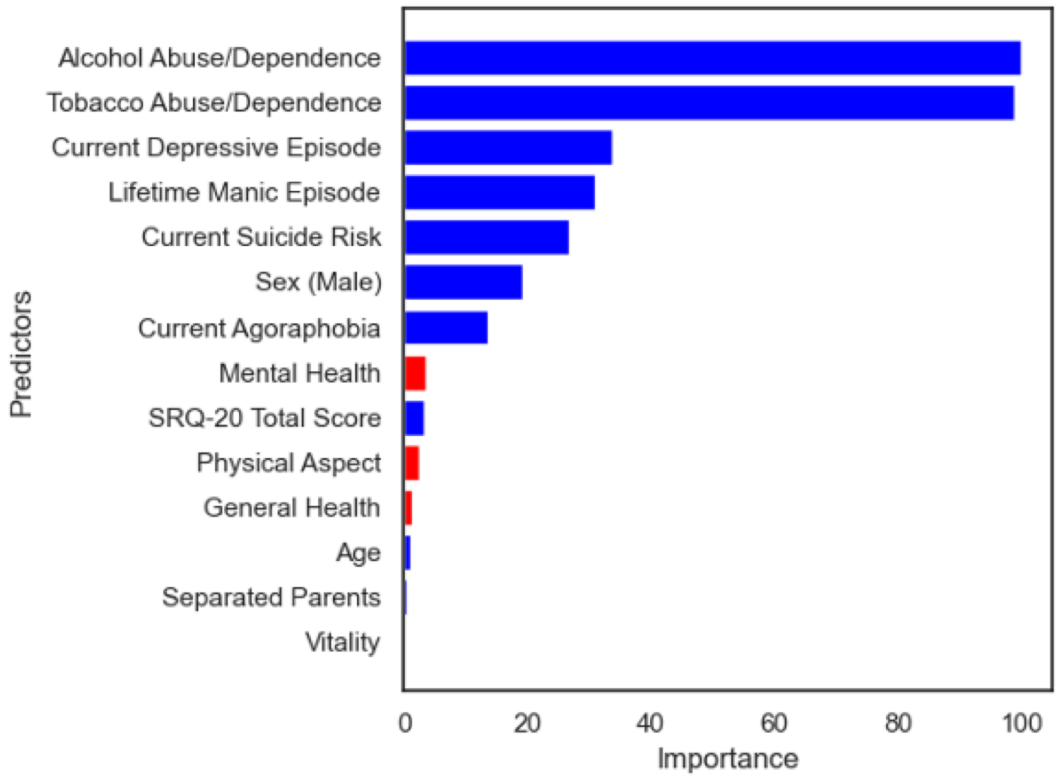


Figure 2. Variable importance for predictors of Illicit Substance Abuse/Dependence at T1. Blue bars represent positive coefficients and red bars are negative coefficients. Coefficients are scaled based on the highest coefficient (Alcohol Abuse/Dependence). Variables included in this figure were the ones with higher than zero absolute value.

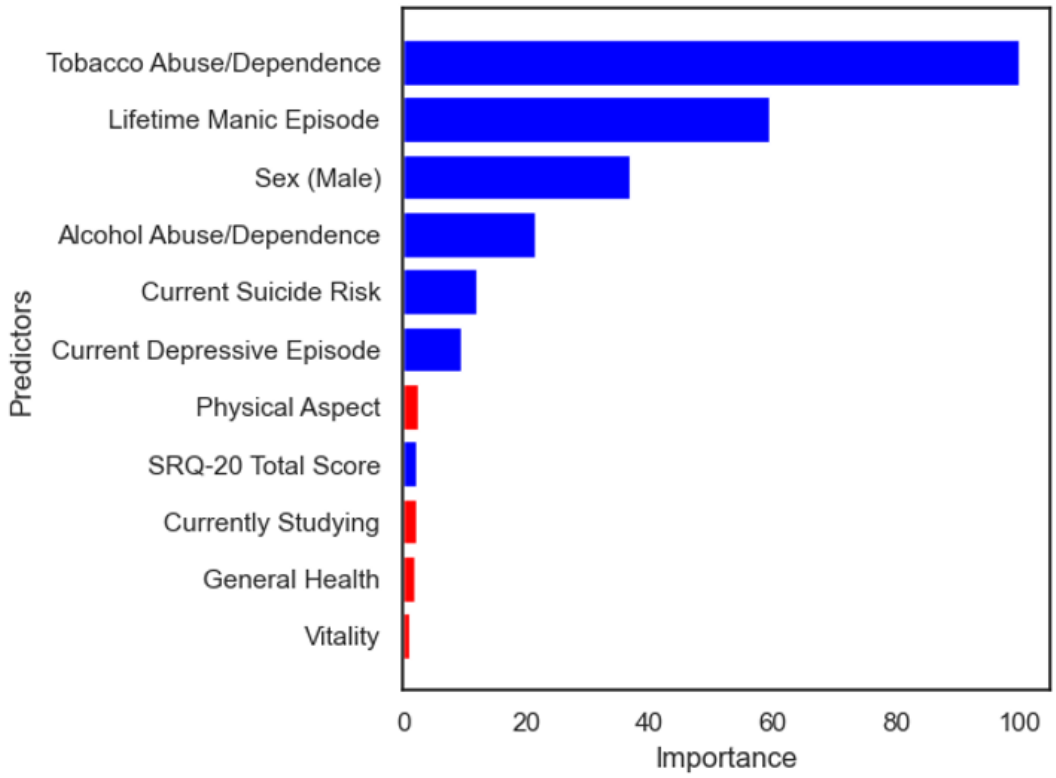


Figure 3. Variable importance for predictors of Illicit Substance Abuse/Dependence at T2. Blue bars represent positive coefficients and red bars are negative coefficients. Coefficients are scaled based on the highest coefficient (Tobacco Abuse/Dependence). Variables included in this figure were the ones with higher than zero absolute value.

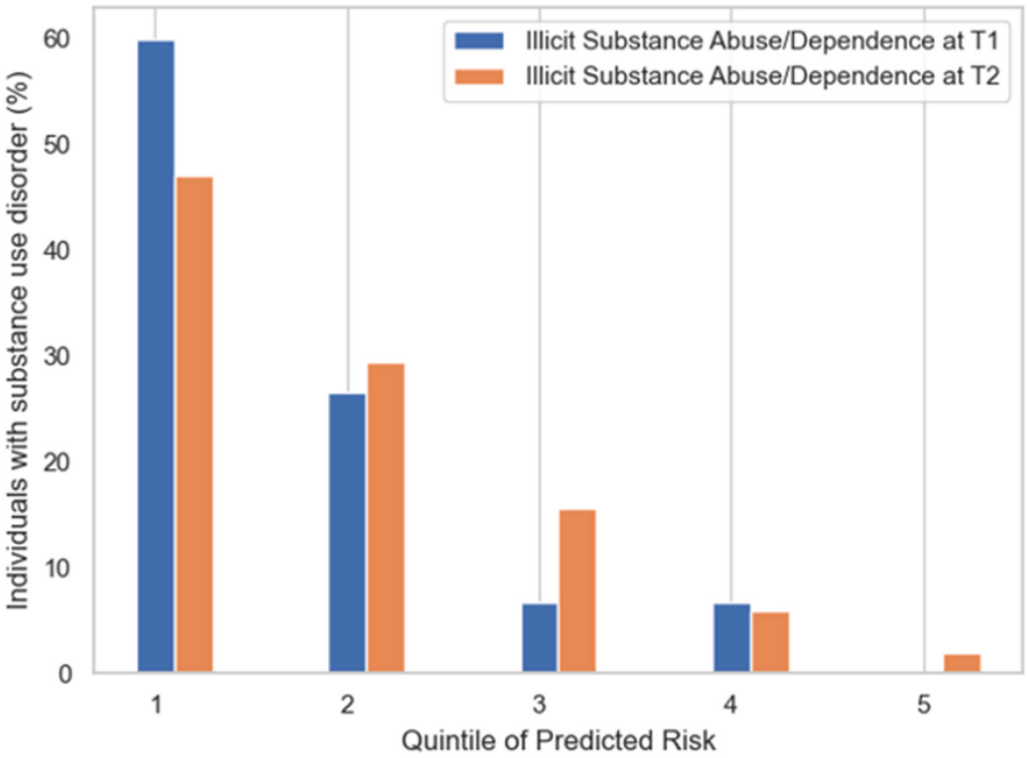


Figure 4. Quintile of predicted risk for T1 and T2 models. Model predictions are sorted split into 5 groups (0-20% highest, 20-40% highest, and so on). Each vertical bar represents the percentage of participants with the positive outcome within each of the 5 groups.

Table 1: Sociodemographic characteristics at T1 between individuals with and without illicit substance abuse/dependence at T1 and T2.

Variables at T1	Illicit substance abuse/dependence (T1)			Illicit substance abuse/dependence (T2)		
	No n (%)/	Yes n (%)/	p-value	No n (%)/	Yes n (%)/	p-value
Sex			0.001			<0.001
Female	799 (58.0)	81 (44.5)		627 (60.6)	92 (44.9)	
Male	579 (42.0)	101 (55.5)		407 (39.4)	113 (55.1)	
Age			0.018			0.655
18–20 years	717 (52.5)	78 (43.1)		543 (52.9)	105 (51.2)	
21–24 years	650 (47.5)	103 (56.9)		483 (47.1)	100 (48.8)	
Skin colour			0.989			0.014
White	1011 (73.5)	133 (73.5)		763 (73.9)	133 (65.5)	
Not white	364 (26.5)	48 (26.5)		269 (26.1)	70 (34.5)	
Currently studying			0.293			0.002
No	738 (53.6)	105 (57.7)		534 (51.6)	130 (63.4)	
Yes	640 (46.4)	77 (42.3)		500 (48.4)	75 (36.6)	
Socioeconomic status (ABEP)			0.095			<0.001
A + B (upper)	518 (37.6)	65 (35.7)		398 (38.5)	66 (32.2)	
C	670 (48.6)	81 (44.5)		520 (50.3)	88 (42.9)	
D + E (lower)	190 (13.8)	36 (19.8)		116 (11.2)	51 (24.9)	
Total	1378 (88.3)	182 (11.7)		1034 (83.5)	205 (16.5)	

Chapter 4: Childhood maltreatment as a predictor of substance use/misuse among youth: A systematic review and meta-analysis

Coral Rakovski[1], Mikayla Lalli[2], Jessica Gu[3], Madison Hobson[4], Bianca Wollenhaupt-Aguiar[5,6], Luciano Minuzzi[1,5,6], Flavio Kapczinski[1,7], Taiane de Azevedo Cardoso[8,#], Benicio N. Frey[1,5,6*,#]

1. Neuroscience Graduate Program, McMaster University, Hamilton, ON, Canada
2. Department of Kinesiology, McMaster University, Hamilton, ON, Canada
3. Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada
4. Honours Integrated Science Program, School of Interdisciplinary Science, McMaster University, Hamilton, ON, Canada
5. Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada
6. Mood Disorders Treatment and Research Centre and Women's Health Concerns Clinic, St. Joseph's Healthcare, Hamilton, Ontario, Canada
7. Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
8. The Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Deakin University, Geelong, Australia

[#]Shared senior co-authorship

This chapter in its entirety has been ***published*** in **Neuroscience and Biobehavioural Reviews.** The final accepted manuscript version of this article is presented within this thesis.

Rakovski, C., Lalli, M., Gu, J., Hobson, M., Wollenhaupt-Aguiar, B., Minuzzi, L., Kapczinski, F., de Azevedo Cardoso, T. and Frey, B.N., 2024. Childhood maltreatment as a predictor of substance use/misuse among youth: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, p.105873. DOI: https://doi.org/10.1016/j.neubiorev.2024.105873

Abstract

This systematic review and meta-analysis aimed to comprehensively describe whether experiencing a variety of childhood maltreatment types predicts a variety of substance use/misuse types among youth, beyond the narrow scope covered in previous systematic reviews on similar topics. A literature search was conducted in June, 2022 using PubMed, PsycInfo, and Embase. 58 studies (total participant n=170,749) were included. These studies were primarily organized by substance type outcomes including alcohol (n=43), cannabis (n=25), unspecified substances (n=25), and other specific substances (n=10). Results were further stratified by maltreatment type. For specific maltreatment and substance type combinations, the majority of studies indicated that childhood maltreatment was a significant predictor of substance use/misuse in youth. Of the 10 meta-analyses we conducted, significant associations were found for the majority (9/10) of maltreatment and substance type combinations. For instance, unspecified childhood maltreatment increased the probability of youth alcohol use by about four times, which was the highest relative risk found. In conclusion, this study shows that childhood maltreatment is a predictor of youth substance use/misuse.

Keywords: Substance use; Childhood maltreatment; Youth; Systematic review; Meta-analysis

4.1 Introduction

Youth between the ages of 16 to 24 years, often referred to as transitional age youth, experience a challenging and vulnerable time in their lives in which substance use tends to begin and reach its peak (Bukstein, 2017; Kaligis et al., 2021; Köck et al., 2022). Globally, the 12-month prevalence of illicit drug use disorders from 1990 to 2019 was the highest among individuals between the ages of 20 to 24 years at about 2.0% in comparison to 0.7% for all ages (IHME, 2019). In the United States, the 12-month prevalence of illicit drug use disorders among youth has increased over the years from a prevalence of 5.1% in 1990 to 5.3% in 2019 for those between the ages of 15 to 19 years and from 6.7% in 1990 to 9.7% in 2019 for those between the ages 20 to 24 years (IHME, 2019). Additionally, a nationally representative study of individuals from 18 to 90 years in the United States found that the 12-month prevalence of alcohol use disorder was at its highest in men at the age of 25 years (32%) and in women at the age of 22 years (24%) (Vasilenko et al., 2017), indicating that the peak prevalence for alcohol use disorder is in young adulthood for men and women. A robust meta-analysis also indicated that the median age at onset for cannabis use disorder is 22 years, while the median age at onset for alcohol use disorder is 27 years (Solmi et al., 2022).

Prior studies have found significant associations between substance use/misuse and subsequent adverse outcomes including psychiatric disorders such as bipolar disorder (Lalli et al., 2021), suicidality (Rioux et al., 2021), as well as deficits in brain function, structure and cognition (Debenham et al., 2021; Lees et al., 2020; Squeglia et al., 2009). Given the developmental significance of this transitional stage and the associated negative effects, substance use/misuse among youth poses an important global public health concern

(Degenhardt et al., 2016). Thus, it is of utmost importance for strategies focused on preventing or minimizing youth substance use/misuse to be developed. The identification of significant predictors of youth substance use/misuse, such as childhood maltreatment types, is important to facilitate the early detection and targeted implementation of preventive or intervention-based measures among youth at the highest risk of substance use/misuse and its associated adverse effects.

Childhood maltreatment encompassing physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect impacts the lives of children across the world with estimated global self-reported prevalences ranging from approximately 13% for sexual abuse up to 36% for emotional abuse (Bernstein et al., 2003; Stoltenborgh et al., 2015; Teicher et al., 2021). A recent study found evidence indicating that childhood trauma as well as specific types of maltreatment were associated with structural brain changes in youth, such as reduced amygdala volumes in particular subregions, and that these brain changes may mediate symptoms of anxiety and depression (Nogovitsyn et al., 2022). Furthermore, childhood maltreatment is associated with psychiatric conditions including depression, anxiety, schizophrenia/schizoaffective disorder, bipolar disorder, attention-deficit/hyperactivity disorder, suicidality, borderline personality disorder, and substance misuse (Angelakis et al., 2019; Baldwin et al., 2023; Halpern et al., 2018; Langevin et al., 2023; Porter et al., 2020; Struck et al., 2020). Notably, a meta-analysis found that there were higher prevalence rates of physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect among individuals with substance use disorders in comparison to individuals from the general population (Zhang et al., 2020).

Two recent systematic reviews with a focus on childhood maltreatment as a predictor of substance use/misuse within youth populations have been conducted (De la Peña-Arteaga et al., 2021; Martínez-Mota et al., 2020). The first of which found evidence to suggest that physical and sexual abuse may increase the risk of cannabis use among adolescents (De la Peña-Arteaga et al., 2021). Similarly, the other systematic review found that physical and sexual abuse increased the risk of adolescent cannabis abuse/dependence (Martínez-Mota et al., 2020). Both of these prior systematic reviews are limited by a narrow focus of maltreatment types (predominantly physical forms of maltreatment including just physical and sexual abuse), as well as a narrow focus on cannabis use/misuse (De la Peña-Arteaga et al., 2021; Martínez-Mota et al., 2020). Therefore, the aim of this current systematic review and meta-analysis is to comprehensively investigate whether experiencing childhood maltreatment (including physical and non-physical maltreatment types) is a predictor of substance use/misuse (including alcohol, cannabis, and other illicit drugs) among youth aged 24 years or younger.

4.2 Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Arya et al., 2021; Page et al., 2021), and it has been registered on PROSPERO (ID: CRD42022360105).

4.2.1 Information sources

A literature search with no year or language restrictions was conducted on June 30, 2022 using the following databases: PubMed, PsycInfo, and Embase. We searched for a combination of the following search terms in each of the three databases: [("childhood

trauma" OR "child abuse" OR "adverse childhood events" OR "childhood maltreatment" OR “sexual abuse” OR “emotional abuse” OR “physical abuse” OR “emotional neglect” OR “physical neglect”) AND ("alcohol use" OR "alcohol dependence" OR "substance use" OR "drug use" OR "illicit substance" OR "substance abuse" OR "drug abuse" OR "drug addiction" OR "substance addiction" OR "alcohol" OR "cannabis" OR "marijuana" OR "cocaine" OR "stimulant" OR "methamphetamine" OR "opioid") AND ("youth" OR "young adults" OR "teens" OR "teenager" OR "children" OR "adolescents" OR "early adulthood")]. The search yielded 9057 titles: (PubMed = 2398, PsycInfo = 2848, and Embase = 3811), with 5490 articles remaining after duplicate removal (Fig. 1) (Page et al., 2021).

4.2.2 Eligibility criteria

We determined our eligibility criteria according to the following PICOS:

Population: Youth aged 24 years or younger.

Intervention/Exposure: Childhood maltreatment (including physical abuse or victimization or violence, sexual abuse or victimization or violence, emotional/psychological/verbal abuse or victimization or violence, and/or neglect).

Comparison: Youth without childhood maltreatment.

Outcome: Substance use/misuse (including the use, abuse, or dependence of alcohol and various illicit substances) which we will refer to as the substance use/misuse outcome throughout this paper.

Study design: Observational studies (cross-sectional and longitudinal).

Thus, to determine whether an article was relevant to our study, we used the following inclusion criteria: (1) the study must have presented original data (including cross-sectional and longitudinal studies); (2) the study must have included individuals aged 24 years or younger; (3) the study must have assessed childhood maltreatment as a dichotomous or categorical or continuous variable (e.g., scores from the Childhood Trauma Questionnaire in which childhood maltreatment was considered as a continuous variable or specific cut-off points used from the Childhood Trauma Questionnaire in which childhood maltreatment was considered as a dichotomous variable, etc.); (4) the study must have assessed substance use/misuse (including alcohol, cannabis, and/or illicit drugs); and (5) the study must have assessed the relationship between childhood maltreatment as the exposure and substance use/misuse as a dichotomous or categorical outcome for one of the primary aims. The exclusion criteria were: (1) reviews and meta-analyses; (2) case reports or case series; (3) publication types other than original peer-reviewed publications (e.g., commentaries, letters, posters, and conference abstracts); (4) clinical trials or randomized controlled trials, qualitative studies, or studies that did not investigate the relationship between childhood maltreatment as the exposure and substance use/misuse as an outcome (e.g., studies that were investigating whether substance use increased the probability of having a history of maltreatment, or studies that were testing the correlation between the total childhood maltreatment score and the total number of alcoholic drinks [or severity of substance use according to a determined scale]); and (5) articles that were not available in English, Spanish, or Portuguese.

4.2.3 Selection process

All the studies retrieved from the literature search were uploaded to the Rayyan platform (Ouzzani et al., 2016). Thus, duplicates that were automatically detected by the software, were manually revised by a rater (CR), and deleted if the duplication was confirmed. Next, the articles were assessed by two blinded raters (CR and ML) who determined whether each study met the inclusion criteria. The two raters assessed the articles independently using the same platform (Ouzzani et al., 2016), and any conflicts were resolved by consensus among three authors (CR, ML, and TAC). A fourth author (BW) also assisted with resolving some of the conflicts, in the absence of TAC. The screening process was divided into two subsequent stages: (1) the articles were screened by title and abstract, and (2) the articles were screened by the full text. All articles not fulfilling the inclusion criteria were excluded. Reasons for the exclusion of the full text articles that did not meet the inclusion criteria are shown in Fig. 1.

4.2.4 Data extraction

Four researchers (CR, ML, JG, and MH) actively participated in the data extraction process using an Excel spreadsheet (Microsoft 365). Prior to beginning the data extraction process, the spreadsheet was created by one researcher (CR) and reviewed by the other two researchers (BW and TAC) to guarantee that all the relevant data was extracted. The following data was extracted for each included article: authorship, publication year, the country/countries where the study was conducted, study design, sample characteristics, study setting, maltreatment types and assessments, substance types and assessments, numeric results, and main results regarding whether there was a significant association between childhood maltreatment as the exposure and substance use/misuse as the outcome.

At the end of the data extraction, one researcher (CR) was responsible for reviewing the spreadsheet to confirm the completeness of the data extracted.

4.2.5 Data synthesis

Considering that there was high heterogeneity among the studies included, based on the different types of childhood maltreatment and substances assessed, the data synthesis was stratified by the type of substance assessed and by the type of maltreatment assessed. Thus, the results are organized to describe the number of studies showing a significant association between a specific type of maltreatment and a specific type of substance use/misuse out of the total number of different studies evaluating this specific association. When categorizing the main results for each study as "yes" or "no" according to whether there was a significant association between childhood maltreatment as the exposure and substance use/misuse as the outcome, the following criteria were followed: (1) in cases where the substance outcome or maltreatment exposure were assessed at multiple timepoints or if they were assessed as both lifetime and current, we considered the main result as "yes" if there was a significant association found at a minimum of one timepoint or for either lifetime, current, or both; (2) in cases where multiple types of analyses (e.g., unadjusted and adjusted) were conducted, the main result was considered as "yes" or "no" based on the results of the most sophisticated analysis conducted (e.g., based on the adjusted analysis if available or based on the unadjusted analysis if no adjusted analysis was conducted); and (3) in cases where there were multiple different outcomes related to a specific type of substance (e.g., alcohol use, binge drinking, alcohol intoxication, etc.) or multiple related exposure types (e.g., any maltreatment, neglect/emotional abuse, physical abuse/neglect/emotional abuse; etc.) the

main result was considered as “yes” if there was a significant association between childhood maltreatment and substance use/misuse for any of the related exposure or outcome measures.

4.2.6 Meta-analyses

Meta-analyses were performed by grouping data from studies that investigated the same or similar maltreatment type exposure with the same or similar substance type outcome. Studies were considered eligible for inclusion in the meta-analysis if all the necessary raw data values were available in the published paper. The following raw data values for each relevant study were collected: (1) the number of individuals with substance use/misuse with childhood maltreatment; (2) the total number of individuals with childhood maltreatment, irrespective of substance use/misuse; (3) the number of individuals with substance use/misuse without childhood maltreatment; and (4) the total number of individuals without childhood maltreatment, irrespective of substance use/misuse. Meta-analyses for each maltreatment type exposure and substance type outcome combination were performed only if all the raw data values were available for at least two different studies investigating the association between the same maltreatment type exposure and substance type outcome. The meta-analyses were conducted in the R Software (version 4.2.1), using the 'meta' package (version 5.5-0). The Mantel-Haenszel method was used to calculate the pooled relative risk (RR) and 95% confidence interval (CI) adopting a random effects model. We reported RR as our measure of effect instead of odds ratio (OR), because OR tends to overestimate the effect size when the outcome is not rare (Higgins et al., 2023) and our outcome is not a rare event (Filho et al., 2012; Hammond et al., 2021). The random effects model was chosen

given the heterogeneity of sample characteristics and types of assessments used to evaluate the exposure (childhood maltreatment) and outcomes (substance use/misuse) in the included studies, as recommended by Field and Gillett (2010). Heterogeneity was tested using the I^2 statistic and the Cochran's Q statistic.

4.3 Results

4.3.1 Characteristics of included studies

58 different studies with a grand total of 170,749 participants were included in this systematic review (Fig. 1). A summary of each article is provided in Table 1 consisting of all relevant data that was extracted for each included study. The publication dates ranged from 1987 (Burgess et al., 1987; Dembo et al., 1987) to 2022 (Grummitt et al., 2022; Valério et al., 2022). The studies were conducted in the following countries: the United States (n = 32), Canada (n = 4), Australia (n = 4), China (n = 2), France (n = 2), Taiwan (n = 2), the United Kingdom (n = 1), Norway (n = 1), Uganda (n = 1), Brazil (n = 1), Denmark (n = 1), Peru (n = 1), New Zealand (n = 1), Bosnia and Herzegovina (n = 1), Namibia (n = 1), Swaziland (n = 1), Zambia (n = 1), Zimbabwe (n = 1), El Salvador (n = 1), Honduras (n = 1), Turkey (n = 1), and Hungary (n = 1). The findings of this systematic review are organized by the types of substances that were investigated including alcohol (n = 43), cannabis (n = 25), unspecified substances [two or more substance types grouped together or no specification of the type of substance investigated] (n = 25), and other specific substance type [other than alcohol or cannabis] (n = 10).

4.3.2 Alcohol

There were 43 studies that assessed use/misuse of alcohol as the outcome (e.g., alcohol use, alcohol abuse or dependence or disorder, binge drinking, harmful or high-risk or problem drinking, drunkenness or alcohol intoxication, etc.). Sexual abuse was the most investigated maltreatment type, with just over half of the studies indicating a significant association between sexual abuse and alcohol use/misuse. Unspecified neglect was the least investigated maltreatment type, with the majority of studies indicating no association between unspecified neglect and alcohol use/misuse.

4.3.2.1 Unspecified childhood maltreatment as a predictor of alcohol use/misuse

Ten studies investigated the association between unspecified childhood maltreatment (two or more maltreatment types grouped together or no specification of the type of maltreatment investigated) and alcohol use/misuse. All ten studies (10/10, 100%) found a significant association between unspecified childhood maltreatment and alcohol use/misuse (Balázs et al., 2017; Berenson et al., 1992; Chau et al., 2019; Cornelius et al., 2016; Cronin et al., 2016; Folk et al., 2021; Kaufman et al., 2007; Martin et al., 1999; Mills et al., 2014; Shin et al., 2009). A meta-analysis was conducted with three of these studies that investigated the association between unspecified childhood maltreatment and alcohol use (Cronin et al., 2016; Kaufman et al., 2007; Shin et al., 2009). The meta-analysis was significant, indicating that individuals who experienced unspecified childhood maltreatment had four times greater probability to use alcohol in comparison to individuals that did not experience unspecified childhood maltreatment (RR: 4.10 [95% CI: 1.08 - 15.58], p = 0.04) (Fig. 2A).

4.3.2.2 Physical abuse as a predictor of alcohol use/misuse

There were 24 studies that investigated the association between physical abuse (or physical punishment/maltreatment or physical violence or physical assault) and alcohol use/misuse. The majority of these studies (15/24, 63%) found a significant association between physical abuse and alcohol use/misuse (Balázs et al., 2017; Fergusson & Lynskey, 1997; Grummitt et al., 2022; Kaplan et al., 1998; Kappel et al., 2021; Kilpatrick et al., 2000; Lo & Cheng, 2007; Martin et al., 1999; Perkins & Jones, 2004; Ramos-Olazagasti et al., 2017; Ramos de Oliveira & Jeong, 2021; Riggs et al., 1990; Shin et al., 2009; Valério et al., 2022; Yen et al., 2008). The remaining 9/24 of these studies found no association between physical abuse and alcohol use/misuse (Baron, 1999; Berenson et al., 1992; Fusco, 2021; Houtepen et al., 2020; Mills et al., 2014; Musa et al., 2018; Thompson et al., 2015; Tyler et al., 2013; Vaughn et al., 2007). A meta-analysis was conducted with four of these studies that investigated the association between physical abuse and alcohol use/misuse (Fergusson & Lynskey, 1997; Kaplan et al., 1998; Perkins & Jones, 2004; Yen et al., 2008). The meta-analysis was significant, indicating that individuals who experienced physical abuse had two times greater probability to use/misuse alcohol in comparison to individuals that did not experience physical abuse (RR: 2.02 [95% CI: 1.38 - 2.98], $p < 0.01$) (Fig. 2B).

4.3.2.3 Sexual abuse as a predictor of alcohol use/misuse

There were 33 studies that investigated the association between sexual abuse (or sexual violence or sexual assault) and alcohol use/misuse. Eighteen (18/33, 55%) of these studies found a significant association between sexual abuse and alcohol use/misuse (Balázs et al., 2017; Berenson et al., 1992; Brown et al., 2009; Burgess et al., 1987; Chau et al., 2019; Cronin et al., 2016; Fusco, 2021; Grummitt et al., 2022; Hussey & Singer, 1993; Kilpatrick

et al., 2000; Lin et al., 2011; Martin et al., 1999; Ramos-Olazagasti et al., 2017; Ramos de Oliveira & Jeong, 2021; Rotheram-Borus et al., 1996; Shin et al., 2009; Solakoglu et al., 2018; Tossone et al., 2018). No association between sexual abuse and alcohol use/misuse was found by the remaining 15/33 studies (Baron, 1999; Burgess et al., 1987; Goodkind et al., 2006; Hébert et al., 2021; Houtepen et al., 2020; Kappel et al., 2021; Lo & Cheng, 2007; Mills et al., 2014; Musa et al., 2018; Pedersen & Skrondal, 1996; Riggs et al., 1990; Rosario et al., 2004; Tyler et al., 2013; Valério et al., 2022; Vaughn et al., 2007). A meta-analysis was conducted with three of these studies that investigated the association between sexual abuse and alcohol use (Cronin et al., 2016; Goodkind et al., 2006; Rotheram-Borus et al., 1996). The meta-analysis was significant, indicating that individuals who experienced sexual abuse had nearly three times greater probability to use alcohol in comparison to individuals that did not experience sexual abuse (RR: 2.82 [95% CI: 1.28 - 6.26], $p = 0.01$) (Fig. 2C).

4.3.2.4 Emotional abuse as a predictor of alcohol use/misuse

Eleven studies investigated the association between emotional abuse (or emotional violence) and alcohol use/misuse. Six (6/11, 55%) of these studies found no association between emotional abuse and alcohol use/misuse (Grummitt et al., 2022; Houtepen et al., 2020; Kappel et al., 2021; Kenny & Schreiner, 2009; Musa et al., 2018; Ramos de Oliveira & Jeong, 2021). The remaining 5/11 studies found a significant association between emotional abuse and alcohol use/misuse (Afifi et al., 2020; Cronin et al., 2016; Fusco, 2021; Ramos-Olazagasti et al., 2017; Valério et al., 2022).

4.3.2.5 Unspecified neglect as a predictor of alcohol use/misuse

Four studies investigated the association between unspecified neglect (two or more types of neglect grouped together or no specification of the type of neglect) and alcohol use/misuse. Most of the studies (3/4, 75%) found no association between unspecified neglect and alcohol use/misuse (Folk et al., 2021; Fusco, 2021; Grummitt et al., 2022). The remaining study found a significant association between unspecified neglect and alcohol use/misuse (Shin et al., 2009).

4.3.2.6 Emotional neglect as a predictor of alcohol use/misuse

Five studies investigated the association between emotional neglect and alcohol use/misuse. The majority of the studies (3/5, 60%) found no association between emotional neglect and alcohol use/misuse (Grummitt et al., 2022; Houtepen et al., 2020; Kenny & Schreiner, 2009). The remaining two studies found a significant association between emotional neglect and alcohol use/misuse (Afifi et al., 2020; Musa et al., 2018).

4.3.2.7 Physical neglect as a predictor of alcohol use/misuse

Six studies investigated the association between physical neglect and alcohol use/misuse. All six studies (6/6, 100%) found no association between physical neglect and alcohol use/misuse (Grummitt et al., 2022; Kenny & Schreiner, 2009; Musa et al., 2018; Thompson et al., 2015; Valério et al., 2022; Vaughn et al., 2007).

4.3.3 Cannabis

There were 25 studies that assessed use/misuse of cannabis as the outcome (e.g., cannabis use, cannabis abuse or dependence, frequent cannabis use, etc.). Sexual abuse was the most investigated maltreatment type, with majority of the studies indicating no association between sexual abuse and cannabis use/misuse. Emotional neglect and physical

neglect were the least investigated maltreatment types with only one study for each, indicating the importance of conducting more studies regarding the association between physical neglect as well as emotional neglect with cannabis use/misuse.

4.3.3.1 Unspecified childhood maltreatment as a predictor of cannabis use/misuse

Six studies investigated the association between unspecified childhood maltreatment and cannabis use/misuse. The findings are inconclusive overall since half of the studies found a significant association between unspecified childhood maltreatment and cannabis use/misuse (Chau et al., 2019; Mills et al., 2017; Rogosch et al., 2010), while the other half found no association (Folk et al., 2021; Perez, 2000; Schneiderman et al., 2016). A meta-analysis was conducted with two of these studies that investigated the association between unspecified childhood maltreatment and cannabis use (Mills et al., 2017; Perez, 2000). The meta-analysis was significant, indicating that individuals who experienced unspecified childhood maltreatment had 1.3 times greater probability to use cannabis in comparison to individuals that did not experience unspecified childhood maltreatment (RR: 1.32 [95% CI: 1.19 - 1.47], $p < 0.01$) (Fig. 2D).

4.3.3.2 Physical abuse as a predictor of cannabis use/misuse

Ten studies investigated the association between physical abuse and cannabis use/misuse. Most studies (6/10, 60%) found a significant association between physical abuse and cannabis use/misuse (Al-Kassab-córdova et al., 2021; Baiden et al., 2014; Fusco, 2021; Kilpatrick et al., 2000; Lo & Cheng, 2007; Perez, 2000). The remaining 4/10 studies found no association between physical abuse and cannabis use/misuse (Baron, 1999; Fergusson & Lynskey, 1997; Tyler et al., 2013; Vaughn et al., 2007). A meta-analysis was conducted with four of these studies that investigated the association between physical

abuse and cannabis use/misuse (Al-Kassab-córdova et al., 2021; Baiden et al., 2014; Fergusson & Lynskey, 1997; Perez, 2000). The meta-analysis was significant, indicating that individuals who experienced physical abuse had 1.3 times greater probability to use/misuse cannabis in comparison to individuals that did not experience physical abuse (RR: 1.32 [95% CI: 1.18 - 1.48], $p < 0.01$) (Fig. 2E).

4.3.3.3 Sexual abuse as a predictor of cannabis use/misuse

Eighteen studies investigated the association between sexual abuse and cannabis use/misuse. The majority (12/18, 67%) of these studies found no association between sexual abuse and cannabis use/misuse (Baron, 1999; Burgess et al., 1987; X. Chen et al., 2004; Fusco, 2021; Goodkind et al., 2006; Kilpatrick et al., 2000; Lo & Cheng, 2007; Perez, 2000; Rosario et al., 2004; Tyler et al., 2013; Vaughn et al., 2007). A significant association between sexual abuse and cannabis use/misuse was found by the remaining 6/18 studies (Baiden et al., 2014; Bailey & McCloskey, 2005; Chau et al., 2019; Hébert et al., 2021; Hussey & Singer, 1993; Tossone et al., 2018). A meta-analysis was conducted with five of these studies that investigated the association between sexual abuse and cannabis use (Baiden et al., 2014; Bailey & McCloskey, 2005; X. Chen et al., 2004; Goodkind et al., 2006; Perez, 2000). The meta-analysis was significant, indicating that individuals who experienced sexual abuse had 1.3 times greater probability to use cannabis in comparison to individuals that did not experience sexual abuse (RR: 1.31 [95% CI: 1.04 - 1.65], $p = 0.02$) (Fig. 2F).

4.3.3.4 Emotional abuse as a predictor of cannabis use/misuse

Three studies investigated the association between emotional abuse and cannabis use/misuse. Most studies (2/3, 67%) found a significant association between emotional

abuse and cannabis use/misuse (Afifi et al., 2020; Fusco, 2021). The remaining study found no association between emotional abuse and cannabis use (Baiden et al., 2014).

4.3.3.5 Unspecified neglect as a predictor of cannabis use/misuse

Two studies investigated the association between unspecified neglect and cannabis use/misuse. Both of these studies (2/2, 100%) found no association between unspecified neglect and cannabis use/misuse (Folk et al., 2021; Fusco, 2021).

4.3.3.6 Emotional neglect as a predictor of cannabis use/misuse

One study investigated the association between emotional neglect and cannabis use. This study (1/1, 100%) found a significant association between emotional neglect and cannabis use (Afifi et al., 2020).

4.3.3.7 Physical neglect as a predictor of cannabis use/misuse

One study investigated the association between physical neglect and cannabis use. This study (1/1, 100%) found no association between physical neglect and cannabis use (Vaughn et al., 2007).

4.3.4 Unspecified substances

There were 25 studies that assessed use/misuse of more than one type of substance grouped together as the outcome or did not specify the type of substance under investigation (e.g., substances or drugs, illicit drugs, hard drugs, other drugs, alcohol and cannabis, etc.). Sexual abuse was the most investigated maltreatment type, and there are a large number of studies indicating a significant association between sexual abuse and substance use/misuse. Unspecified neglect was the least investigated maltreatment type, and the few studies investigating the association between unspecified neglect and substance use/misuse

presented conflicting results, indicating the importance of conducting more studies regarding the association between unspecified neglect and substance use/misuse.

4.3.4.1 Unspecified childhood maltreatment as a predictor of unspecified substance use/misuse

Seven studies investigated the association between unspecified childhood maltreatment and unspecified substance use/misuse. The majority (5/7, 71%) of these studies found that there was a significant association between unspecified childhood maltreatment and unspecified substance use/misuse (Berenson et al., 1992; Chau et al., 2019; Martin et al., 1999; Smith et al., 2005; Wang et al., 2020). Interestingly, Berenson et al. (1992) found that youth with a history of both physical abuse and sexual abuse presented 17 times greater risk to use illicit drugs as compared to youth without a history of physical or sexual abuse. Although the association between childhood maltreatment and substance use/misuse seems to be well established, two studies did not find a significant association (Aarons et al., 2008; Russotti et al., 2021).

4.3.4.2 Physical abuse as a predictor of unspecified substance use/misuse

Fifteen studies investigated the association between physical abuse and unspecified substance use/misuse. Nine (9/15, 60%) of these studies found a significant association between physical abuse and unspecified substance use/misuse (Berenson et al., 1992; Dembo et al., 1987; Houtepen et al., 2020; Kappel et al., 2021; Kilpatrick et al., 2000; Martin et al., 1999; Perkins & Jones, 2004; Smith et al., 2005; Valério et al., 2022). No association between physical abuse and unspecified substance use/misuse was found by the remaining 6/15 studies (Aarons et al., 2008; Baron, 1999; Grummitt et al., 2022; Musa et al., 2018; Riggs et al., 1990; Vaughn et al., 2007).

4.3.4.3 Sexual abuse as a predictor of unspecified substance use/misuse

There were 22 studies that investigated the association between sexual abuse and unspecified substance use/misuse. Most of the studies (15/22, 68%) found a significant association between sexual abuse and unspecified substance use/misuse (Aarons et al., 2008; Bailey & McCloskey, 2005; Berenson et al., 1992; Brown et al., 2009; Chau et al., 2019; Dembo et al., 1987; Grummitt et al., 2022; Hussey & Singer, 1993; Kappel et al., 2021; Kilpatrick et al., 2000; Martin et al., 1999; Smith et al., 2005; Solakoglu et al., 2018; Tossone et al., 2018; Valério et al., 2022). The remaining 7/22 of these studies found no association between sexual abuse and unspecified substance use/misuse (Baron, 1999; Goodkind et al., 2006; Hébert et al., 2021; Houtepen et al., 2020; Musa et al., 2018; Riggs et al., 1990; Vaughn et al., 2007). A meta-analysis was conducted with two of these studies that investigated the association between sexual abuse and unspecified substance use (Bailey & McCloskey, 2005; Goodkind et al., 2006). The meta-analysis was significant, indicating that individuals who experienced sexual abuse had three times greater probability to use unspecified substances in comparison to individuals that did not experience sexual abuse (RR: 3.15 [95% CI: 1.89 - 5.24], $p < 0.01$) (Fig. 2G).

4.3.4.4 Emotional abuse as a predictor of unspecified substance use/misuse

Five studies investigated the association between emotional abuse and unspecified substance use/misuse. The majority (4/5, 80%) of these studies found that there was a significant association between emotional abuse and unspecified substance use/misuse (Houtepen et al., 2020; Kappel et al., 2021; Musa et al., 2018; Valério et al., 2022). The remaining study found no association between emotional abuse and unspecified substance use/misuse (Grummitt et al., 2022).

4.3.4.5 Unspecified neglect as a predictor of unspecified substance use/misuse

Only two studies investigated the association between unspecified neglect and unspecified substance use/misuse. The findings are inconclusive since one study found a significant association between unspecified neglect and unspecified substance use/misuse (Smith et al., 2005), while the other study found no association between unspecified neglect and unspecified substance use/misuse (Grummitt et al., 2022).

4.3.4.6 Emotional neglect as a predictor of unspecified substance use/misuse

Three studies investigated the association between emotional neglect and unspecified substance use/misuse. The majority of these studies (2/3, 67%) found no association between emotional neglect and unspecified substance use/misuse (Grummitt et al., 2022; Houtepen et al., 2020). The remaining study found a significant association between emotional neglect and unspecified substance use/misuse (Musa et al., 2018).

4.3.4.7 Physical neglect as a predictor of unspecified substance use/misuse

Five studies investigated the association between physical neglect and unspecified substance use/misuse. Most of these studies (4/5, 80%) found no association between physical neglect and unspecified substance use/misuse (Grummitt et al., 2022; Musa et al., 2018; Valério et al., 2022; Vaughn et al., 2007). The remaining study found a significant association between physical neglect and unspecified substance use/misuse (Aarons et al., 2008).

4.3.5 Other specific substances

There were 10 studies that assessed a specific substance type outcome including substance use/misuse that fit outside of the other three substance type categories listed above (e.g., inhalants, cocaine or crack, amphetamines including methamphetamine or

crank, psychedelics or hallucinogens including lysergic acid diethylamide (LSD), injecting drugs, opioids or opiates including heroin, depressants or downers including tranquilizers and barbiturates, and stimulants or uppers). Sexual abuse was the most investigated maltreatment type, and the studies presented conflicting results depending on the specific substance type category investigated. Unspecified childhood maltreatment, emotional abuse, and emotional neglect were the least investigated maltreatment types, with one study conducted for each, indicating a significant association between each of these maltreatment types and other specific substances.

4.3.5.1 Unspecified childhood maltreatment as a predictor of other specific substance use/misuse

One study investigated the association between a history of both physical abuse and sexual victimization with three different other specific substance type outcomes including the use of cocaine, LSD, and uppers (Perez, 2000). This study (1/1, 100%) found a significant association between both physical abuse and sexual victimization with each of the three outcomes including cocaine use, LSD use, and uppers use (Perez, 2000).

4.3.5.2 Physical abuse as a predictor of other specific substance use/misuse

Four studies investigated the association between physical abuse and other specific substance use/misuse as the outcome including the use/misuse of psychedelics, stimulants, cocaine, opioids, and depressants. The majority of these studies (3/4, 75%) found a significant association between physical abuse and other specific substance use/misuse including psychedelics use, non-medical opioid use, cocaine use, LSD use, and uppers use as separate outcomes (Baron, 1999; Lei et al., 2018; Perez, 2000). The remaining study

found that physical abuse was a protective factor against the use of stimulants, as well as no association between physical abuse and the use of depressants (Vaughn et al., 2007).

4.3.5.2.1 *Physical abuse as a predictor of psychedelics use/misuse*

Two studies investigated the association between physical abuse and the use/misuse of psychedelics, or LSD. Both of these studies (2/2, 100%) found a significant association between physical abuse and the use of psychedelics, or LSD (Baron, 1999; Perez, 2000).

4.3.5.2.2 *Physical abuse as a predictor of stimulants use/misuse*

Two studies investigated the association between physical abuse and the use/misuse of stimulants or uppers. The findings are inconclusive overall since one study found a significant association between physical abuse and the use of stimulants (Perez, 2000), while the other study found that physical abuse was a protective factor against the use of stimulants (Vaughn et al., 2007).

4.3.5.3 Sexual abuse as a predictor of other specific substance use/misuse

Ten studies investigated the association between sexual abuse and other specific substance use/misuse including the use/misuse of psychedelics, amphetamines, cocaine, opioids, depressants, stimulants, inhalants, and injecting drugs.

4.3.5.3.1 *Sexual abuse as a predictor of psychedelics use/misuse*

Five studies investigated the association between sexual abuse and the use/misuse of psychedelics, hallucinogens, or LSD. The majority (3/5, 60%) of these studies found a significant association between sexual abuse and the use/misuse of psychedelics, hallucinogens, or LSD (Burgess et al., 1987; X. Chen et al., 2004; Perez, 2000). The remaining two studies found no association between sexual abuse and the use of psychedelics (Baron, 1999; Burgess et al., 1987). A meta-analysis was conducted with two

of these studies that investigated the association between sexual abuse and hallucinogen or LSD use (X. Chen et al., 2004; Perez, 2000). The meta-analysis was significant, indicating that individuals who experienced sexual abuse had 1.6 times greater probability to use hallucinogens or LSD in comparison to individuals that did not experience sexual abuse (RR: 1.60 [95% CI: 1.31 - 1.94], $p < 0.01$) (Fig. 2H).

4.3.5.3.2 *Sexual abuse as a predictor of amphetamines use/misuse*

Four studies investigated the association between sexual abuse and the use/misuse of amphetamines including methamphetamine or crank. The findings are inconclusive since two studies found a significant association between sexual abuse and the use of amphetamines (Bailey & McCloskey, 2005; Burgess et al., 1987), while the other two studies found no association (Burgess et al., 1987; X. Chen et al., 2004).

4.3.5.3.3 *Sexual abuse as a predictor of cocaine use/misuse*

Four studies investigated the association between sexual abuse and the use/misuse of cocaine. Most of the studies (3/4, 75%) found a significant association between sexual abuse and cocaine use (Bailey & McCloskey, 2005; X. Chen et al., 2004; Perez, 2000). The remaining study found no association between sexual abuse and the use of cocaine (Hussey & Singer, 1993). A meta-analysis was conducted with three of these studies that investigated the association between sexual abuse and cocaine use (Bailey & McCloskey, 2005; X. Chen et al., 2004; Perez, 2000). The meta-analysis was significant, indicating that individuals who experienced sexual abuse had nearly two times greater probability to use cocaine in comparison to individuals that did not experience sexual abuse (RR: 1.81 [95% CI: 1.22 - 2.71], $p < 0.01$) (Fig. 2I).

4.3.5.3.4 *Sexual abuse as a predictor of opioids use/misuse*

Four studies investigated the association between sexual abuse and the use/misuse of opioids or opiates or heroin. The findings are inconclusive since two studies found a significant association between sexual abuse and the use of opioids (Burgess et al., 1987; Lei et al., 2018), while the remaining two studies found no such association (Burgess et al., 1987; X. Chen et al., 2004).

4.3.5.3.5 Sexual abuse as a predictor of depressants use/misuse

Three studies investigated the association between sexual abuse and the use/misuse of depressants or downers or tranquilizers or barbiturates. The majority of these studies (2/3, 67%) found no association between sexual abuse and the use of depressants (Hussey & Singer, 1993; Vaughn et al., 2007). The remaining study found a significant association between sexual abuse and the use of tranquilizers, as well as between sexual abuse and the use of barbiturates (X. Chen et al., 2004).

4.3.5.3.6 Sexual abuse as a predictor of stimulants use/misuse

Three studies investigated the association between sexual abuse and the use/misuse of stimulants or uppers. Most of the studies (2/3, 67%) found a significant association between sexual abuse and the use of stimulants (Hussey & Singer, 1993; Perez, 2000). The remaining study found no association between sexual abuse and the use of stimulants (Vaughn et al., 2007).

4.3.5.3.7 Sexual abuse as a predictor of inhalant use/misuse

Two studies investigated the association between sexual abuse and the use/misuse of inhalants. The findings are inconclusive since one study found a significant association between sexual abuse and the use of inhalants (X. Chen et al., 2004), while the other study

found no association between sexual abuse and the use of inhalants (Bailey & McCloskey, 2005). A meta-analysis was conducted with both of these studies which investigated the association between sexual abuse and inhalant use (Bailey & McCloskey, 2005; X. Chen et al., 2004). This meta-analysis was not significant (RR: 1.23 [95% CI: 0.43 - 3.55], p = 0.70) (Fig. 2J).

4.3.5.3.8 Sexual abuse as a predictor of injecting drugs use/misuse

One study investigated the association between sexual abuse and the use of injecting drugs (Roy et al., 2011). This study (1/1, 100%) found no association between sexual abuse and the use of injecting drugs (Roy et al., 2011).

4.3.5.4 Emotional abuse as a predictor of other specific substance use/misuse

One study investigated the association between emotional abuse and non-medical opioid use (Lei et al., 2018). This study (1/1, 100%) found a significant association between emotional abuse and non-medical opioid use (Lei et al., 2018).

4.3.5.5 Emotional neglect as a predictor of other specific substance use/misuse

One study investigated the association between emotional neglect and non-medical opioid use (Lei et al., 2018). This study (1/1, 100%) found a significant association between emotional neglect and non-medical opioid use (Lei et al., 2018).

4.3.5.6 Physical neglect as a predictor of other specific substance use/misuse

Two studies investigated the association between physical neglect and other specific substance use/misuse as the outcome including the use of non-medical opioids, stimulants, and depressants. The findings are inconclusive since one study found a significant association between physical neglect and the use of non-medical opioids (Lei et al., 2018),

while the other study found no association between physical neglect and the use of stimulants as well as depressants as separate outcomes (Vaughn et al., 2007).

4.4 Discussion

This systematic review and meta-analysis comprehensively investigated whether a history of any childhood maltreatment is predictive of various types of substance use/misuse among a large sample of 170,749 youth. Overall, the findings indicate that childhood maltreatment is an important predictor of substance use/misuse among youth.

Unspecified childhood maltreatment, physical abuse, and sexual abuse were found to be predictors of alcohol use/misuse among youth by this systematic review and meta-analysis. Although no other systematic reviews and meta-analyses on this particular topic with alcohol use/misuse among youth as an outcome have been conducted, a previous systematic review including adults with a broader focus on the association between interpersonal trauma and addictive behaviours found that alcohol was the most frequently investigated substance which is consistent with our findings (Konkolÿ Thege et al., 2017).

Additionally, our meta-analysis found that unspecified childhood maltreatment, physical abuse, and sexual abuse were predictors of youth cannabis use/misuse, while the systematic review supported this association for physical abuse, emotional abuse, and emotional neglect. The discrepancies in main results for emotional neglect, physical neglect, and unspecified neglect with cannabis use/misuse may be due to the relatively small number of studies conducted and high heterogeneity among these different studies. For instance, the one study that found a significant association between emotional neglect with cannabis use included a community-based sample of adolescents (Afifi et al., 2020),

while the one study that found no association between physical neglect with cannabis use included a sample of youth in foster care (Vaughn et al., 2007) and different criteria were used to assess cannabis use. Consistent with the current findings, two previous meta-analyses on similar topics found that childhood sexual abuse and childhood physical abuse were both significantly associated with adolescent cannabis use or misuse (De la Peña-Arteaga et al., 2021; Martínez-Mota et al., 2020).

Sexual abuse was a predictor of unspecified substance use/misuse among youth based on our meta-analysis, while the systematic review supported this association for unspecified childhood maltreatment, physical abuse, sexual abuse, and emotional abuse. A prior systematic review with a focus on risk and protective factors of drug abuse among adolescents, also found preliminary evidence to support a positive association between childhood maltreatment and adolescent drug abuse (Nawi et al., 2021).

Fewer studies investigated the association between childhood maltreatment and other specific types of illicit substance use/misuse. Preliminary evidence indicating that unspecified childhood maltreatment, physical abuse, sexual abuse, emotional abuse, emotional neglect, and physical neglect were predictors of some other specific types of illicit substance use/misuse (including cocaine, stimulants or uppers, psychedelics or LSD or hallucinogens, and opioids) was found by our systematic review and meta-analysis. It is important to note that only a limited number of studies have investigated neglect or emotional abuse as well as other specific illicit substance use/misuse among youth, highlighting the need to conduct more studies on this topic with a focus on these particular childhood maltreatment and substance types. While physical forms of maltreatment

including sexual and physical abuse have been more frequently investigated as shown by our findings, there is some prior evidence to suggest that emotional abuse and neglect are also important predictors of substance use/misuse in youth (Dubowitz et al., 2019; Martínez-Mota et al., 2020; Rosenkranz et al., 2012). Considering that emotional abuse, emotional neglect, and physical neglect are among the most prevalent types of childhood maltreatment worldwide, it is especially important for further studies to investigate the potential role of emotional abuse and neglect in predicting subsequent substance use/misuse among youth (Stoltenborgh et al., 2015).

Notably, prior research has shown that most individuals with histories of childhood maltreatment have experienced multiple different types, and this is associated with poorer clinical outcomes regarding areas such as psychopathology, level of psychosocial functioning, health-related quality of life, and youth substance use (Mishra et al., 2022; Witt et al., 2016). While our current systematic review and meta-analysis did not specifically focus on the synergistic effects of experiencing multiple childhood maltreatment types on substance use/misuse among youth, a few of the included studies investigated a history of experiencing multiple childhood maltreatment types as well as individual maltreatment types as the exposure (Berenson et al., 1992; Cronin et al., 2016; Martin et al., 1999; Perez, 2000; Shin et al., 2009). Overall, these studies found similar trends in which experiencing multiple types of childhood maltreatment increased the risk of youth substance use/misuse in comparison to almost all individual childhood maltreatment types (Berenson et al., 1992; Cronin et al., 2016; Martin et al., 1999; Perez, 2000; Shin et al., 2009). For instance, Berenson et al., 1992 found a particularly strong

effect of multiple childhood maltreatment types in comparison to individual childhood maltreatment types such that physical abuse increased the odds of adolescent illicit drug use by about 7 times, sexual abuse increased the odds by about 13 times, while both physical abuse and sexual abuse increased the odds by about 17 times. These findings suggest a synergistic effect of multiple childhood maltreatment types on youth substance use/misuse, thus this should be taken into consideration for future studies on similar topics.

Critical neurodevelopment occurs during adolescence and young adulthood, particularly in areas of the brain that are related to motivation and impulsivity (Chambers et al., 2003; Debenham et al., 2021; Somerville & Casey, 2010). As adolescents experience maturation in neural circuitry (e.g.., changes to the prefrontal cortex, and subcortical monoaminergic systems) this drives adaptive learning behaviours that enable the transition to adulthood (Chambers et al., 2003; Somerville & Casey, 2010). However, this also increases the vulnerability of adolescents and young adults to initiate substance use as well as to experience subsequent deficits in brain development due to substance use/misuse (Chambers et al., 2003; Debenham et al., 2021). Prior findings indicate that a history of childhood maltreatment is predictive of deficits in executive functioning even when internalizing psychopathology symptoms are taken into consideration (Letkiewicz et al., 2021; Lund et al., 2020). Furthermore, heightened reward sensitivity during adolescence coupled with poor executive control has been shown to predict progression toward substance use disorders from experimental drug use, whereas when heightened reward sensitivity is balanced by strong executive control adolescent drug use progression is less likely (Khurana et al., 2015; Peeters et al., 2017). Thus, the early implementation of

interventions that are able to enhance executive control among adolescents may in turn aid in the prevention of progression from occasional experimental drug use toward substance use disorders, especially among adolescents with a history of childhood maltreatment (Khurana et al., 2015). There is also evidence to suggest that childhood maltreatment is associated with downregulation of hypothalamic-pituitary-adrenal (HPA) axis activity leading to attenuated cortisol responses to stress and potential impacts on pubertal development (Negriff et al., 2020; Schär et al., 2022). Additionally, associations between childhood maltreatment and changes in brain structures that are known to have a role in controlling HPA axis activity, including limbic regions (e.g., the hippocampus, prefrontal cortex, and amygdala) have been found (Nogovitsyn et al., 2022; Schär et al., 2022; Teicher et al., 2016). Altogether, this may explain the trajectory between childhood maltreatment and subsequent adverse mental health outcomes, such as substance use, among youth (Negriff et al., 2020; Nogovitsyn et al., 2022; Schär et al., 2022).

The identification of the potential adverse effects and predictors of substance use/misuse in youth, is important to inform policy making that could aid with prevention efforts (Babor, 2010). The most promising methods to prevent alcohol misuse or its associated adverse effects in youth include the implementation of a minimum legal purchase age, measures to prevent impaired driving (e.g., sobriety checkpoints, a 'zero' tolerance policy for young drivers, and graduated licensing for new drivers), and taxation on alcoholic beverages to increase costs (Azofeifa et al., 2015; Babor, 2010; Stockings et al., 2016). While many of these measures are not relevant in the context of managing illicit substance use/misuse, there is evidence to suggest that preventive or treatment-based

interventions for illicit drug use/misuse among youth such as individual therapy, structured family therapy, school-based interventions, motivational interviewing, and medication-assisted treatment, are effective (T. D. Becker et al., 2023; Kulak & Griswold, 2019; Stockings et al., 2016).

Interestingly, some previous studies have also explored the influence of sex or gender differences on the relationship between childhood maltreatment and substance use/misuse in youth (Abajobir et al., 2017; Annor et al., 2020; Anteghini et al., 2001; D. F. Becker & Grilo, 2006; J. Q. Chen et al., 2004; Cronin et al., 2016; Hébert et al., 2019, 2021; Karamanos et al., 2022; Sutton & Simons, 2021; Zhu et al., 2015). Several of these studies found that the associations between childhood maltreatment and substance use/misuse tended to be particularly strong for females in comparison to males (Abajobir et al., 2017; D. F. Becker & Grilo, 2006; Cronin et al., 2016; Hébert et al., 2019, 2021; Karamanos et al., 2022; Sutton & Simons, 2021). In contrast, a few of these studies found either similar main results across the sexes or genders, or a stronger association for males when compared to females (Annor et al., 2020; Anteghini et al., 2001; J. Q. Chen et al., 2004; Zhu et al., 2015). Thus, another important future direction for research in this area is to further investigate the role of sociodemographic characteristics such as sex or gender differences in the context of childhood maltreatment as a predictor of substance use/misuse in youth.

Considering that substance use/misuse among youth may contribute to adverse clinical outcomes (Debenham et al., 2021; Lalli et al., 2021; Lees et al., 2020; Rioux et al., 2021), the prompt detection of predictors such as childhood maltreatment is important to facilitate the implementation of early interventions. Resilience often refers to the ability of an

individual to successfully adapt in a way that allows one to overcome an adverse or traumatic situation, thus avoiding further potential negative outcomes (Fergus & Zimmerman, 2005; Hodder et al., 2017). Notably, resilience has been shown to mediate the relationship between childhood maltreatment and psychiatric conditions such as mood disorders in young adults, by reducing the impact of maltreatment on mood disorder diagnosis as well as depressive symptoms (Vieira et al., 2020). Furthermore, there is evidence to suggest that young adults with greater resilience have shown more favourable responses to psychological interventions including cognitive psychotherapy and that resilience can also be enhanced by such interventions (Konradt et al., 2018). A systematic review and meta-analysis by Hodder et al., 2017 found that universal school-based interventions addressing individual resilience protective factors (e.g., cooperation and communication, empathy, problem-solving or decision making, self-esteem, etc.) and environmental resilience protective factors (e.g., community adult high expectations, peer caring relationships, school meaningful participation, school support, etc.) reduced illicit substance use among adolescents, thus indicating the promising potential of implementing such interventions early on.

The findings of this current systematic review and meta-analysis should be interpreted in consideration of some limitations. First, is the heterogeneity of the studies included in this systematic review and meta-analysis (e.g., various maltreatment types and assessment criteria used, various substance types and assessment criteria used, different timeframes considered for the substance use/misuse outcome such as lifetime or current use/misuse, various settings such as population-based or clinical-based studies, and various study

designs such as cross-sectional and longitudinal). Second, cross-sectional studies were also included since maltreatment was often assessed retrospectively to reflect the period of time during childhood which often occurred before substance use/misuse, however, this precludes making inferences regarding causality. Another major limitation is that most studies did not report raw data, which precluded their inclusion in the meta-analyses. Importantly, many of the studies that found no significant association between maltreatment and substance use/misuse did not include the relevant raw data which could potentially influence the results of the meta-analyses. Furthermore, there were a small number of studies included for each meta-analysis, due to the limited number of studies that investigated similar maltreatment type and substance type combinations. Despite these limitations, this is the first systematic review and meta-analysis to comprehensively investigate whether exposure to a wide variety of maltreatment types is associated with a wide variety of types of substance use/misuse among youth.

In conclusion, the findings of this systematic review and meta-analysis indicate that childhood maltreatment predicts various types of substance use/misuse in youth. Due to the limited number of studies investigating emotional abuse and neglect, as well as other specific illicit substances (e.g., inhalants, cocaine, amphetamines, psychedelics, injecting drugs, opioids, depressants, and stimulants), more studies with a focus on these particular maltreatment and substance types should be conducted before relevant conclusions can be made. To further elucidate the trajectory of the association between childhood maltreatment and subsequent substance use/misuse in youth, future research in this area should incorporate a longitudinal design and focus on other sociodemographic factors including

sex or gender that may have an impact on this relationship. Additional research into early interventions and the mechanisms underlying risk or resilience, especially among youth with histories of maltreatment, will better inform preventive or treatment-based intervention methods and potentially improve outcomes for youth that are at the highest risk of using/misusing substances.

4.5 Acknowledgements

Dr. de Azevedo Cardoso acknowledges her postdoctoral fellowship from the Canadian Institutes of Health Research (CIHR). Coral Rakovski acknowledges her Ontario Graduate Scholarship (OGS). This work was partially funded by the Centre for Clinical Neurosciences, St. Joseph's Healthcare Hamilton and McMaster University.

4.6 References

Aarons, G. A., Monn, A. R., Hazen, A. L., Connelly, C. D., Leslie, L. K., Landsverk, J. A., Hough, R. L., & Brown, S. A. (2008). Substance Involvement Among Youths in Child Welfare: The Role of Common and Unique Risk Factors. *American Journal of Orthopsychiatry*, *78*(3), 340–349. https://doi.org/10.1037/A0014215

Abajobir, A. A., Kisely, S., Williams, G., Clavarino, A., Strathearn, L., & Najman, J. M. (2017). Gender-based differences in injecting drug use by young adults who experienced maltreatment in childhood: Findings from an Australian birth cohort study. *Drug and Alcohol Dependence*, *173*, 163–169. https://doi.org/10.1016/J.DRUGALCDEP.2016.12.027

Afifi, T. O., Taillieu, T., Salmon, S., Davila, I. G., Stewart-Tufescu, A., Fortier, J., Struck, S., Asmundson, G. J. G., Sareen, J., & MacMillan, H. L. (2020). Adverse childhood experiences (ACEs), peer victimization, and substance use among adolescents. *Child Abuse & Neglect*, *106*. https://doi.org/10.1016/J.CHIABU.2020.104504

Al-Kassab-córdova, A., Cornejo-Venegas, G., Gacharna-Madrigal, N., Baquedano-Rojas, C., de la Borda-Prazak, G., & Mejia, C. R. (2021). Factors associated with frequent marijuana consumption in young people before admission to juvenile detention centers in Peru. *Adicciones*. https://doi.org/10.20882/ADICCIONES.1506

Angelakis, I., Gillespie, E. L., & Panagioti, M. (2019). Childhood maltreatment and adult suicidality: a comprehensive systematic review with meta-analysis. *Psychological Medicine*, *49*(7), 1057. https://doi.org/10.1017/S0033291718003823

Annor, F. B., Gilbert, L. K., Davila, E. P., Massetti, G. M., Kress, H., Onotu, D., &

Ogbanufe, O. (2020). Emotional violence in childhood and health conditions, risk-taking behaviors, and violence perpetration among young adults in Nigeria. *Child Abuse & Neglect*, *106*. https://doi.org/10.1016/J.CHIABU.2020.104510

Anteghini, M., Fonseca, H., Ireland, M., & Blum, R. W. (2001). Health risk behaviors and associated risk and protective factors among Brazilian adolescents in Santos, Brazil. *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine*, *28*(4), 295–302. https://doi.org/10.1016/S1054-139X(00)00197-X

Arya, S., Kaji, A. H., & Boermeester, M. A. (2021). PRISMA Reporting Guidelines for Meta-analyses and Systematic Reviews. *JAMA Surgery*, *156*(8), 789–790. https://doi.org/10.1001/JAMASURG.2021.0546

Azofeifa, A., Mattson, M. E., & Lyerla, R. (2015). Driving Under the Influence of Alcohol, Marijuana, and Alcohol and Marijuana Combined Among Persons Aged 16-25 Years - United States, 2002-2014. *MMWR. Morbidity and Mortality Weekly Report*, *64*(48), 1325–1329. https://doi.org/10.15585/MMWR.MM6448A1

Babor, T. F. (2010). Alcohol: No Ordinary Commodity - a summary of the second edition. *Addiction*, *105*(5), 769–779. https://doi.org/10.1111/j.1360-0443.2010.02945.x

Baiden, P., Stewart, S. L., & Den Dunnen, W. (2014). Childhood abuse and cannabis use among adolescents with mental health needs in Ontario, Canada. *Journal of Substance Use*, *19*(1–2), 18–24. https://doi.org/10.3109/14659891.2012.727522

Bailey, J. A., & McCloskey, L. A. (2005). Pathways to adolescent substance use among

sexually abused girls. *Journal of Abnormal Child Psychology*, *33*(1), 39–53. https://doi.org/10.1007/S10802-005-0933-0

Balázs, M., Piko, B. F., & Fitzpatrick, K. M. (2017). Youth Problem Drinking: The Role of Parental and Familial Relationships. *Substance Use and Misuse*, *52*(12), 1538–1545. https://doi.org/10.1080/10826084.2017.1281311

Baldwin, J. R., Wang, B., Karwatowska, L., Schoeler, T., Tsaligopoulou, A., Munafò, M. R., & Pingault, J. B. (2023). Childhood Maltreatment and Mental Health Problems: A Systematic Review and Meta-Analysis of Quasi-Experimental Studies. *The American Journal of Psychiatry*, *180*(2), 117–126. https://doi.org/10.1176/APPI.AJP.20220174/ASSET/IMAGES/LARGE/APPI.AJP.20220174F4.JPEG

Baron, S. W. (1999). Street Youths and Substance Use: The Role of Background, Street Lifestyle, and Economic Factors. *Youth and Society*, *31*(1), 3–26. https://doi.org/10.1177/0044118X99031001001

Becker, D. F., & Grilo, C. M. (2006). Prediction of drug and alcohol abuse in hospitalized adolescents: Comparisons by gender and substance type. *Behaviour Research and Therapy*, *44*(10), 1431–1440. https://doi.org/10.1016/j.brat.2005.10.009

Becker, T. D., Castañeda Ramirez, S., Bruges Boude, A., Leong, A., Ivanov, I., & Rice, T. R. (2023). Interventions for prevention and treatment of substance use in youth with traumatic childhood experiences: a systematic review and synthesis of the literature. *European Child and Adolescent Psychiatry*, 1–20. https://doi.org/10.1007/S00787-023-02265-X/METRICS

Berenson, A. B., San Miguel, V. V., & Wilkinson, G. S. (1992). Violence and its relationship to substance use in adolescent pregnancy. *Journal of Adolescent Health*, *13*(6), 470–474. https://doi.org/10.1016/1054-139X(92)90009-Z

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., & Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*, *27*(2), 169–190. https://doi.org/10.1016/S0145-2134(02)00541-0

Brown, D. W., Riley, L., Butchart, A., Meddings, D. R., Kann, L., & Harvey, A. P. (2009). Exposure to physical and sexual violence and adverse health behaviours in African children: results from the Global School-based Student Health Survey. *Bulletin of the World Health Organization*, *87*(6), 447–455. https://doi.org/10.2471/BLT.07.047423

Bukstein, O. G. (2017). Challenges and Gaps in Understanding Substance Use Problems in Transitional Age Youth. *Child and Adolescent Psychiatric Clinics of North America*, *26*(2), 253–269. https://doi.org/10.1016/J.CHC.2016.12.005

Burgess, A. W., Hartman, C. R., & McCormack, A. (1987). Abused to abuser: antecedents of socially deviant behaviors. *The American Journal of Psychiatry*, *144*(11), 1431–1436. https://doi.org/10.1176/AJP.144.11.1431

Chambers, R. A., Taylor, J. R., & Potenza, M. N. (2003). Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *The American Journal of Psychiatry*, *160*(6), 1041–1052.

https://doi.org/10.1176/APPI.AJP.160.6.1041

Chau, K., Mayet, A., Legleye, S., Beck, F., Hassler, C., Khlat, M., Choquet, M., Falissard, B., & Chau, N. (2019). Association between cumulating substances use and cumulating several school, violence and mental health difficulties in early adolescents. *Psychiatry Research*, *280*. https://doi.org/10.1016/j.psychres.2019.112480

Chen, J. Q., Dunne, M. P., & Han, P. (2004). Child sexual abuse in China: a study of adolescents in four provinces. *Child Abuse & Neglect*, *28*(11), 1171–1186. https://doi.org/10.1016/J.CHIABU.2004.07.003

Chen, X., Tyler, K. A., Whitbeck, L. B., & Hoyt, D. R. (2004). Early Sexual Abuse, Street Adversity, and Drug Use among Female Homeless and Runaway Adolescents in the Midwest. *Journal of Drug Issues*, *34*(1), 1–21. https://doi.org/10.1177/002204260403400101

Cornelius, M. D., De Genna, N., Goldschmidt, L., Larkby, C., & Day, N. (2016). Adverse Environmental Exposures During Gestation and Childhood: Predictors of Adolescent Drinking. *Substance Use and Misuse*, *51*(10), 1253–1263. https://doi.org/10.3109/10826084.2016.1162812

Cronin, S., Murphy, S., & Elklit, A. (2016). Investigating the relationship between childhood maltreatment and alcohol misuse in a sample of Danish young adults: Exploring gender differences. *NAD Nordic Studies on Alcohol and Drugs*, *33*(3), 287–298. https://doi.org/10.1515/NSAD-2016-0022

De la Peña-Arteaga, V., Nogueira, S. O., Lynskey, M., & Hines, L. A. (2021). The

Relationship Between Childhood Physical and Sexual Abuse and Adolescent Cannabis Use: A Systematic Review. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/FPSYT.2021.631245

Debenham, J., Birrell, L., Champion, K., Lees, B., Yücel, M., & Newton, N. (2021). Neuropsychological and neurophysiological predictors and consequences of cannabis and illicit substance use during neurodevelopment: A systematic review of longitudinal studies. *The Lancet. Child & Adolescent Health*, *5*(8), 589–604. https://doi.org/10.1016/S2352-4642(21)00051-1

Degenhardt, L., Stockings, E., Patton, G., Hall, W. D., & Lynskey, M. (2016). The increasing global health priority of substance use in young people. *The Lancet. Psychiatry*, *3*(3), 251–264. https://doi.org/10.1016/S2215-0366(15)00508-8

Dembo, R., Dertke, M., La Voie, L., Borders, S., Washburn, M., & Schmeidler, J. (1987). Physical abuse, sexual victimization and illicit drug use: a structural analysis among high risk adolescents. *Journal of Adolescence*, *10*(1), 13–34. https://doi.org/10.1016/S0140-1971(87)80030-1

Dubowitz, H., Roesch, S., Arria, A. M., Metzger, R., Thompson, R., Kotch, J. B., & Lewis, T. (2019). Timing and chronicity of child neglect and substance use in early adulthood. *Child Abuse & Neglect*, *94*. https://doi.org/10.1016/J.CHIABU.2019.104027

Fergus, S., & Zimmerman, M. A. (2005). Adolescent resilience: a framework for understanding healthy development in the face of risk. *Annual Review of Public Health*, *26*, 399–419.

https://doi.org/10.1146/ANNUREV.PUBLHEALTH.26.021304.144357

Fergusson, D. M., & Lynskey, M. T. (1997). Physical punishment/maltreatment during childhood and adjustment in young adulthood. *Child Abuse & Neglect*, *21*(7), 617–630. https://doi.org/10.1016/S0145-2134(97)00021-5

Field, A. P., & Gillett, R. (2010). How to do a meta-analysis. *The British Journal of Mathematical and Statistical Psychology*, *63*(Pt 3), 665–694. https://doi.org/10.1348/000711010X502733

Filho, V. C. B., De Campos, W., & Lopes, A. da S. (2012). Prevalence of alcohol and tobacco use among Brazilian adolescents: A systematic review. *Revista de Saude Publica*, *46*(5), 901–917. https://doi.org/10.1590/S0034-89102012000500018

Folk, J. B., Ramos, L. M. C., Bath, E. P., Rosen, B., Marshall, B. D. L., Kemp, K., Brown, L., Conrad, S., & Tolou-Shams, M. (2021). The prospective impact of adverse childhood experiences on justice-involved youth's psychiatric symptoms and substance use. *Journal of Consulting and Clinical Psychology*, *89*(6), 483–498. https://doi.org/10.1037/CCP0000655

Fusco, R. A. (2021). Frequent Marijuana or Alcohol Use in Low-Income Emerging Adults: Impact of Adverse Life Experiences. *Substance Use & Misuse*, *56*(5), 711–717. https://doi.org/10.1080/10826084.2021.1892140

Goodkind, S., Ng, I., & Sarri, R. C. (2006). The impact of sexual abuse in the lives of young women involved or at risk of involvement with the juvenile justice system. *Violence Against Women*, *12*(5), 456–477. https://doi.org/10.1177/1077801206288142

Grummitt, L. R., Kelly, E. V., Barrett, E. L., Lawler, S., Prior, K., Stapinski, L. A., & Newton, N. C. (2022). Associations of childhood emotional and physical neglect with mental health and substance use in young adults. *The Australian and New Zealand Journal of Psychiatry*, *56*(4), 365–375. https://doi.org/10.1177/00048674211025691

Halpern, S. C., Schuch, F. B., Scherer, J. N., Sordi, A. O., Pachado, M., Dalbosco, C., Fara, L., Pechansky, F., Kessler, F., & Von Diemen, L. (2018). Child Maltreatment and Illicit Substance Abuse: A Systematic Review and Meta-Analysis of Longitudinal Studies. *Child Abuse Review*, *27*(5), 344–360. https://doi.org/10.1002/CAR.2534

Hammond, D., Wadsworth, E., Reid, J. L., & Burkhalter, R. (2021). Prevalence and modes of cannabis use among youth in Canada, England, and the US, 2017 to 2019. *Drug and Alcohol Dependence*, *219*, 108505. https://doi.org/10.1016/J.DRUGALCDEP.2020.108505

Hébert, M., Amédée, L. M., Blais, M., & Gauthier-Duchesne, A. (2019). Child Sexual Abuse among a Representative Sample of Quebec High School Students: Prevalence and Association with Mental Health Problems and Health-Risk Behaviors. *Canadian Journal of Psychiatry*, *64*(12), 846–854. https://doi.org/10.1177/0706743719861387

Hébert, M., Smith, K., Caouette, J., Cénat, J. M., Karray, A., Cartierre, N., Veuillet-Combier, C., Mazoyer, A. V., & Derivois, D. (2021). Prevalence and associated mental health outcomes of child sexual abuse in youth in France: Observations from a convenience sample. *Journal of Affective Disorders*, *282*, 820–828.

https://doi.org/10.1016/J.JAD.2020.12.100

Higgins, J. P. T., Li, T., & Deeks, J. J. (2023). *Chapter 6: Choosing effect measures and computing estimates of effect*. Cochrane Handbook for Systematic Reviews of Interventions Version 6.4; Cochrane. https://training.cochrane.org/handbook/current/chapter-06

Hodder, R. K., Freund, M., Wolfenden, L., Bowman, J., Nepal, S., Dray, J., Kingsland, M., Yoong, S. L., & Wiggers, J. (2017). Systematic review of universal school-based "resilience" interventions targeting adolescent tobacco, alcohol or illicit substance use: A meta-analysis. *Preventive Medicine*, *100*, 248–268. https://doi.org/10.1016/J.YPMED.2017.04.003

Houtepen, L. C., Heron, J., Suderman, M. J., Fraser, A., Chittleborough, C. R., & Howe, L. D. (2020). Associations of adverse childhood experiences with educational attainment and adolescent health and the role of family and socioeconomic factors: A prospective cohort study in the UK. *PLoS Medicine*, *17*(3), e1003031. https://doi.org/10.1371/JOURNAL.PMED.1003031

Hussey, D. L., & Singer, M. (1993). Psychological distress, problem behaviors, and family functioning of sexually abused adolescent inpatients. *Journal of the American Academy of Child and Adolescent Psychiatry*, *32*(5), 954–961. https://doi.org/10.1097/00004583-199309000-00010

IHME. (2019). *Global Burden of Disease Study (2019) – processed by Our World in Data. "All ages" [original dataset]*. https://ourworldindata.org/grapher/prevalence-of-drug-use-disorders-by-age

Kaligis, F., Ismail, R. I., Wiguna, T., Prasetyo, S., Indriatmi, W., Gunardi, H., Pandia, V., & Magdalena, C. C. (2021). Mental health problems and needs among transitional-age youth in Indonesia. *International Journal of Environmental Research and Public Health 2021, Vol. 18, Page 4046*, *18*(8), 4046. https://doi.org/10.3390/IJERPH18084046

Kaplan, S. J., Pelcovitz, D., Salzinger, S., Weiner, M., Mandel, F. S., Lesser, M. L., & Labruna, V. E. (1998). Adolescent physical abuse: Risk for adolescent psychiatric disorders. *American Journal of Psychiatry*, *155*(7), 954–959. https://doi.org/10.1176/AJP.155.7.954/ASSET/IMAGES/LARGE/AC18T3.JPEG

Kappel, R. H., Livingston, M. D., Patel, S. N., Villaveces, A., & Massetti, G. M. (2021). Prevalence of Adverse Childhood Experiences (ACEs) and associated health risks and risk behaviors among young women and men in Honduras. *Child Abuse & Neglect*, *115*. https://doi.org/10.1016/J.CHIABU.2021.104993

Karamanos, A., Stewart, K., Harding, S., Kelly, Y., & Lacey, R. E. (2022). Adverse childhood experiences and adolescent drug use in the UK: The moderating role of socioeconomic position and ethnicity. *SSM - Population Health*, *19*. https://doi.org/10.1016/J.SSMPH.2022.101142

Kaufman, J., Yang, B. Z., Douglas-Palumberi, H., Crouse-Artus, M., Lipschitz, D., Krystal, J. H., & Gelernter, J. (2007). Genetic and environmental predictors of early alcohol use. *Biological Psychiatry*, *61*(11), 1228–1234. https://doi.org/10.1016/J.BIOPSYCH.2006.06.039

Kenny, D. T., & Schreiner, I. (2009). Predictors of high-risk alcohol consumption in

young offenders on community orders: Policy and Treatment Implications. *Psychology, Public Policy, and Law*, *15*(1), 54–79. https://doi.org/10.1037/A0015079

Khurana, A., Romer, D., Betancourt, L. M., Brodsky, N. L., Giannetta, J. M., & Hurt, H. (2015). Experimentation versus progression in adolescent drug use: A test of an emerging neurobehavioral imbalance model. *Development and Psychopathology*, *27*(3), 901–913. https://doi.org/10.1017/S0954579414000765

Kilpatrick, D. G., Acierno, R., Saunders, B., Resnick, H. S., Best, C. L., & Schnurr, P. P. (2000). Risk factors for adolescent substance abuse and dependence: Data from a national sample. *Journal of Consulting and Clinical Psychology*, *68*(1), 19–30. https://doi.org/10.1037/0022-006X.68.1.19

Köck, P., Meyer, M., Elsner, J., Dürsteler, K. M., Vogel, M., & Walter, M. (2022). Co-occurring Mental Disorders in Transitional Aged Youth With Substance Use Disorders – A Narrative Review. *Frontiers in Psychiatry*, *13*, 827658. https://doi.org/10.3389/FPSYT.2022.827658/FULL

Konkolÿ Thege, B., Horwood, L., Slater, L., Tan, M. C., Hodgins, D. C., & Wild, T. C. (2017). Relationship between interpersonal trauma exposure and addictive behaviors: a systematic review. *BMC Psychiatry*, *17*(1). https://doi.org/10.1186/S12888-017-1323-1

Konradt, C. E., Cardoso, T. de A., Mondin, T. C., Souza, L. D. de M., Kapczinski, F., da Silva, R. A., & Jansen, K. (2018). Impact of resilience on the improvement of depressive symptoms after cognitive therapies for depression in a sample of young

adults. *Trends in Psychiatry and Psychotherapy*, *40*(3), 226–231. https://doi.org/10.1590/2237-6089-2017-0047

Kulak, J. A., & Griswold, K. S. (2019). Adolescent Substance Use and Misuse: Recognition and Management. *American Family Physician*, *99*(11), 689–696. www.aafp.org/afp

Lalli, M., Brouillette, K., Kapczinski, F., & de Azevedo Cardoso, T. (2021). Substance use as a risk factor for bipolar disorder: A systematic review. *Journal of Psychiatric Research*, *144*, 285–295. https://doi.org/10.1016/J.JPSYCHIRES.2021.10.012

Langevin, R., Marshall, C., Wallace, A., Gagné, M. E., Kingsland, E., & Temcheff, C. (2023). Disentangling the Associations Between Attention Deficit Hyperactivity Disorder and Child Sexual Abuse: A Systematic Review. *Trauma, Violence, and Abuse*, *24*(2), 369–389. https://doi.org/10.1177/15248380211030234/ASSET/IMAGES/LARGE/10.1177_15248380211030234-FIG1.JPEG

Lees, B., Meredith, L. R., Kirkland, A. E., Bryant, B. E., & Squeglia, L. M. (2020). Effect of alcohol use on the adolescent brain and behavior. In *Pharmacology Biochemistry and Behavior* (Vol. 192). Elsevier Inc. https://doi.org/10.1016/j.pbb.2020.172906

Lei, Y., Xi, C., Li, P., Luo, M., Wang, W., Pan, S., Gao, X., Xu, Y., Huang, G., Deng, X., Guo, L., & Lu, C. (2018). Association between childhood maltreatment and non-medical prescription opioid use among Chinese senior high school students: The moderating role of gender. *Journal of Affective Disorders*, *235*, 421–427. https://doi.org/10.1016/J.JAD.2018.04.070

Letkiewicz, A. M., Funkhouser, C. J., & Shankman, S. A. (2021). Childhood maltreatment predicts poorer executive functioning in adulthood beyond symptoms of internalizing psychopathology. *Child Abuse & Neglect*, *118*. https://doi.org/10.1016/J.CHIABU.2021.105140

Lin, D., Li, X., Fan, X., & Fang, X. (2011). Child sexual abuse and its relationship with health risk behaviors among rural children and adolescents in Hunan, China. *Child Abuse & Neglect*, *35*(9), 680–687. https://doi.org/10.1016/J.CHIABU.2011.05.006

Lo, C. C., & Cheng, T. C. (2007). The impact of childhood maltreatment on young adults' substance abuse. *The American Journal of Drug and Alcohol Abuse*, *33*(1), 139–146. https://doi.org/10.1080/00952990601091119

Lund, J. I., Toombs, E., Radford, A., Boles, K., & Mushquash, C. (2020). Adverse Childhood Experiences and Executive Function Difficulties in Children: A Systematic Review. *Child Abuse & Neglect*, *106*. https://doi.org/10.1016/J.CHIABU.2020.104485

Martin, S. L., Clark, K. A., Lynch, S. R., Kupper, L. L., & Cilenti, D. (1999). Violence in the lives of pregnant teenage women: associations with multiple substance use. *The American Journal of Drug and Alcohol Abuse*, *25*(3), 425–440. https://doi.org/10.1081/ADA-100101870

Martínez-Mota, L., Jiménez-Rubio, G., Hernández-Hernández, O. T., & Páez-Martínez, N. (2020). Influence of the type of childhood violence on cannabis abuse and dependence among adolescents: a systematic review and meta-analysis. *Adicciones*, *32*(1), 63–76. https://doi.org/10.20882/ADICCIONES.1050

Mills, R., Alati, R., Strathearn, L., & Najman, J. M. (2014). Alcohol and tobacco use among maltreated and non-maltreated adolescents in a birth cohort. *Addiction (Abingdon, England)*, *109*(4), 672–680. https://doi.org/10.1111/ADD.12447

Mills, R., Kisely, S., Alati, R., Strathearn, L., & Najman, J. M. (2017). Child maltreatment and cannabis use in young adulthood: a birth cohort study. *Addiction (Abingdon, England)*, *112*(3), 494–501. https://doi.org/10.1111/ADD.13634

Mishra, A. A., Marceau, K., Christ, S. L., Schwab Reese, L. M., Taylor, Z. E., & Knopik, V. S. (2022). Multi-type childhood maltreatment exposure and substance use development from adolescence to early adulthood: A GxE study. *Child Abuse & Neglect*, *126*. https://doi.org/10.1016/J.CHIABU.2022.105508

Musa, S., Peek-Asa, C., Jovanović, N., & Selimović, E. (2018). Association of adverse childhood experiences and health risk behaviors among young adults visiting a regional primary healthcare center, Federation of Bosnia and Herzegovina. *PloS One*, *13*(3). https://doi.org/10.1371/JOURNAL.PONE.0194439

Nawi, A. M., Ismail, R., Ibrahim, F., Hassan, M. R., Manaf, M. R. A., Amit, N., Ibrahim, N., & Shafurdin, N. S. (2021). Risk and protective factors of drug abuse among adolescents: a systematic review. *BMC Public Health*, *21*(1). https://doi.org/10.1186/S12889-021-11906-2

Negriff, S., Gordis, E. B., Susman, E. J., Kim, K., Peckins, M. K., Schneiderman, J. U., & Mennen, F. E. (2020). The Young Adolescent Project: A longitudinal study of the effects of maltreatment on adolescent development. *Development and Psychopathology*, *32*(4), 1440–1459. https://doi.org/10.1017/S0954579419001391

Nogovitsyn, N., Addington, J., Souza, R., Placsko, T. J., Stowkowy, J., Wang, J., Goldstein, B. I., Bray, S., Lebel, C., Taylor, V. H., Kennedy, S. H., & MacQueen, G. (2022). Childhood trauma and amygdala nuclei volumes in youth at risk for mental illness. *Psychological Medicine*, *52*(6), 1192–1199. https://doi.org/10.1017/S0033291720003177

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews*, *5*(1). https://doi.org/10.1186/S13643-016-0384-4

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, *372*. https://doi.org/10.1136/BMJ.N71

Pedersen, W., & Skrondal, A. (1996). Alcohol and sexual victimization: a longitudinal study of Norwegian girls. *Addiction*, *91*(4), 565–581. https://doi.org/10.1046/J.1360-0443.1996.91456511.X

Peeters, M., Oldehinkel, T., & Vollebergh, W. (2017). Behavioral Control and Reward Sensitivity in Adolescents' Risk Taking Behavior: A Longitudinal TRAILS Study. *Frontiers in Psychology*, *8*(FEB). https://doi.org/10.3389/FPSYG.2017.00231

Perez, D. M. (2000). The relationship between physical abuse, sexual victimization, and adolescent illicit drug use. *Journal of Drug Issues*, *30*(3), 641–662.

https://doi.org/10.1177/002204260003000308

Perkins, D. F., & Jones, K. R. (2004). Risk behaviors and resiliency within physically abused adolescents. *Child Abuse and Neglect*, *28*(5), 547–563. https://doi.org/10.1016/j.chiabu.2003.12.001

Porter, C., Palmier-Claus, J., Branitsky, A., Mansell, W., Warwick, H., & Varese, F. (2020). Childhood adversity and borderline personality disorder: a meta-analysis. *Acta Psychiatrica Scandinavica*, *141*(1), 6–20. https://doi.org/10.1111/ACPS.13118

Ramos-Olazagasti, M. A., Bird, H. R., Canino, G. J., & Duarte, C. S. (2017). Childhood Adversity and Early Initiation of Alcohol Use in Two Representative Samples of Puerto Rican Youth. *Journal of Youth and Adolescence*, *46*(1), 28–44. https://doi.org/10.1007/S10964-016-0575-2

Ramos de Oliveira, C. V., & Jeong, J. (2021). Exposure to violence, polyvictimization and youth's mental health and alcohol use in El Salvador. *Child Abuse & Neglect*, *118*, 105158. https://doi.org/10.1016/J.CHIABU.2021.105158

Riggs, S., Alario, A. J., & McHorney, C. (1990). Health risk behaviors and attempted suicide in adolescents who report prior maltreatment. *The Journal of Pediatrics*, *116*(5), 815–821. https://doi.org/10.1016/S0022-3476(05)82679-4

Rioux, C., Huet, A. S., Castellanos-Ryan, N., Fortier, L., Le Blanc, M., Hamaoui, S., Geoffroy, M. C., Renaud, J., & Seguin, J. R. (2021). Substance use disorders and suicidality in youth: A systematic review and meta-analysis with a focus on the direction of the association. *PloS One*, *16*(8). https://doi.org/10.1371/JOURNAL.PONE.0255799

Rogosch, F. A., Oshri, A., & Cicchetti, D. (2010). From child maltreatment to adolescent cannabis abuse and dependence: a developmental cascade model. *Development and Psychopathology*, *22*(4), 883–897. https://doi.org/10.1017/S0954579410000520

Rosario, M., Schrimshaw, E. W., & Hunter, J. (2004). Predictors of substance use over time among gay, lesbian, and bisexual youths: An examination of three hypotheses. *Addictive Behaviors*, *29*(8), 1623–1631. https://doi.org/10.1016/j.addbeh.2004.02.032

Rosenkranz, S. E., Muller, R. T., & Henderson, J. L. (2012). Psychological maltreatment in relation to substance use problem severity among youth. *Child Abuse & Neglect*, *36*(5), 438–448. https://doi.org/10.1016/J.CHIABU.2012.01.005

Rotheram-Borus, M. J., Mahler, K. A., Koopman, C., & Langabeer, K. (1996). Sexual abuse history and associated multiple risk behavior in adolescent runaways. *The American Journal of Orthopsychiatry*, *66*(3), 390–400. https://doi.org/10.1037/H0080189

Roy, É., Godin, G., Boudreau, J. F., Côté, P. B., Denis, V., Haley, N., Leclerc, P., & Boivin, J. F. (2011). Modeling initiation into drug injection among street youth. *Journal of Drug Education*, *41*(2), 119–134. https://doi.org/10.2190/DE.41.2.A

Russotti, J., Warmingham, J. M., Duprey, E. B., Handley, E. D., Manly, J. T., Rogosch, F. A., & Cicchetti, D. (2021). Child maltreatment and the development of psychopathology: The role of developmental timing and chronicity. *Child Abuse & Neglect*, *120*. https://doi.org/10.1016/J.CHIABU.2021.105215

Schär, S., Mürner-Lavanchy, I., Schmidt, S. J., Koenig, J., & Kaess, M. (2022). Child

maltreatment and hypothalamic-pituitary-adrenal axis functioning: A systematic review and meta-analysis. *Frontiers in Neuroendocrinology*, *66*, 100987. https://doi.org/10.1016/J.YFRNE.2022.100987

Schneiderman, J. U., Kennedy, A. K., Negriff, S., Jones, J., & Trickett, P. K. (2016). Maltreated and comparison adolescents' recollections of lifetime residences: Relationship to delinquency and marijuana use. *Journal of Child and Family Studies*, *25*(12), 3481–3487. https://doi.org/10.1007/S10826-016-0506-6

Shin, S. H., Edwards, E. M., & Heeren, T. (2009). Child abuse and neglect: relations to adolescent binge drinking in the national longitudinal study of Adolescent Health (AddHealth) Study. *Addictive Behaviors*, *34*(3), 277–280. https://doi.org/10.1016/J.ADDBEH.2008.10.023

Smith, C. A., Ireland, T. O., & Thornberry, T. P. (2005). Adolescent maltreatment and its impact on young adult antisocial behavior. *Child Abuse & Neglect*, *29*(10), 1099–1119. https://doi.org/10.1016/J.CHIABU.2005.02.011

Solakoglu, O., Driver, N., & Belshaw, S. H. (2018). The Effect of Sexual Abuse on Deviant Behaviors Among Turkish Adolescents: The Mediating Role of Emotions. *International Journal of Offender Therapy and Comparative Criminology*, *62*(1), 24–49. https://doi.org/10.1177/0306624X16642810

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J. B., Jones, P., Kim, J. H., Kim, J. Y., Carvalho, A. F., Seeman, M. V., Correll, C. U., & Fusar-Poli, P. (2022). Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. *Molecular Psychiatry*,

27(1), 281–295. https://doi.org/10.1038/S41380-021-01161-7

Somerville, L. H., & Casey, B. J. (2010). Developmental neurobiology of cognitive control and motivational systems. *Current Opinion in Neurobiology*, *20*(2), 236–241. https://doi.org/10.1016/J.CONB.2010.01.006

Squeglia, L. M., Jacobus, J., & Tapert, S. F. (2009). The Influence of Substance Use on Adolescent Brain Development. *Clinical EEG and Neuroscience : Official Journal of the EEG and Clinical Neuroscience Society (ENCS)*, *40*(1), 31. https://doi.org/10.1177/155005940904000110

Stockings, E., Hall, W. D., Lynskey, M., Morley, K. I., Reavley, N., Strang, J., Patton, G., & Degenhardt, L. (2016). Prevention, early intervention, harm reduction, and treatment of substance use in young people. *The Lancet Psychiatry*, *3*(3), 280–296. https://doi.org/10.1016/S2215-0366(16)00002-X

Stoltenborgh, M., Bakermans-Kranenburg, M. J., Alink, L. R. A., & van Ijzendoorn, M. H. (2015). The Prevalence of Child Maltreatment across the Globe: Review of a Series of Meta-Analyses. *Child Abuse Review*, *24*(1), 37–50. https://doi.org/10.1002/CAR.2353

Struck, N., Krug, A., Yuksel, D., Stein, F., Schmitt, S., Meller, T., Brosch, K., Dannlowski, U., Nenadić, I., Kircher, T., & Brakemeier, E. L. (2020). Childhood maltreatment and adult mental disorders – the prevalence of different types of maltreatment and associations with age of onset and severity of symptoms. *Psychiatry Research*, *293*. https://doi.org/10.1016/J.PSYCHRES.2020.113398

Sutton, T. E., & Simons, L. G. (2021). A Longitudinal Test of a Feminist Pathways

Model Among Black Youth: Incorporating Racial Discrimination and School Difficulties. *Feminist Criminology*, *16*(1), 26–46. https://doi.org/10.1177/1557085120923042

Teicher, M. H., Gordon, J. B., & Nemeroff, C. B. (2021). Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. *Molecular Psychiatry 2021 27:3*, *27*(3), 1331–1338. https://doi.org/10.1038/S41380-021-01367-9

Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nature Reviews. Neuroscience*, *17*(10), 652–666. https://doi.org/10.1038/NRN.2016.111

Thompson, S. J., Bender, K., Ferguson, K. M., & Kim, Y. (2015). Factors Associated With Substance Use Disorders Among Traumatized Homeless Youth. *Journal of Social Work Practice in the Addictions*, *15*(1), 66–89. https://doi.org/10.1080/1533256X.2014.996229

Tossone, K., Wheeler, M., Butcher, F., & Kretschmar, J. (2018). The Role of Sexual Abuse in Trauma Symptoms, Delinquent and Suicidal Behaviors, and Criminal Justice Outcomes Among Females in a Juvenile Justice Diversion Program. *Violence against Women*, *24*(8), 973–993. https://doi.org/10.1177/1077801217724921

Tyler, K. A., Gervais, S. J., & Davidson, M. M. (2013). The Relationship Between Victimization and Substance Use Among Homeless and Runaway Female Adolescents. *Journal of Interpersonal Violence*, *28*(3), 474–493. https://doi.org/10.1177/0886260512455517

Valério, I. D., Soares, A. L. G., Menezes, A. M. B., Wehrmeister, F. C., & Gonçalves, H. (2022). Child maltreatment and substances use throughout adolescence and adulthood: Data from a Brazilian Birth Cohort. *Child Abuse & Neglect*, *131*. https://doi.org/10.1016/J.CHIABU.2022.105766

Vasilenko, S. A., Evans-Polce, R. J., & Lanza, S. T. (2017). *Age trends in rates of substance use disorders across ages 18-90: Differences by gender and race/ethnicity*. https://doi.org/10.1016/j.drugalcdep.2017.08.027

Vaughn, M. G., Ollie, M. T., McMillen, J. C., Scott, L., & Munson, M. (2007). Substance use and abuse among older youth in foster care. *Addictive Behaviors*, *32*(9), 1929–1935. https://doi.org/10.1016/J.ADDBEH.2006.12.012

Vieira, I. S., Pedrotti Moreira, F., Mondin, T. C., Cardoso, T. de A., Branco, J. C., Kapczinski, F., Jansen, K., Souza, L. D. de M., & da Silva, R. A. (2020). Resilience as a mediator factor in the relationship between childhood trauma and mood disorder: A community sample of young adults. *Journal of Affective Disorders*, *274*, 48–53. https://doi.org/10.1016/J.JAD.2020.04.011

Wang, D. S., Chung, C. H., Chang, H. A., Kao, Y. C., Chu, D. M., Wang, C. C., Chen, S. J., Tzeng, N. S., & Chien, W. C. (2020). Association between child abuse exposure and the risk of psychiatric disorders: A nationwide cohort study in Taiwan. *Child Abuse & Neglect*, *101*. https://doi.org/10.1016/J.CHIABU.2020.104362

Witt, A., Münzer, A., Ganser, H. G., Fegert, J. M., Goldbeck, L., & Plener, P. L. (2016). Experience by children and adolescents of more than one type of maltreatment: Association of different classes of maltreatment profiles with clinical outcome

variables. *Child Abuse & Neglect*, *57*, 1–11. https://doi.org/10.1016/J.CHIABU.2016.05.001

Yen, C. F., Yang, M. S., Chen, C. C., Yang, M. J., Su, Y. C., Wang, M. H., & Lan, C. M. (2008). Effects of childhood physical abuse on depression, problem drinking and perceived poor health status in adolescents living in rural Taiwan. *Psychiatry and Clinical Neurosciences*, *62*(5), 575–583. https://doi.org/10.1111/J.1440-1819.2008.01836.X

Zhang, S., Lin, X., Liu, J., Pan, Y., Zeng, X., Chen, F., & Wu, J. (2020). Prevalence of childhood trauma measured by the short form of the Childhood Trauma Questionnaire in people with substance use disorder: A meta-analysis. *Psychiatry Research*, *294*. https://doi.org/10.1016/J.PSYCHRES.2020.113524

Zhu, Q., Gao, E., Cheng, Y., Chuang, Y. L., Zabin, L. S., Emerson, M. R., & Lou, C. (2015). Child Sexual Abuse and Its Relationship With Health Risk Behaviors Among Adolescents and Young Adults in Taipei. *Asia-Pacific Journal of Public Health*, *27*(6), 643–651. https://doi.org/10.1177/1010539515573075

4.7 Figures and Tables

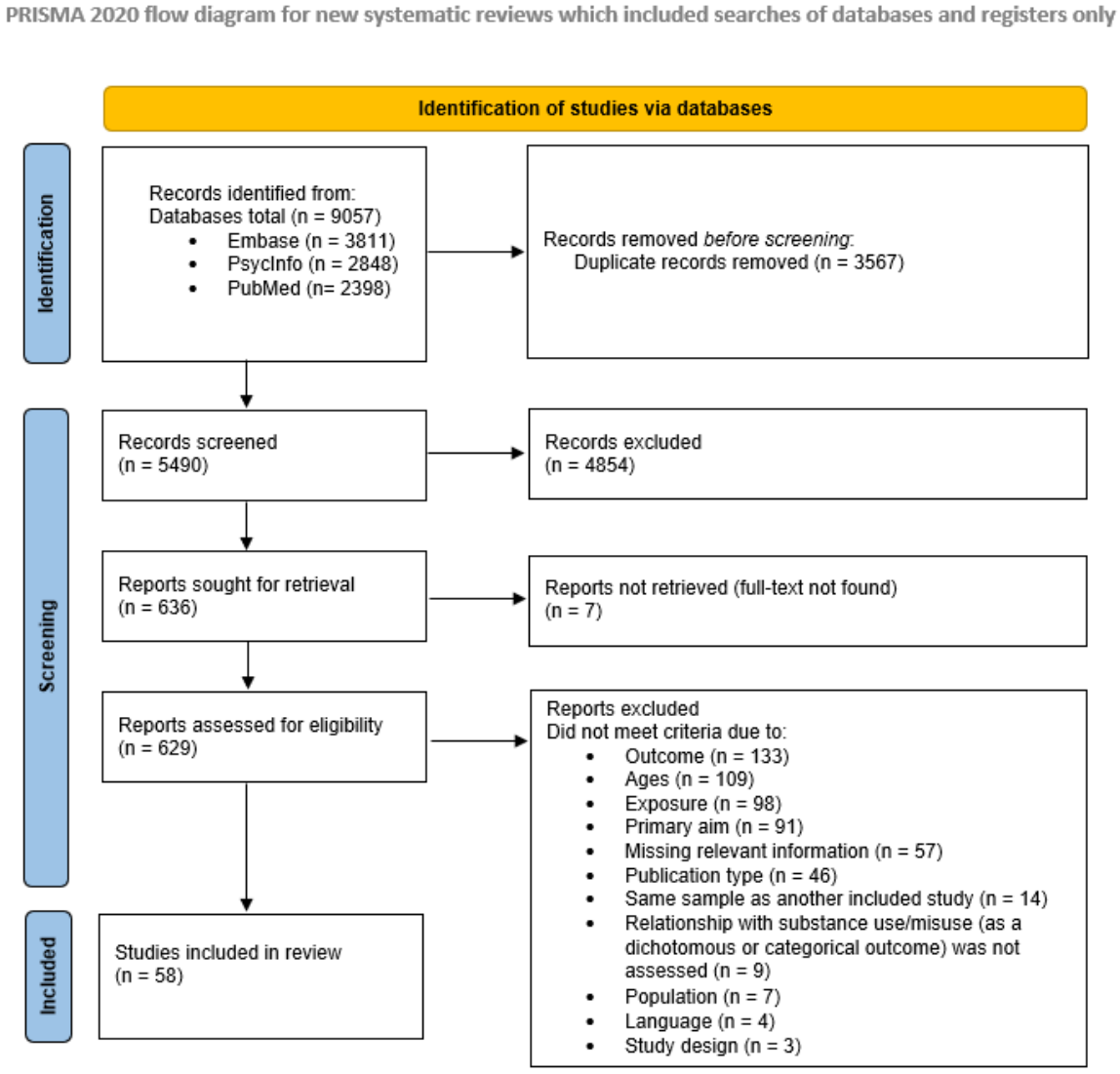
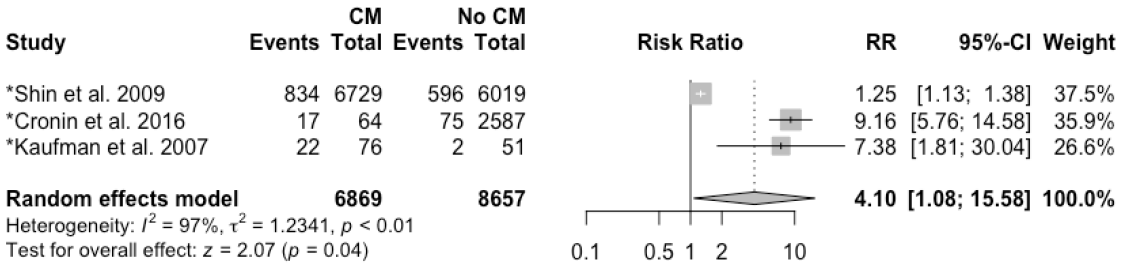
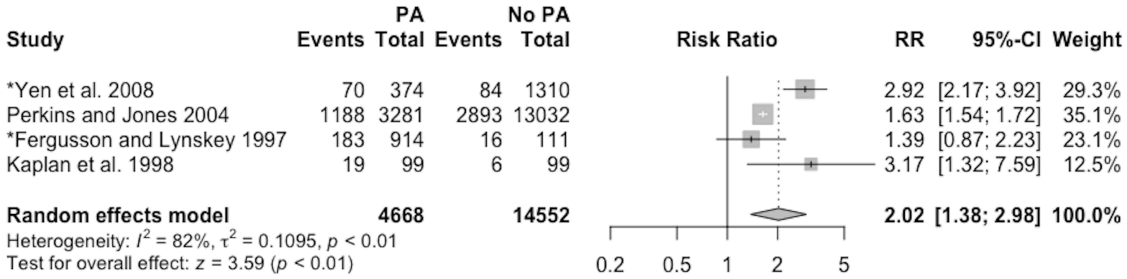


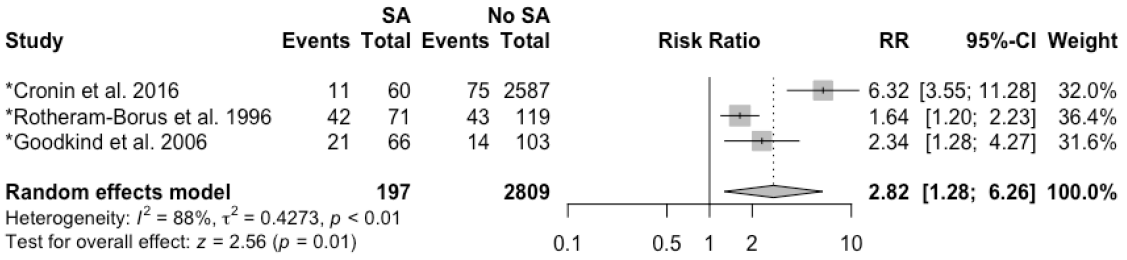
Figure 1. PRISMA flow diagram.



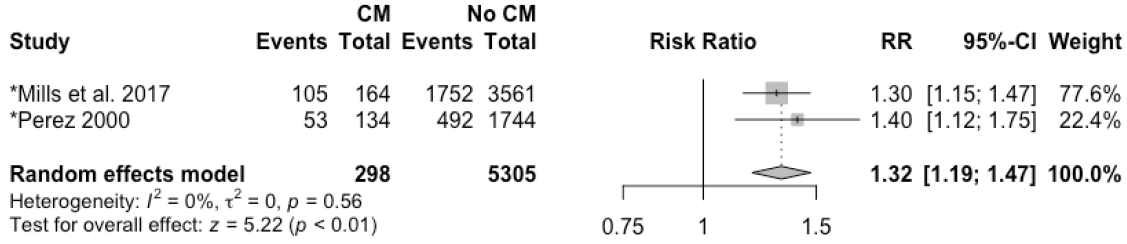
A) Unspecified childhood maltreatment with alcohol use



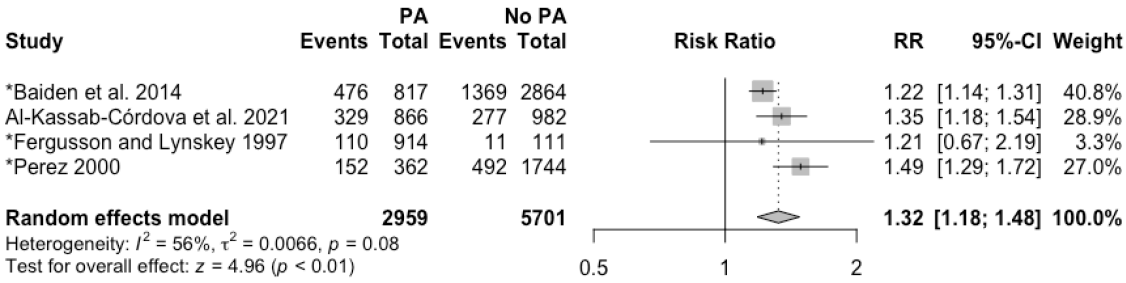
B) Physical abuse with alcohol use/misuse



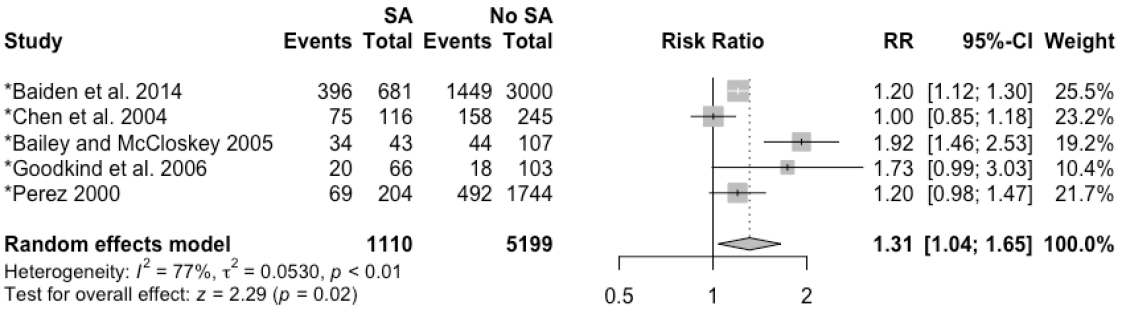
C) Sexual abuse with alcohol use



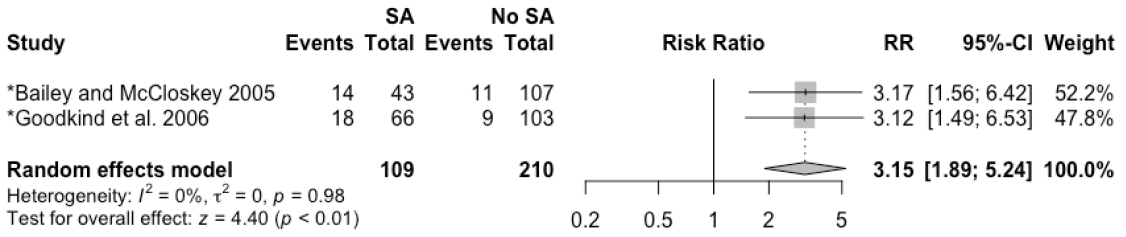
D) Unspecified childhood maltreatment with cannabis use



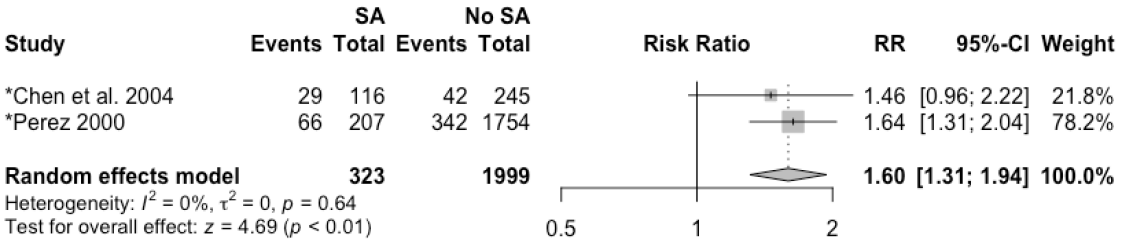
E) Physical abuse with cannabis use/misuse



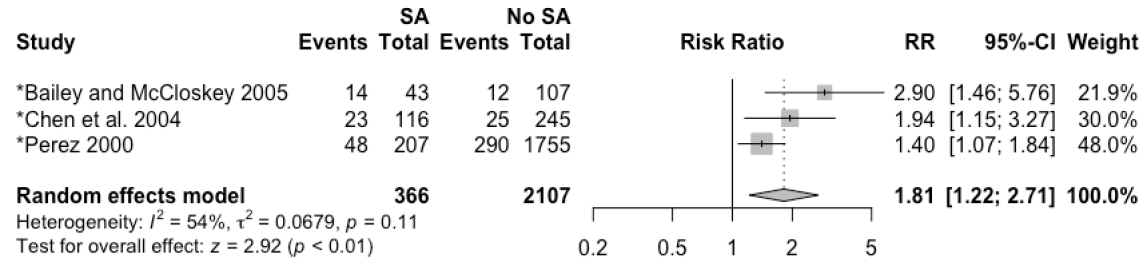
F) Sexual abuse with cannabis use



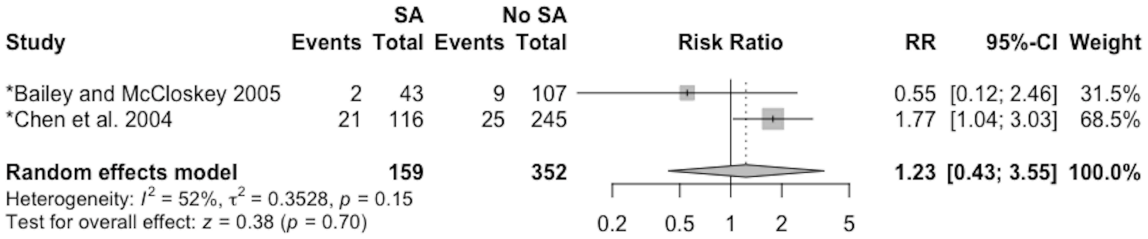
G) Sexual abuse with unspecified substance use



H) Sexual abuse with hallucinogen or LSD use



I) Sexual abuse with cocaine use



J) Sexual abuse with inhalant use

Figure 2. Meta-analysis results according to maltreatment type and substance type. A) Unspecified childhood maltreatment with alcohol use. B) Physical abuse with alcohol use/misuse. C) Sexual abuse with alcohol use. D) Unspecified childhood maltreatment with cannabis use. E) Physical abuse with cannabis use/misuse. F) Sexual abuse with cannabis use. G) Sexual abuse with unspecified substance use. H) Sexual abuse with hallucinogen or LSD use. I) Sexual abuse with cocaine use. J) Sexual abuse with inhalant use. An asterisk (*) indicates that calculations were made by the first author of the current paper to obtain all the required raw data numbers for the meta-analysis since the corresponding study did not explicitly state all the required raw data numbers. CI = Confidence Interval; CM = Childhood Maltreatment; PA = Physical Abuse; RR = Risk Ratio; SA = Sexual Abuse.

Table 1

Characteristics of the included studies.

Publication Description [Author(s), Publication year; Country in which the study was conducted]	Study Design	Sample Characteristics	Setting	Maltreatment Types and Assessments	Substance Types and Assessments	Numeric Results	Was there a significant association between childhood maltreatment as the exposure and substance use/misuse as the outcome? YES or NO
Aarons et al., 2008; The United States	Cross-sectional	N = 214 Percentage of females = 56.1% Age range = 13-18 years	Youth with an active child-welfare case	**PA, SA, PN, Emotional MAL (EA or EN):** CTQ categorized based on the Hierarchical Type classification scheme	**Lifetime SU and substance use disorder including alcohol, cannabis, amphetamines, hallucinogens, cocaine, and opiates:** The PEI and the CIDI-SAM "Youths were assigned a score from 0 to 3 based on degree of substance involvement: 0 (less than six lifetime occasions of substance use), 1 (more than five lifetime incidents of use, but did not meet criteria for a substance use disorder), 2 (criteria met for DSM–IV diagnosis of substance abuse), and 3 (criteria met for DSM–IV diagnosis of substance dependence)"	**Hierarchical regression analysis of SU involvement (step 3):** **SA:** B = 0.330, β = 0.184, $p < 0.01$ **PA:** B = -0.200, β = 0.096, $p < 0.1$, not significant **PN:** B = 0.378, β = 0.143, $p < 0.01$ **Emotional MAL (EA or EN):** B = -0.085, β = -0.021, not significant	YES: SA; PN NO: PA; Emotional MAL (EA or EN)

Afifi et al., 2020; Canada	Cross-sectional	N = 210 Percentage of females = 51.7% Age range = 14-17 years	Community-based sample of adolescents in Manitoba, Canada	**EA:** "How many times in the past 12 months has a parent or other adult living in your home said hurtful or mean things to you?" **EN:** 5 items related to EN from the CTQ asked in the present tense	**Alcohol use:** "In the past 12 months, how often did you drink alcohol?" **BD:** "How many times in the past 30 days have you had five or more drinks of alcohol on the same occasion?" **Alcohol intoxication:** "How many times in the past 30 days has drinking alcohol made you drunk (that is, you had so much to drink that you could not do what you wanted to do, or you threw up)?" **Cannabis use: "**In the past 12 months, how many times have you used marijuana/hashish (e.g., pot, weed)?" and "In a typical month (30 days), on average, how often do you use marijuana/hashish (e.g., pot, weed)?"	**EA and alcohol use (past 12 months):** OR = 2.00, 95% CI = [1.46, 2.73], $p \leq 0.001$; adjusted odds ratio (AOR) = 2.11, 95% CI = [1.47, 3.04], $p \leq 0.001$ **EA and BD (past 30 days):** OR = 2.25, 95% CI = [1.57, 3.22], $p \leq 0.001$; AOR = 2.31, 95% CI = [1.56, 3.43], $p \leq 0.001$ **EA and alcohol intoxication (past 30 days):** OR = 2.73, 95% CI = [1.88, 3.98], $p \leq 0.001$; AOR = 2.54, 95% CI = [1.69, 3.82], $p \leq 0.001$ **EN and alcohol use (past 12 months):** OR = 1.65, 95% CI = [1.02, 2.67], $p \leq 0.05$; AOR = 1.56, 95% CI = [0.90, 2.71], p = not significant **EN and BD (past 30 days):** OR = 2.19, 95% CI = [1.30, 3.69], $p \leq 0.01$; AOR = 2.11, 95% CI = [1.18, 3.80], $p \leq 0.05$ **EN and alcohol intoxication (past 30 days):** OR = 2.54, 95% CI = [1.49, 4.34], $p \leq 0.001$; AOR = 2.19, 95% CI = [1.21, 3.98], $p \leq 0.01$ **EA and cannabis use (past 12 months):** OR = 2.51, 95% CI = [1.78, 3.55], $p \leq 0.001$; AOR = 2.63, 95% CI = [1.81, 3.82], $p \leq 0.001$ **EA and cannabis use (typical month):** OR = 2.79, 95% CI = [1.78, 4.39], $p \leq 0.001$; AOR = 2.69, 95% CI = [1.66, 4.36], $p \leq 0.001$ **EN and cannabis use (past 12 months):** OR = 2.36, 95% CI = [1.42, 3.93], $p \leq 0.001$; AOR = 2.34, 95% CI = [1.35, 4.08], $p \leq 0.01$ **EN and cannabis use (typical month):** OR = 2.99, 95% CI = [1.64, 5.46], $p \leq 0.001$; AOR = 2.98, 95% CI = [1.53, 5.82], $p \leq 0.001$	YES: All listed MAL exposures and substance outcomes except for the one listed in the NO section, below NO: EN and alcohol use

Al-Kassab-Córdova et al., 2021; Peru	Cross-sectional	N = 1848 Percentage of females = 4.4% Age range = 14-22 years	Juvenile detention centers	**PA:** Questions about PA during childhood from a face-to-face questionnaire	**Frequent marijuana use:** The following 3 questions, "Did you use drugs before entering the juvenile detention center?, What type of drug did you use?, How often did you consume before entering the youth center?"; "frequent marijuana consumption was defined as the use of marijuana at least once a week, prior to entering the center"	**Bivariate analysis for PA during childhood and prevalence of frequent marijuana use:** PA = 37.99%, no PA = 28.21%; 95% CI = [34.8, 41.27], $p < 0.001$ **Multivariate analysis (Poisson regression) for PA during childhood and frequent marijuana use:** **Crude analysis:** Crude prevalence ratio = 1.35, 95% CI = [1.18, 1.53], $p < 0.001$ **Adjusted model:** Adjusted prevalence ratio = 1.23, 95% CI = [1.07, 1.40], $p = 0.002$	YES
Baiden et al., 2014; Canada	Cross-sectional	N = 3681 Percentage of females = 48.9% Age range = 12-18 years	Inpatient psychiatric hospital	**PA:** "any form of physical abuse experienced by the child (e.g. any incident resulting in non-accidental injury, physical confinement, excessive physical discipline or withdrawal of necessities of life such as food and shelter)" **SA**: "any form of non-consensual sexual contact (including but not limited to a child being subjected to non-consenting fondling, exposure of genitals, sexual intercourse/rape) experienced by the child" **EA**: "the ongoing emotional environment created by an abuser for the purposes of control such that the abused child's self-esteem, identity, energy, ability to feel and question, wants and needs are invalidated by the abuser"	**Cannabis use**: "Time since use of cannabis" over the past year; "cannabis use was measured as a binary variable and coded 1 if the adolescent reported using cannabis within the last 12 months, otherwise, it was coded as 0"	**Adjusted (multivariate logistic regression) and unadjusted (bivariate) OR for cannabis use:** **EA:** % without EA that used cannabis = 48.0%, % with EA that used cannabis: 54.3%; UOR = 1.29, 95% CI = [1.12, 1.48], $p < 0.001$; AOR = 1.04, 95% CI = [0.86, 1.27], not significant **PA:** % without PA that used cannabis = 47.8%, % with PA that used cannabis: 58.3%; UOR = 1.53, [1.30, 1.79], $p < 0.001$; AOR = 1.28, 95% CI [1.02, 1.60], $p < 0.05$ **SA:** % without SA that used cannabis = 48.3%, % with SA that used cannabis: 58.1%; UOR = 1.48, [1.25, 1.76], $p < 0.001$; AOR = 1.49 (1.19, 1.85), $p < 0.001$	YES: PA, and SA with cannabis use NO: EA with cannabis use

Bailey and McCloskey, 2005; The United States	Longitudinal; Prospective	N = 150 Percentage of females = 100% Age range = 6-19 years	Families recruited either from battered women's shelters or from the community	**CSA:** Mothers and children were asked open-ended questions about the child's sexual victimization including noncontact and contact SA prior to 14 years	**DU including marijuana, inhalants, crack or cocaine, crystal methamphetamine, and other drugs like heroin, uppers, or hallucinogens:** "Participants were asked whether they had ever tried any of the substances, and if so, how often they had used them in the month prior to the interview"	**Chi-square analyses for differences in substance use rates by sexual abuse group:** **Marijuana:** No SA = 41%, SA = 80%, $p < 0.01$ **Inhalants:** No SA = 8%, SA = 5%, not significant **Cocaine:** No SA = 11%, SA = 33%, $p < 0.01$ **Crystal methamphetamine:** No SA = 8%, SA = 31%, $p < 0.01$ **Other drugs (e.g., heroin, uppers, hallucinogens, etc.):** No SA = 10%, SA = 33%, $p < 0.01$	YES: Marijuana; cocaine; crystal methamphetamine; other drugs NO: Inhalants
Balázs et al., 2017; Hungary	Cross-sectional	N = 1981 Percentage of females = 49.1% Age range = 13-18 years	School-based sample including high school (grades 9-12) and primary school (grades 7-8) students	**SA:** "Have you ever been suffered from a sexual harassment by an older person?" **PA:** "Have you ever been abused physically by your parents or any other adults who live with you?" **Negative family interactions:** "During the past month, how often have your parents yelled at you/criticized your ideas/put their needs ahead of your needs/hit you?"	**Alcohol problem drinking behavior**: AUDIT	**Multiple linear regression models for adolescents' problem drinking (Model 2):** **PA:** $\beta = 0.09$, $p < 0.01$ **SA:** $\beta = 0.13$, $p < 0.001$ **Negative family interactions:** $\beta = 0.13$, $p < 0.001$	YES

Baron, 1999; Canada	Cross-sectional	N = 200 Percentage of females = 0% Age range = Preteens to 24 years	Selected youth from downtown who spend at least 3 hours a day, 3 days a week on the street or in a mall	**PA, and SA**: Asked about their experiences	**Alcohol use:** Asked if they had drunk any alcohol in the previous month **Marijuana/hash use, use of psychedelics or LSD, use of hard drugs (e.g., cocaine, amphetamines, heroin, etc.):** Asked how many times used in the last year	**Standardized betas for regression models:** **SA:** **Alcohol:** $\beta = 0.06$, $p > 0.05$ **Marijuana:** $\beta = 0.07$, $p > 0.05$ **Psychedelics:** $\beta = 0.07$, $p > 0.05$ **Hard drugs:** $\beta = 0.12$, $p > 0.05$ **PA:** **Alcohol:** $\beta = -0.13$, $p > 0.05$ **Marijuana:** $\beta = 0.09$, $p > 0.05$ **Psychedelics:** $\beta = 0.16$, $p < 0.05$ **Hard drugs:** $\beta = -0.00$, $p > 0.05$	YES: PA and psychedelics NO: All other listed MAL exposures and substance outcomes except for the one listed in the YES section, above
Berenson et al., 1992; The United States	Cross-sectional	N = 342 Percentage of females = 100% Age range = All 17 years and younger	Adolescents at their first prenatal visit at a teen pregnancy clinic	**PA, and SA:** Surveyed for history	**Alcohol use:** Questionnaire about use during pregnancy **Illicit DU:** Questionnaire about use during the previous 12 months	**Relative risk of SU among those with a history of violence compared to those without a history of violence (all subjects):** **PA and alcohol use:** OR = 1.6, 95% CI = [0.4, 7.0] **PA and illicit DU:** OR = 7.1, 95% CI = [2.2, 23.0] **SA and alcohol use:** OR = 6.1, 95% CI = [2.0, 19.0] **SA and illicit DU:** OR = 12.8, 95% CI = [4.0, 41.4] **Both (PA and SA) and alcohol use:** OR = 9.7, 95% CI = [3.1, 30.3] **Both (PA and SA) and illicit DU:** OR = 17.0, 95% CI = [5.1, 57.7]	YES: All listed MAL exposures and SU outcomes except for the one listed in the NO section, below NO: PA and alcohol use
Brown et al., 2009; Namibia, Swaziland, Uganda, Zambia, and Zimbabwe	Cross-sectional	N = 28,108 Percentage of females = 48.4% Age range = Approximately 13-16 years	School-based survey	**SV:** Survey question that asked, "Have you ever been physically forced to have sexual intercourse when you did not want to?"	**Alcohol use:** Survey question that asked, "During the past 30 days, on how many days did you have at least one drink containing alcohol?" **Lifetime DU:** Survey question that asked, "During your life, how many times have you used drugs, such as marijuana, njaga, bangi, opium, njaye, cocaine, crack, ecstasy, dagga, glue?"	**Relative frequency and AOR logistic regression results:** **SV with current alcohol use:** AOR = 2.48, 95% CI = [2.17, 2.83] **SV with lifetime DU:** AOR = 2.54, 95% CI = [2.15, 3.01]	YES

Burgess et al., 1987; The United States	Longitudinal; Prospective	**Study 1:** N = 34 Percentage of females = 64.7% Age range = 6-20 years	Sexually abused children were recruited upon identification of being involved in a sex ring; a control group of non-sexually abused siblings was used for comparison	**SA:** The sexually abused individuals participated in a semi-structured interview consisting of a section covering detailed information regarding each participant's SA experience including "descriptions of the sexual contact, the background of the offenders, the sex rings, and the prostitution; reports of abuse; and a summary of what happened in the criminal justice system"; the non-sexually abused control individuals participated in a semi-structured interview that consisted of questions regarding "any history of sexual abuse and exploitation and included a behaviour checklist, a delinquent behaviour checklist, the subject's sexual behaviour status..."	**Use of alcohol, marijuana, amphetamines, heroin, and psychedelics:** Semi-structured interview which included a behaviour checklist, a delinquent behaviour checklist, various scales (e.g., the Impact of Event Scale), and covered questions regarding the use of various substances	**Study 1:** **Alcohol use:** The only substance used significantly more frequently among abused participants in comparison to non-abused participants ($p = 0.05$)	YES: Alcohol NO: Marijuana; amphetamines; heroin; psychedelics
Burgess et al., 1987; The United States	Longitudinal; Prospective	**Study 2:** N = 34 Percentage of females = 0% Age range = 11-21 years	Sexually abused children were recruited upon identification of being involved in a sex ring; a control group of non-sexually abused children from the same schools as the sexually abused victims were	**SA:** The sexually abused individuals participated in a semi-structured interview consisting of a section covering detailed information regarding each participant's SA experience including "descriptions of the sexual contact, the background of the offenders, the sex rings, and the prostitution; reports of abuse; and a summary of what happened in the criminal justice	**Use of alcohol, marijuana, amphetamines, heroin, and psychedelics:** Semi-structured interview which included a behaviour checklist, a delinquent behaviour checklist, various scales (e.g., the Impact of Event Scale), and covered questions regarding the use of various substances	**Study 2:** **Use of amphetamines, heroin, and psychedelics:** These substances were used significantly more frequently among abused participants in comparison to non-abused participants ($p < 0.001$)	YES: Amphetamines; heroin; psychedelics NO: Alcohol; marijuana

			used for comparison	system"; the non-sexually abused control individuals participated in a semi-structured interview that consisted of questions regarding "any history of sexual abuse and exploitation and included a behaviour checklist, a delinquent behaviour checklist, the subject's sexual behaviour status..."			
Chau et al., 2019; France	Cross-sectional	N = 1559 Percentage of females = 50.1% Age range = 10-19 years	School-based sample of adolescents from middle schools in north-eastern France	**Sustained physical/verbal violence, and SA:** A 20-item scale was used to assess sustained physical/verbal violence, while SA referred to having experienced SA a minimum of one time	**Use of alcohol, cannabis, and other illicit drugs:** A self-administered questionnaire was used to obtain data regarding the use of alcohol, cannabis, and other illicit drugs over the last 30 days	**Negative binomial regression model:** **Sustained physical/verbal violence:** **Alcohol use:** gaRR = 1.90, 95% CI = [1.49, 2.42], $p < 0.001$ **Cannabis use:** gaRR = 3.84, 95% CI = [2.44, 6.07], $p < 0.001$ **Other illicit DU:** gaRR = 3.72, 95% CI = [1.94, 7.16], $p < 0.001$ **SA:** **Alcohol use:** gaRR = 2.55, 95% CI = [1.36, 4.77], $p < 0.01$ **Cannabis use:** gaRR = 8.38, 95% CI = [3.84, 18.3], $p < 0.001$ **Other illicit DU:** gaRR = 19.11, 95% CI = [8.39, 43.5], $p < 0.001$	YES

Chen et al., 2004; The United States	Cross-sectional	N = 361 Percentage of females = 100% Age range = 12-22 years	Homeless and runaway adolescents	**SA:** Asked, "how often a parent, a foster parent, adult relatives, or any other adult who was supposed to be taking care of the respondent had made verbal requests for sexual activity, or how often they made the respondents do something sexually or 'messed around' with them sexually"	**Use of marijuana, crank, other amphetamines, cocaine, opiates, hallucinogens, tranquilizers, barbiturates, and inhalants:** Asked, "how often respondents smoked marijuana, crank, other amphetamines, cocaine, opiates, hallucinogens, tranquilizers, barbiturates, and inhalants in the last 12 months"	**DU among female homeless and runaway adolescents:** **Marijuana:** No SA = 64.5%, SA = 65%, not significant **Crank (crank with amphetamines):** No SA = 10.8%, SA = 17.0%, not significant **Other amphetamines:** No SA = 20.8%, SA = 25.9%, not significant **Cocaine:** No SA = 10.0.%, SA = 19.6%, $p < 0.01$ **Opiates:** No SA = 38.0.%, SA = 5.4%, not significant **Hallucinogens:** No SA = 17.1.%, SA = 25.0%, $p < 0.05$ **Tranquilizers:** No SA = 5.0.%, SA = 9.8%, $p < 0.05$ **Barbiturates:** No SA = 5.0.%, SA = 10.7%, $p < 0.05$ **Inhalants:** No SA = 10.0.%, SA = 17.9%, $p < 0.05$	YES: Cocaine; hallucinogens; tranquilizers; barbiturates; inhalants NO: Marijuana; crank; other amphetamines; opiates
Cornelius et al., 2016; The United States	Longitudinal; Prospective	N = 917 Percentage of females = 49% Age range = 15.9-19.5 years at the 16-year follow-up assessment (followed from birth to about 16 years)	Offspring of mothers who were recruited from a prenatal clinic in Pennsylvania	**CM:** CTQ cumulative MAL exposure over the past 16 years as a continuous variable and as an ordinal variable with a cut point of moderate/severe MAL	**Drinking level (alcohol use):** Questions by Donovan (1994) which covered the frequency and quantity of alcohol use over the past years during the 16-year follow-up assessment; the average number of daily drinks was used to determine drinking level	**CM exposure and offspring level of drinking (bivariate relations):** Offspring drinking level: None = 2.0, ≤1 drink per week = 2.27, >1 drink per week = 2.4, $p < 0.001$ **CM exposure as a predictor of drinking level (multivariate analysis):** Coefficient = 0.25, cumulative OR = 1.40, $p < 0.01$	YES

Cronin et al., 2016; Denmark	Cross-sectional	N = 2980 Percentage of females = 47.8% Age range = All 24 years	Household telephone or home-based survey	**CM including PA, SA, EA, and NEG:** 20 questions across 4 CM domains	**Alcohol misuse:** "Have you ever had problems with alcohol (abuse or where you or others thought you had too large a consumption)?"	**Frequencies of MAL groups with alcohol misuse:** **Multiple abuse:** 26.6% **SA:** 16.9% **EA:** 10.3% **Non-abused:** 2.9% **Differences between MAL groups and alcohol misuse:** $\chi 2$ (3) = 135, $p < 0.001$ **Binary logistic analysis for alcohol misuse:** **Multiple abuse (overall):** OR = 13.09, 95% CI = [6.90, 24.83], $p < 0.001$ **SA (overall):** OR = 7.46, 95% CI = [3.66, 15.19], $p < 0.001$ **EA (overall):** OR = 4.23, 95% CI = [2.53, 7.07], $p < 0.001$	YES
Dembo et al., 1987; The United States	Cross-sectional	N = 145 Percentage of females = 48% Age range = 12-17 years	Youth detainees housed at a regional facility for at least 96 hours	**PA:** "(1) beaten or really hurt by being hit; (2) beaten or hit with a whip, strap, or belt; (3) beaten or hit with something "hard" (like a club or stick); (4) claimed a weapon had been used against them; (5) been hurt badly enough by an adult to need a doctor, bandages, or other medical treatment; (6) spent time in a hospital as a result of being physically injured by an adult" **Sexual victimization:** "All children who were 13 years of age or younger at the time of their first sexual experience with a person over the age of 18" or "youths whose first sexual experience with an adult took place between 14 and 17 years of age and who claimed they were forced or who reacted to the experience with shock or fear or had	**Lifetime illicit DU:** Adopted from the National Institute on Drug Abuse Survey; asked about age of first use, frequency, and lifetime use of marijuana/hashish, inhalants, hallucinogens, cocaine, heroin, barbiturates, sedatives, tranquilizers, stimulants, and analgesics (all nonmedical)	**Direct effects of PA on lifetime illicit DU:** Unstandardized coefficient = 0.279, $p < 0.05$; standardized coefficient = 0.248, significant **Direct effects of sexual victimization on lifetime illicit DU:** Unstandardized coefficient = 0.616, $p < 0.05$; standardized coefficient = 0.310, significant	YES

				this experience with a parent or stepparent"			
Fergusson and Lynskey, 1997; New Zealand	Cross-sectional analysis from a longitudinal study	N = 1025 Percentage of females = Not stated Age range = All 18 years	Birth cohort of children born in the urban Christchurch region of New Zealand	**Physical punishment/MAL:** Participants reported the extent to which their parent figures used physical methods of punishment on a five-point scale ranging from "parent never used physical punishment" to "parent treated me in a harsh and abusive way"	**Alcohol abuse/dependence, and cannabis abuse/dependence:** Questionnaires developed by Casswell, Stewart, Connolly, and Silva (1991), CIDI-SAM, and DSM-IV to assess substance abuse/dependence during the period from 16 to 18 years	**Rates of alcohol abuse/dependence (%) by extent of exposure to physical punishment:** **None:** 14.4 (unadjusted); 15.2 (adjusted) **Seldom:** 17.7 (unadjusted): 19.3 (adjusted) **Regular:** 37.2 (unadjusted); 24.2 (adjusted) **Severe/Harsh:** 32.5 (unadjusted); 29.7 (adjusted) $p < 0.001$ (unadjusted); $p < 0.05$ (adjusted) **Rates of cannabis abuse/dependence (%) by extent of exposure to physical punishment:** **None:** 9.9 (unadjusted); 10.1 (adjusted) **Seldom:** 10.6 (unadjusted); 11.3 (adjusted) **Regular:** 21.8 (unadjusted); 12.6 (adjusted) **Severe/Harsh:** 22.5 (unadjusted); 14.0 (adjusted) $p < 0.005$ (unadjusted); $p > 0.40$ (adjusted)	YES: Alcohol abuse/ dependence NO: Cannabis abuse/ dependence
Folk et al., 2021; The United States	Longitudinal; Prospective	N = 271 Percentage of females = 45.7% Age range = 12-18 years	Youth with an open status or delinquent petition filed through a large family court	**Abuse including EA, PA, and SA; NEG including EN, and PN:** CTQ short-Form; the Traumatic Life Events Inventory was also used to assess sexual assault which was considered as SA	**Alcohol use, and cannabis use:** Adolescent Risk Behaviour Assessment to assess past 120-day use	**Alcohol use:** **Abuse:** B = 0.61 (SE = 0.20), OR = 1.83, 95% CI = [1.24, 2.70]; $p < 0.01$ **NEG:** B = 0.25 (SE = 0.23), OR = 1.29, 95% CI = [0.82, 2.03]; not significant **Cannabis use:** **Abuse:** B = 0.29 (SE = 0.19), OR = 1.34, 95% CI = [0.93, 1.94]; not significant **NEG:** B = 0.11 (SE = 0.22), OR = 1.11, 95% CI = [0.73, 1.70]; not significant	YES: Abuse with alcohol use NO: Abuse with cannabis use; NEG with cannabis use; NEG with alcohol use

Fusco, 2021; The United States	Cross-sectional	N = 185 Percentage of females = 49.0% Age range = 18-24 years	Community sample of young adults recruited from an agency for those with a low-income	**PA, SA, EA, and NEG:** CTQ short-form	**Alcohol use:** Frequency of use in the past 30 days and in the past 90 days **Marijuana use:** Frequency of use in the past 30 days and in the past 90 days Note: "Frequent alcohol use and frequent marijuana use was defined as drinking alcohol or using marijuana, respectively, once a week or more in the past 90 days"	**Logistic regression model predicting frequent alcohol use:** **PA:** OR = 1.14, 95% CI = [0.88, 1.44], p = 0.086 (not significant) **SA:** OR = 2.63, 95% CI = [1.22, 5.73], p = 0.019 **EA:** OR = 4.01, 95% CI = [1.66, 7.21], p = 0.033 **NEG:** OR = 1.01, 95% CI = [0.49, 2.26], p = 0.946 (not significant) **Logistic regression model predicting frequent marijuana use:** **PA:** OR = 3.46, 95% CI = [1.92, 6.97], p = 0.039 **SA:** OR = 1.01, 95% CI = [0.93, 2.52], p = 0.781 (not significant) **EA:** OR = 9.38, 95% CI = [6.26, 12.14], p = 0.000 **NEG:** OR = 1.21, 95% CI = [0.69, 3.10], p = 0.862 (not significant)	YES: SA, and EA with alcohol use; PA, and EA with marijuana use NO: PA, and NEG with alcohol use; SA, and NEG with marijuana use

Goodkind et al., 2006; The United States	Cross-sectional analysis from a longitudinal study	N = 169 Percentage of females = 100% Age range = 11-21 years	Young women receiving services at agencies participating in the Female Adolescents and Justice study	**SA:** 1 item from the CTQ, "I believe that I was sexually abused"	**Alcohol consumption, marijuana consumption, and consumption of other illegal drugs:** Items from the Monitoring the Future Study, "asked to indicate the number of times they had used a variety of substances"; extensive use of alcohol and of marijuana was indicated by a cut-off of having used that substance 40 times or more, while consumption of other illegal drugs was indicated by ever using any other illegal drug since this was a rare occurrence	**Bivariate analyses (chi-square) comparisons of young women who have and have not experienced SA:** **40+ occasions of alcohol consumption in lifetime:** SA = 0.32, no SA = 0.14; $\chi 2$ = 7.53, $p < 0.01$ **40+ occasions of marijuana consumption in lifetime:** SA = 0.31, no SA = 0.17; $\chi 2$ = 4.39, $p < 0.05$ **Ever used other drugs:** SA = 0.27, no SA = 0.09; $\chi 2$ = 9.10, $p < 0.01$ **Regression analyses for effects of SA on:** **40+ occasions of alcohol consumption in lifetime:** Estimate = 0.90 (SE = 0.62); OR = 2.45, $R^2 = 0.20$, not significant **40+ occasions of marijuana consumption in lifetime:** Estimate = 0.39 (SE = 0.59); OR = 1.48, $R^2 = 0.21$, not significant **Ever used other drugs:** Estimate = 0.46 (SE = 0.68); OR = 1.58, $R^2 = 0.26$, not significant	NO
Grummitt et al., 2022; Australia	Cross-sectional	N = 569 Percentage of females = 70% Age range = 18-20 years	Young adults from Australia were recruited using online advertisements as well as professional networks	**EN, PN, EA, SA, and PA:** The Family Health History Questionnaire was used to assess the listed 5 types of MAL prior to 18 years **Combined NEG:** The scores of EN and PN were totaled to reflect combined NEG	**Alcohol use:** The AUDIT was used to assess problematic alcohol use and alcohol dependence **DU:** The Drug Use Disorders Identification Test was used to assess DU	**Linear regression for alcohol use as the outcome (Model 1 with combined NEG):** **SA:** b = 2.407, β = 0.147, 95% CI = [0.959, 3.855], p = 0.001 **PA:** b = 1.123, β = 0.100, 95% CI = [0.036, 2.211], p = 0.043 **Combined NEG:** b = 1.090, β = 0.088, 95% CI = [-0.175, 2.354], p = 0.091 (not significant) **Linear regression for alcohol use as the outcome (Model 2 with separate EN and PN):** **EN:** b = 0.587, β = 0.051, 95% CI = [-0.620, 1.794], p = 0.340 (not significant) **PN:** b = -0.722, β = -0.047, 95% CI = [-2.327, 0.782], p = 0.329 (not significant) **SA:** b = 2.511, β = 0.153, 95% CI = [1.051, 3.971], p = 0.001 **PA:** b = 1.238, β = 0.110, 95% CI = [0.144, 2.332], p = 0.027	YES: SA with DU; SA with alcohol use; PA with alcohol use NO: Combined NEG with DU, EN with DU; PN with DU; PA with DU; EA with DU; combined NEG with alcohol use; EN with alcohol use; PN with alcohol use; EA with alcohol use

						Linear regression for DU as the outcome (Model 1 with combined NEG): **SA:** b = 2.289, β = 0.178, 95% CI = [1.196, 3.382], p = 0.000 **Combined NEG:** b = -0.201, β = -0.021, 95% CI = [-1.151, 0.749], p = 0.677 (not significant) **Linear regression for DU as the outcome (Model 2 with separate EN and PN):** **EN:** b = 0.270, β = 0.030, 95% CI = [-0.635, 1.174], p = 0.559 (not significant) **PN:** b = 0.091, β = 0.007, 95% CI = [-1.077, 1.260], p = 0.878 (not significant) **SA:** b = 2.257, β = 0.175, 95% CI = [1.158, 3.355], p = 0.000	
Hébert et al., 2021; France	Cross-sectional	N = 2309 Percentage of females = 79.3% Age range = 14-23 years	Undergraduate students	**CSA:** Screening questions about sexual abuse ("Have you ever been touched sexually when you did not want to, or have you ever been manipulated, blackmailed, or physically forced to touch sexually?" and "Has anyone ever used manipulation, blackmail or physical force, to force or obligate you to have sex [including all sexual activities involving oral, vaginal, or anal penetration]")	**Alcohol use, cannabis use, and other DU (e.g., ecstasy, amphetamines, speed, cocaine, acid, etc.):** Screening tool for problematic consumption of alcohol and drugs for adolescents (DEP-ADO); "This scale measures how often, in the last 12 months, participants ingested alcohol, cannabis, or other drugs (e.g., ecstasy, amphetamines, speed, cocaine, acid, etc.)"	**Logistic regression models:** **CSA and alcohol use:** Estimate = 0.346, SE = 0.255, Z = 1.355, p = 0.175 **CSA and cannabis use:** Estimate = 0.546, SE = 0.164, Z = 3.333, p = 0.001 **CSA and other DU:** Estimate = 0.546, SE = 0.345, Z = 1.582, p = 0.114	YES: Cannabis use NO: Alcohol use; other DU
Houtepen et al., 2020; The United Kingdom	Longitudinal; Prospective and Retrospective	N = 4917 Percentage of females = 50.1% Age range = 0-22 years	A population-based sample of offspring involved in a birth cohort study in the United Kingdom that collected data during pregnancy and throughout	**SA:** "Ever sexually abused or forced to perform sexual acts or touch someone in a sexual way" **PA:** "Adult in family was ever physically cruel towards or hurt the child" **EA:** "Parent was ever emotionally cruel towards the child or often said hurtful/insulting	**Harmful alcohol use:** At 17 years, the AUDIT was used to assess harmful alcohol use (indicated by a score of greater than or equal to 16) **Illicit DU:** At 17 years, any use of the following substances during the prior 12 months was assessed: "cocaine,	**Results of the logistic regression analyses:** **Harmful alcohol use:** **PA (basic model):** AOR = 1.28, 95% CI = [1.00, 1.65], p = 0.051 (not significant) **PA (adjusted model):** AOR = 1.22, 95% CI = [0.94, 1.58], p = 0.144 (not significant) **SA (basic model):** AOR = 1.53, 95% CI = [1.00, 2.34], p = 0.052 (not significant) **SA (adjusted model):** AOR = 1.46, 95% CI = [0.93, 2.27], p	YES: PA with illicit DU; EA with illicit DU NO: All MAL exposures with harmful alcohol use; SA with illicit DU; EN with illicit DU

the subsequent years up until the children were 22 years	things to the child" **EN:** "Child always felt excluded, misunderstood, or never important to family, parents never asked or never listened when child talked about their free time" Note: Data from ages 0 to 8 years were reported by parents, data at subsequent ages were self-reported, and data at ages 20 years and older were retrospective since CM was assessed from birth to 16 years	amphetamines, inhalants, sedatives, hallucinogens, or opioids"; additionally, the 6-item cannabis abuse screen test was used to measure problematic cannabis use over the past 12 months	= 0.097 (not significant) **EA (basic model):** AOR = 1.22, 95% CI = [0.93, 1.59], p = 0.146 (not significant) **EA (adjusted model):** AOR = 1.12, 95% CI = [0.84, 1.49], p = 0.435 (not significant) **EN (basic model):** AOR = 0.96, 95% CI = [0.71, 1.29], p = 0.783 (not significant) **EN (adjusted model):** AOR = 0.94, 95% CI = [0.69, 1.28], p = 0.706 (not significant) **Illicit DU:** **PA (basic model):** AOR = 1.68, 95% CI = [1.35, 2.10], p < 0.001 **PA (adjusted model):** AOR = 1.58, 95% CI = [1.25, 2.00], p < 0.001 **SA (basic model):** AOR = 1.54, 95% CI = [1.02, 2.32], p = 0.040 **SA (adjusted model):** AOR = 1.41, 95% CI = [0.91, 2.17], p = 0.121 (not significant) **EA (basic model):** AOR = 1.85, 95% CI = [1.49, 2.29], p < 0.001 **EA (adjusted model):** AOR = 1.65, 95% CI = [1.31, 2.08], p < 0.001 **EN (basic model):** AOR = 1.12, 95% CI = [0.87, 1.44], p = 0.376 (not significant) **EN (adjusted model):** AOR = 1.09, 95% CI = [0.84, 1.42], p = 0.496 (not significant)

Hussey and Singer, 1993; The United States	Cross-sectional	N = 174 Percentage of females = 74.71% Age range = 12-18 years	Psychiatric inpatients	**SA:** Adolescent Sexual Questionnaire	**Use of alcohol, and DU including cocaine, downers (depressants), marijuana, and uppers (stimulants):** Adolescent Drug and Alcohol Inventory	**Patterns of SA and DU:** **No DU and SA:** 49.4%; **no DU and no SA:** 70.2%, $\chi2$ = 7.690, df = 1, p = 0.005 **Marijuana use and SA:** 43.7%; **marijuana use and no SA:** 26%, $\chi2$ = 4.946, df = 1, p = 0.026 **Uppers use and SA:** 11.5%; **uppers use and no SA:** 0%, $\chi2$ = 10.254, df = 1, p = 0.001 **Cocaine use and SA:** 6.9%; **cocaine use and no SA:** 2.3%, $\chi2$ = 1.954, df = 1, p = 0.162 (not significant) **Downers use and SA:** 2.3%; **downers use and no SA:** 1.1%, $\chi2$ = 3.046, df = 1, p = 0.581 (not significant) **Used drugs 2-3 times/month:** SA = 31%; no SA = 13.8%, t = 2.31, df = 163, p = 0.044 **Patterns of SA and alcohol use:** **Drank 2+ times/month:** SA = 20.6%; no SA = 13.8%, not significant **Been very drunk 3+ times in the past 2 months:** SA = 22.8%; no SA = 14.8%, t = 1.66, df = 171, p = 0.049	YES: DU; marijuana use; uppers use; frequency of DU (2-3 times/month); recent drunkenness NO: Cocaine use; downers use; frequency of alcohol use (2+ times/ month)
Kaplan et al., 1998; The United States	Cross-sectional	N = 198 Percentage of females = 50% Age range = 12-18 years	PA participants were recruited from the CA register for the New York State Department of Social Services following the confirmation of PA; probability sampling was used to recruit non-abused participants from the same communities as the PA participants	**PA:** Severity of PA was calculated using a scoring system and CPS reports which included information regarding evidence of physical assault or injury; Any potential participants with confirmed SA were excluded based on a 12-item screening questionnaire and any potential non-abused comparison participants with confirmed PA were excluded based on the Conflict Tactics Scale	**Alcohol abuse or dependence:** A blinded best-estimate procedure was used independently by the first two authors to determine each adolescent diagnosis while referring to The Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version modified for DSM-III-R and school/medical records	**Number of PA participants and non-abused comparison participants with lifetime and current alcohol abuse or dependence diagnoses:** **Lifetime alcohol abuse or dependence:** PA group: n = 19/99; comparison group: n = 6/99; $\chi2$ (df = 1) = 6.59, p = 0.01 **Current alcohol abuse or dependence:** PA group: n = 6/99; comparison group: n = 3/99; Fisher's exact test = not significant	YES

			for comparison				
Kappel et al., 2021; Honduras	Cross-sectional	N = 2701 Percentage of females = 53.2% Age range = 18-24 years	Geographically clustered design; individuals selected from randomly selected households in randomly selected geographic locations within Honduras	**SV, PV, and EV:** ISPCAN Child Abuse Screening Tool-Retrospective	**BD:** Females were asked "in the past 30 days, on how many days did you have 4 or more drinks of alcohol in a row?" and males were asked "in the past 30 days, on how many days did you have 5 or more drinks of alcohol in a row?" **DU:** Participants were asked "if they used drugs such as marijuana, pills, ecstasy, or sniffed any chemical such as petrol or glue in the last 30 days, with yes or no response options"	**BD:** **SV:** AOR = 1.2, 95% CI = [0.8, 1.7], p = 0.3639 (not significant) **PV:** AOR = 1.4, 95% CI = [1.1, 1.9], p = 0.0064 **EV:** AOR = 1.3, 95% CI = [0.9, 2.0], p = 0.1955 (not significant) **DU:** **SV:** AOR = 2.3, 95% CI =[1.1, 4.6], p = 0.0245 **PV:** AOR = 4.2, 95% CI = [2.3, 7.7], p < 0.001 **EV:** AOR = 2.2, 95% CI = [1.2, 4.2], p = 0.0170	YES: PV, SV, and EV with DU; PV with BD NO: SV, and EV with BD
Kaufman et al., 2007; The United States	Longitudinal; Prospective	N = 127 Percentage of females = 58% Age range = 8.1-16.5 years	MAL group children were recruited from a Connecticut State intervention program, SAFE Homes; demographically matched community control children were recruited from targeted mail and newspaper ads	**MAL:** "Multiple informants and data sources (e.g., caseworkers, parents, the children, and protective-services case records)"; MAL children were "removed from parental care as a result of reports of abuse or neglect"	**Alcohol use:** The PEI; asked "Have you had alcoholic beverages including beer, wine, or liquor to drink?" as well as additional questions about age of first alcohol use, regular alcohol use, and intoxication episodes	**Generalized estimating equation analysis examining the effect of MAL in predicting the onset of early alcohol use:** $\chi 2$ (df = 1) = 4.84, p = 0.03 **MAL and having had first alcoholic beverage:** MAL group = 29%; control group = 4%, Fisher's exact test = 12.1, p < 0.001 **MAL and ever gotten drunk:** MAL group = 11%; control group = 0%, Fisher's exact test = 5.7, p < 0.02	YES

Kenny and Schreiner, 2009; Australia	Cross-sectional	N = 777 Percentage of females = 14.7% Age range = 16-21 years	Young offenders on community orders supervised by the Department of Juvenile Justice	**EA, EN, and PN:** CTQ	**High-risk drinking (alcohol use):** Participants were asked to indicate the number of standard drinks (according to the National Health and Medical Research Council) they consumed on a regular basis; problem drinkers were identified on the basis of average daily number of standard drinks according to the Australian Alcohol Guidelines, "high-risk drinking was determined as 28 or more standard drinks per week consumed by males and 15 or more standard drinks per week consumed by females"	**EA and high-risk drinking:** not significant **EN and high-risk drinking:** not significant **PN and high-risk drinking:** not significant	NO
Kilpatrick et al., 2000; The United States	Cross-sectional	N = 3907 Percentage of females = 48.73% Age range = 12-17 years	Household probability sample of adolescents, interviewed by telephone	**Sexual assault, and physical assault:** Highly structured telephone interview involving "Contextually orienting prefatory statements followed by behaviorally specific closed-ended questions"	**Substance abuse/dependence including alcohol, marijuana, and other hard drugs:** DSM-IV criteria for abuse or dependence of each type of substance over the past year	**Physical assault (univariate analyses):** **Alcohol abuse/dependence:** OR = 3.93, P < 0.001 **Marijuana abuse/dependence:** OR = 4.84, p < 0.001 **Hard drug abuse/dependence:** OR = 12.35, p < 0.001 **Sexual assault (univariate analyses):** **Alcohol abuse/dependence:** OR = 4.55, p < 0.001 **Marijuana abuse/dependence:** OR = 3.80, p < 0.001 **Hard drug abuse/dependence:** OR = 8.59, p < 0.001 **Physical assault (multivariate analyses final model):** **Alcohol abuse/dependence:** B = 0.54, SE = 0.20, OR = 1.71, p < 0.01 **Marijuana abuse/dependence:** B = 0.57, SE = 0.20, OR = 1.76, p < 0.01	YES: All listed MAL exposures and substance outcomes except for the one listed in the NO section, below NO: Sexual assault with marijuana abuse/ dependence

Hard drug abuse/dependence: B = 1.19, SE = 0.45, OR = 3.28, $p < 0.01$

Sexual assault (multivariate analyses final model):
Alcohol abuse/dependence: B = 0.87, SE = 0.24, OR = 2.40, $p < 0.01$
Marijuana abuse/dependence: B = 0.45, SE = 0.25, OR = 1.56, not significant
Hard drug abuse/dependence: B = 0.94, SE = 0.42, OR = 2.56, $p < 0.05$

Lei et al., 2018; China	Cross-sectional	N = 10,904 Percentage of females = 52.9% Age range = 12-20 years	A senior high school-based sample was recruited from Chongqing, China using multi-stage stratified cluster random sampling	**PA, EA, SA, PN, and EN:** The 5 subscales of the CTQ in Chinese were used to determine whether participants had experienced PA, EA, SA, PN, and EN	**NMPOU:** "Have you ever used the following list of prescription opioid drugs even once not to treat an illness but for the feeling or experience caused by the drug without a doctor's prescription?"; the list of drugs consisted of "cough syrup compounded with codeine (codeine), compounded licorice tablets (opium), tramadol hydrochloride, and diphenoxylate"	**Association with lifetime NMPOU:** **CTQ PA scores:** t-test = -8.774, $p < 0.001$ **CTQ EA scores:** t-test = -8.657, $p < 0.001$ **CTQ SA scores:** t-test = -7.202, $p < 0.001$ **CTQ PN scores:** t-test = -7.742, $p < 0.001$ **CTQ EN scores:** t-test = -7.410, $p < 0.001$ **Univariate logistic regression model for lifetime NMPOU (unadjusted model 1):** **PA:** OR = 1.13, 95% CI = [1.10, 1.16], $p < 0.001$ **EA:** OR = 1.08, 95% CI = [1.06, 1.10], $p < 0.001$ **SA:** OR = 1.10, 95% CI = [1.07, 1.12], $p < 0.001$ **PN:** OR = 1.08, 95% CI = [1.06, 1.11], $p < 0.001$ **EN:** OR = 1.04, 95% CI = [1.03, 1.06], $p < 0.001$ **Multivariate logistic regression model for lifetime NMPOU (adjusted model 2):** **PA:** AOR = 1.11, 95% CI = [1.07, 1.14], $p < 0.001$ **EA**: AOR = 1.05, 95% CI = [1.03, 1.08], $p < 0.001$ **SA**: AOR = 1.04, 95% CI = [1.01, 1.07], $p < 0.019$ **PN:** AOR = 1.06, 95% CI = [1.04, 1.09], $p < 0.001$ **EN:** AOR = 1.03, 95% CI = [1.02, 1.04], $p < 0.001$	YES

Lin et al., 2011; China	Cross-sectional	N = 683 Percentage of females = 51.5% Age range = 8-18 years	Children and adolescents in rural areas of Hunan province in China were recruited using a multi-stage, convenience sampling technique	**CSA:** CSA, including 3 items regarding non-physical contact CSA and 9 items regarding physical contact CSA, prior to 16 years was assessed using the Child Sexual Abuse Scale	**BD:** One item asking about the "number of days having 5 or more drinks in 1 drinking episode" was used to assess BD	**Logistic regression of the effect of overall CSA on BD:** OR = 2.68, 95% CI = [1.26, 5.73], $p < 0.05$	YES
Lo and Cheng, 2007; The United States	Longitudinal; Prospective	N = 762 Percentage of females = 51% Age range = 10-24 years	First 5 + 7th waves of National Youth Survey interviews	**PA, and chronic PA:** Reported "being the subject of one of 3 acts: an attack with a weapon, a physical beating by parents, or a physical beating at the hands of others" **SA, and chronic SA:** Reported "being the subject of a sexual attack"	**Current abuse of alcohol, and marijuana:** Asked about "eight behaviors manifesting interpersonal problems, failed role fulfillment, and harmful consequences of use" over the past year based on the DSM-IV criteria for current alcohol abuse, and current marijuana abuse	**Logistic regression results for substance abuse models:** **Current alcohol abuse:** **PA:** b = 0.31, $p < 0.05$ **Chronic PA:** b = 0.15, $p < 0.01$ **SA:** b = -0.01, not significant **Chronic SA:** b = 0.12, not significant **Current marijuana abuse:** **PA:** b = 0.59, $p < 0.05$ **Chronic PA:** b = 0.23, $p < 0.01$ **SA:** b = 0.01, not significant **Chronic SA:** b = -0.10, not significant	YES: PA with all substance outcomes NO: SA with all substance outcomes
Martin et al., 1999; The United States	Cross-sectional	N = 703 Percentage of females = 100% Age range = 12-19 years	Patients in a prenatal care program	**PV, and SV:** Abuse Assessment Screen	**Alcohol use, and illicit DU:** Asked questions regarding use over the past year	**Alcohol use:** **PV:** OR = 2.54, 95% CI = [1.62, 3.98] **SV:** OR = 2.39, 95% CI = [1.20, 4.77] **Both PV and SV:** OR = 5.90, 95% CI = [3.22, 10.80] **Illicit DU:** **PV:** OR = 4.25, 95% CI = [2.43, 7.43] **SV:** OR = 3.11, 95% CI = [1.34, 7.22] **Both PV and SV:** OR = 6.44, 95% CI = [3.42, 12.09]	YES

Mills et al., 2014; Australia	Longitudinal; Prospective	N = 5158 Percentage of females = About 48% Age range = About 0-14 years	Birth cohort study that recruited pregnant women attending the Mater Misericordiae Mothers' Hospital for their first prenatal visit	**CM including any reported MAL, PA only, SA only, NEG/EA, SA +1 or more other, and PA + NEG/EA:** Records of the Queensland Department of Families, Youth and Community Care including reports of suspected abuse and NEG that met the threshold for investigation	**Alcohol use including any drinking, and heavy drinking:** "How often do you drink alcohol? (daily; a few times a week; a few times a month; a few times a year; rarely; and never)", "how much do you drink on those occasions? (seven or more glasses; three or four glasses; one or two glasses; less than one glass; never drink)"; any alcohol use referred to ever drunk a full glass of alcohol, while heavy alcohol use referred to having had five or more drinks in a session or three or more each month at the 14-year follow-up period	**Any alcohol use:** **Any reported MAL:** UOR = 1.62, 95% CI = [1.27, 2.06], p < 0.001; AOR = 1.42, 95% CI = [1.10, 1.83], p = 0.007; additional AOR = 1.13, 95% CI = [0.85, 1.50], p = 0.413 **PA only:** UOR = 1.09, 95% CI = [0.45, 2.63], p = 0.845; AOR = 1.11, 95% CI = [0.45, 2.71], p = 0.822; additional AOR = 0.79, 95% CI = [0.30, 2.12], p = 0.641 **SA only:** UOR = 0.61, 95% CI = [0.24, 1.53], p = 0.291; AOR = 0.52, 95% CI = [0.20, 1.33], p = 0.171, additional AOR = 0.44, 95% CI = [0.16, 1.21], p = 0.112 **NEG/EA:** UOR = 2.91, 95% CI = [1.89, 4.46], p < 0.001; AOR = 2.38, 95% CI = [1.52, 3.74], p < 0.001; additional AOR = 1.78, 95% CI = [1.06, 2.97], p = 0.028 **SA +1 or more other:** UOR = 1.60, 95% CI = [0.95, 2.68], p = 0.077; AOR = 1.40, 95% CI = [0.82, 2.40], p = 0.216; additional AOR = 1.24, 95% CI = [0.68, 2.25], p = 0.486 **PA + NEG/EA:** UOR = 1.48, 95% CI = [1.01, 2.19], p = 0.045; AOR = 1.33, 95% CI = [0.89, 1.99], p = 0.169; additional AOR = 1.05, 95% CI = [0.67, 1.65], p = 0.819 **Heavy alcohol use:** **Any reported MAL:** UOR = 2.55, 95% CI = [1.80, 3.61], p < 0.001; AOR = 1.95, 95% CI = [1.34, 2.84], p < 0.001; additional AOR = 1.36, 95% CI = [0.89, 2.09], p = 0.890 **PA only:** UOR = 0.65, 95% CI = [0.09, 4.76], p = 0.669; AOR = 0.61, 95% CI = [0.08, 4.58], p = 0.634; additional AOR = 0.34, 95% CI = [0.04, 2.80], p = 0.318 **SA only:** UOR = 0.86, 95% CI = [0.21, 3.58], p = 0.838; AOR = 0.67, 95% CI = [0.16, 2.85], p = 0.590; additional AOR = 0.56, 95% CI = [0.12, 2.69], p = 0.472 **NEG/EA:** UOR = 5.63, 95%	YES: NEG/EA with any alcohol use; NEG/EA with heavy alcohol use NO: All listed MAL exposures and substance outcomes except for the ones listed in the YES section, above

						CI = [3.27, 9.69], p < 0.001; AOR = 3.82, 95% CI = [2.13, 6.84], p < 0.001; additional AOR = 2.63, 95% CI = [1.31, 5.26], p = 0.006 **SA +1 or more other:** UOR = 1.79, 95% CI = [0.77, 4.18], p = 0.178; AOR = 1.34, 95% CI = [0.56, 3.24], p = 0.510; additional AOR = 1.00, 95% CI = [0.37, 2.70], p = 0.999 **PA + NEG/EA:** UOR = 2.48, 95% CI = [1.45, 4.26], p = 0.001; AOR = 1.98, 95% CI = [1.11, 3.50], p = 0.019; additional AOR = 1.37, 96% CI = [0.71, 2.63], p = 0.349	
Mills et al., 2017; Australia	Longitudinal; Prospective	N = 3778 Percentage of females = 52.62% Age range = About 0-21 years	Birth cohort study that recruited pregnant women attending the Mater Misericordiae Mothers' Hospital for their first prenatal visit	**CM including any MAL, any SA (+/- other abuse/NEG), any PA (+/- EA/NEG), and EA +/- NEG:** Records of the Queensland state child protection agency; "exposure to child maltreatment is defined by the occurrence of one or more substantiated notifications"	**Cannabis use:** Participants were asked questions regarding whether they had ever used cannabis before, the age at which they had first used cannabis, and their frequency of cannabis use **Cannabis abuse/dependence:** CIDI-SAM based on DSM-IV	**Any lifetime cannabis use:** **Any MAL:** AOR = 1.83, 95% CI = [1.32, 2.53], p < 0.001; additional AOR = 1.60, 95% CI = [1.08, 2.39], p = 0.020 **Any SA (+/- other abuse/NEG):** AOR = 1.75, 95% CI = [1.00, 3.08], p = 0.050; additional AOR = 1.45, 95% CI = [0.77, 2.72], p = 0.247 **Any PA (+/- EA/NEG):** AOR = 1.99, 95% CI = [1.16, 3.44], p = 0.013; additional AOR = 1.74, 955 CI = [0.91, 3.34], p = 0.095 **EA +/- NEG:** AOR = 1.73, 95% CI = [0.98, 3.06], p = 0.059; additional AOR= 1.66, 95% CI = [0.75, 3.64], p = 0.210 **Early cannabis use (prior to 17):** **Any MAL:** AOR = 2.36, 95% CI = [1.72, 3.24], p < 0.001; additional AOR = 2.47, 95% CI = [1.67, 3.65], p < 0.001 **Any SA (+/- other abuse/NEG):** AOR = 2.10, 95% CI = [1.22, 3.64], p = 0.008; additional AOR = 2.11, 95% CI = [1.13, 3.94], p = 0.02 **Any PA (+/- EA/NEG):** AOR = 2.34, 95% CI = [1.38, 3.96], p = 0.002; additional AOR = 2.59, 95% CI = [1.37, 4.89], p = 0.003 **EA +/- NEG:** AOR = 2.68, 95% CI = [1.53, 4.67], p =	YES: Any MAL with all cannabis outcomes; SA (+/- other abuse/NEG), PA (+/- EA/NEG), and EA +/- NEG with early cannabis use; SA (+/- other abuse/NEG), and PA (+/- EA/NEG) with daily cannabis use NO: SA (+/- other abuse/NEG), PA (+/- EA/NEG), and EA +/- NEG with lifetime cannabis use; EA +/- NEG with daily cannabis use; SA (+/- other abuse/NEG), PA (+/- EA/NEG), and EA +/- NEG with cannabis abuse/ dependence

						0.001; additional AOR = 2.91, 95% CI = [1.36, 6.24], p = 0.006 **Daily cannabis use:** **Any MAL:** AOR = 2.77, 95% CI = [1.72, 4.48], p < 0.001; additional AOR = 2.68, 95% CI = [1.49, 4.81], p = 0.01 **Any SA (+/- other abuse/NEG):** AOR = 2.43, 95% CI = [0.94, 6.27], p = 0.067; additional AOR = 3.08, 95% CI = [1.14, 8.29], p = 0.026 **Any PA (+/- EA/NEG):** AOR = 2.80, 95% CI = [1.35, 5.82], p = 0.006; additional AOR = 2.94, 95% CI = [1.24, 6.99], p = 0.015 **EA +/- NEG:** AOR = 3.01, 95% CI = [1.38, 6.56], p = 0.005; additional AOR = 2.02, 95% CI = [0.67, 6.08], p = 0.211 **Cannabis abuse/dependence (DSM-IV):** **Any MAL:** AOR = 1.79, 95% CI = [1.19, 2.68], p = 0.005; additional AOR = 1.72, 95% CI = [1.07, 2.77], p = 0.025 **Any SA (+/- other abuse/NEG):** AOR = 1.20, 95% CI = [0.54, 2.68], p = 0.650; additional AOR = 1.17, 95% CI = [0.49, 2.78], p = 0.719 **Any PA (+/- EA/NEG):** AOR = 2.33, 95% CI = [1.24, 4.39], p = 0.009; additional AOR = 1.95, 95% CI = [0.93, 4.07], p = 0.076 **EA +/- NEG:** AOR = 1.83, 95% CI = [0.92, 3.61], p = 0.083; additional AOR = 2.24, 95% CI = [0.93, 5.37], p = 0.072	
Musa et al., 2018; Bosnia and Herzegovina	Cross-sectional	N = 400 Percentage of females = 58.5% Age range = 18-24 years	Convenience-based sample of young adults that were recruited from a primary healthcare institution	**EA:** "How often did a parent or other adult in your household swear at you, insult you, put you down or humiliate you?" and "How often did a parent or other adult in your household	**Alcohol use:** "During the past 30 days, on how many days did you have at least one drink of alcohol?" and "During the past 30 days, on how many days did you have 5 or more drinks of	**Interrelatedness with alcohol use:** **EA:** AROR = 0.84, 95% CI = [0.38, 1.85] **PA:** AROR = 2.46, 95% CI = [0.92, 6.56] **SA:** AROR = 0.98, 95% CI = [0.36, 2.67] **EN:** AROR = 2.18, 95% CI = [1.03, 4.64]	YES: EA with drug abuse; EN with alcohol use; EN with drug abuse NO: EA with alcohol use; PA with alcohol use; PA with drug abuse; SA with alcohol use; SA with drug abuse; PN with alcohol use; PN with drug abuse

act in a way that made you afraid that you might be physically hurt?" **PA:** "How often did a parent or other adult in the household push, grab, slap, or throw something at you?" **SA:** "Did an adult or person at least 5 years older than you ever touch or fondle you or have you touch their body in a sexual way?" and "Did an adult or person at least 5 years older than you attempt or actually have oral, anal, or vaginal intercourse with you?" **EN:** "How often did you feel that no one in your family loved you or thought you were important or special?" and "How often did you feel that your family didn't look out for each other, feel close to each other, or support each other?" **PN:** "How often did you feel that you didn't have enough to eat, had to wear dirty clothes, or had no one to protect you?" Note: ACEs including all types of abuse and NEG were assessed to reflect experiences prior to the age of 18 years	alcohol in a row, that is, within a couple of hours?" **Drug abuse:** "During your life, how many times did you use marijuana?", "During the last month, how many times did you use marijuana?", "Have you ever used drugs intravenously?", and "Have you ever used other types of drugs: cocaine, sniffed glue, methamphetamines (speed), ecstasy, pills (without a doctor's prescription)?"	**PN:** AROR = 0.76, 95% CI = [0.29, 1.96] **Interrelatedness with drug abuse:** **EA:** AROR = 2.78, 95% CI = [1.31, 5.90] **PA:** AROR = 0.65, 95% CI = [0.24, 1.75] **SA:** AROR = 1.30, 95% CI = [0.43, 3.91] **EN:** AROR = 3.35, 95% CI = [1.59, 7.06] **PN:** AROR = 0.78, 95% CI = [0.32, 1.92]	

Pedersen and Skrondal, 1996; Norway	Longitudinal; Retrospective	N = 249 Percentage of females = 100% Age range = 12-21 years	School-based sample of adolescents from junior high schools	**CSA**: A short questionnaire was used to assess CSA with the following initial question, "People are sometimes involuntarily exposed to sexual acts they do not want, have you had such experiences?"; a positive response to this initial question was followed by additional questions on "the number of victimization episodes, victim's and offender's age, degree of force, and further to ask the subjects to describe possible events in their own words"	**Alcohol consumption**: Information regarding alcohol consumption was obtained at each timepoint (T1 to T5) based on a previously established quantity/frequency approach which involved asking questions regarding the amount of alcohol consumed during a participant's most recent drinking episode as well as the amount of drinking episodes in the past month	**Direct effects of CSA on the development of alcohol consumption from T1 to T5:** p = not significant at all timepoints (T1, T2, T3, T4, and T5)	NO
Perez, 2000; The United States	Cross-sectional	N = 2468 Percentage of females = 44.1% Age range = 12-18 years	Mexican-American and non-Hispanic White school dropouts with a comparison group of students	**PA, sexual victimization, and both (PA and sexual victimization):** Respondents were asked how many times they had been "beaten by parents" to assess PA, and how many times they had been "raped or sexually assaulted" to assess sexual victimization	**Marijuana use, cocaine use, "uppers" (stimulants) use, and LSD use:** Clinical Drug Assessment Scale from the American Drug and Alcohol Survey; respondents were asked about the number of times they had used specific substances in the past month or the past year	**Logistic regression:** **Past month marijuana use:** **PA:** B = 0.44, OR = 1.56, Wald $\chi2 = 9.36$, $p < 0.01$ **Sexual victimization:** B = 0.36, OR = 1.43, Wald $\chi2 = 3.36$, not significant **Both:** B = 0.33, OR = 1.38, Wald $\chi2 = 2.05$, not significant **Past year cocaine use:** **PA:** B = 0.40, OR = 1.50, Wald $\chi2 = 5.57$; $p < 0.05$ **Sexual victimization:** B = 0.49, OR = 1.64, Wald $\chi2 = 4.52$; $p < 0.05$ **Both:** B = 0.57, OR = 1.77, Wald $\chi2 = 4.70$; $p < 0.05$ **Past year uppers use:** **PA:** B = 0.54, OR = 1.71, Wald $\chi2 = 11.31$; $p < 0.001$ **Sexual victimization:** B = 0.60, OR = 1.82, Wald $\chi2 = 8.52$; $p < 0.01$ **Both:** B = 0.98, OR = 2.66, Wald $\chi2 = 19.05$; $p < 0.001$ **Past year LSD use:** **PA:** B = 0.57, OR = 1.77,	YES: All listed MAL exposures and SU outcomes except for the ones listed in the NO section, below NO: Sexual victimization with past month marijuana use; both with past month marijuana use

						Wald $\chi2 = 14.03$; $p < 0.001$ **Sexual victimization:** B = 0.58, OR = 1.79, Wald $\chi2 = 8.55$; $p < 0.01$ **Both:** B = 0.75, OR = 2.12, Wald $\chi2 = 11.05$; $p < 0.001$	
Perkins and Jones, 2004; The United States	Cross-sectional	N = 16,313 Percentage of females = 53.3% Age range = 12-17 years	Middle and high school students	**PA:** "Have you ever been physically abused by an adult (i.e., where an adult caused you to have a scar, black and blue marks, welts, bleeding, or a broken bone)?"	**Problem alcohol use:** "How many times, if any, have you had alcohol to drink during the last 30 days?" and "Think back over the last 2 weeks. How many times have you had five or more drinks in a row?" **DU:** "How many times, if any, have you used marijuana (grass, pot) or hashish (hash, hash oil) during the last 30 days?" and similar questions about cocaine use and amphetamine use	**Alcohol use:** Non-abused: N = 2893 (22.2%); abused: N = 1188 (36.2%), contingency coefficient = 0.128, $p < 0.001$ **DU:** Non-abused: N = 1903 (14.6%); abused: N = 948 (28.9%), contingency coefficient = 0.149, $p < 0.001$	YES

Ramos de Oliveira and Jeong, 2021; El Salvador	Cross-sectional	N = 2436 Percentage of females = 43.3% Age range = 13-24 years	Nationally representative household survey	**PV:** Asked if participants had experienced being "(a) punched, kicked, whipped, beaten with an object; (b) choked, smothered, having someone try to drown or burn them intentionally; or (c) someone used or threatened to use a knife, gun, or other weapon against them" **SV:** Asked if participants had experienced "(a) unwanted touching in a sexual way, such as unwanted touching, kissing, grabbing, or fondling; (b) unwanted attempted sex in which the perpetrator used physical coercion or pressure but did not succeed in completing sex; (c) pressured sex in which the respondent was pressured in a non-physical way to have sex against their will and sex occurred; or (d) physically forced sex in which they were physically forced to have sex against their will" **EV:** Asked if participants had experienced the following: "(a) told that they were not loved, or did not deserve to be loved; (b) wished they had never been born or were dead; (c) ridiculed or put down; (d) threatened to get rid of them"	**Alcohol use:** Survey question that asked, "In the past 30 days, on how many days did you drink alcohol to the point that you became drunk?"	**Independent (OR) and joint (AOR) associations between broad violence exposure types and alcohol use:** **Any PV:** OR = 3.15, 95% CI = [2.02, 4.89], $p < 0.001$; AOR = 2.42, 95% CI = [1.48, 3.96], $p < 0.001$ **Any SV:** OR = 3.78, 95% CI = [2.06, 6.93], $p < 0.001$; AOR = 2.33, 95% CI = [1.19, 4.54], $p < 0.05$ **Any EV:** OR = 2.83, 95% CI = [1.61, 4.99], $p < 0.001$; AOR = 1.52, 95% CI = [0.81, 2.86], p = not significant	YES: PV; SV NO: EV

Ramos-Olazagasti et al., 2017; The United States/Puerto Rico	Longitudinal; Prospective	N = 1259 Percentage of females = 48.85% Age range = About 10-16 years	Household interview	**NEG:** "left alone more than once, left without food, not taken to a hospital/doctor, parents so drunk/high that they could not care for you" and reported experiences based on an adapted version of the Parent–Child Conflict Tactics Scale **PA:** "Has anyone ever beat you up very hard?" and reported experiences based on an adapted version of the Parent–Child Conflict Tactics Scale **SA**: "Has anyone tried to touch you, grab you, or kiss you in a sexual way, or has done something sexual that made you feel afraid, bad, or used?" and reported experiences based on the Sexual Victimization Scale **EA**: "Has anyone ever sworn or cursed at you?" and reported experiences based on an adapted version of the Parent–Child Conflict Tactics Scale	**Alcohol use:** Responses to the alcohol abuse module of the DISC version IV, as well as interview questions about lifetime alcohol use; early initiation of alcohol use referred to having a full alcoholic beverage by the age of 14 years	**Partially adjusted survival models (adjusted for age, site, and poverty) predicting early initiation of alcohol use from childhood adversities (main effects entire sample):** **NEG:** HR = 1.52, CI = [0.84, 2.74], p = 0.17, not significant **PA:** HR = 2.11, CI = [1.46, 3.04], p < 0.0001 **SA:** HR = 1.44, CI = [0.77, 2.68], p = 0.25, not significant **EA:** HR = 2.39, CI = [1.84, 3.12], p < 0.0001 **Mutually adjusted survival models (adjusted for age, gender, site, and poverty) predicting early initiation of alcohol use from childhood adversities:** **PA:** HR = 1.68, CI = [1.16, 2.44], p = 0.01 **SA**: HR = 2.16, CI = [1.15, 4.07], p = 0.02 **EA**: HR = 1.77, CI = [1.34, 2.35], p = 0.0001	YES
Riggs et al., 1990; The United States	Cross-sectional	N = 600 Percentage of females = 51.6% Age range = 14-17 years	High-school based survey	**PA:** "Have you ever been physically hurt or abused by someone close to you?" **SA:** "Have you ever been sexually abused by someone close to you and, if so, at what age?"	**Alcohol use, and illicit DU (e.g., marijuana, and cocaine):** Survey that assessed usage	**PA and alcohol use:** OR = 3.29, 95% CI = [1.13, 9.62], p ≤ 0.01 **PA and illicit DU:** OR = 1.86, 95% CI = [0.68, 5.06] (not significant) **SA and alcohol use:** OR = 1.35, 95% CI = [0.51, 3.60] (not significant) **SA and illicit DU:** OR = 1.03, 95% CI = [0.38, 2.73] (not significant)	YES: PA and alcohol use NO: PA and illicit DU; SA and alcohol use; SA and illicit DU

Rogosch et al., 2010; The United States	Longitudinal; Prospective	N = 415 Percentage of females = 39.52% Age range = 7-15 years	Children attending a summer camp research program for school-aged low-income children	**CM:** County presence of documented records of CA (including emotional MAL, PA, and SA) and/or NEG reports in the DHS (based on the MCS)	**Cannabis abuse and dependence symptoms:** DISC	**Direct role of CM on the development of cannabis abuse and dependence symptoms:** **CM prior to Wave 1 and cannabis abuse and dependence symptoms at Wave 3:** Critical ratio = 2.77, $p < 0.001$	YES
Rosario et al., 2004; The United States	Longitudinal; Prospective	N = 156 Percentage of females = 48.72% Age range = 14-21 years	Participants recruited from gay-focused and college organizations	**CSA:** Participants were asked whether they had ever had sexual experiences before the age of 13 years with an adult or another child more than 5 years older than them	**Alcohol use, and marijuana use:** Alcohol and Drugs Schedule	**Multivariate relations between CSA with marijuana use or CSA with alcohol use:** not significant	NO
Rotheram-Borus et al., 1996; The United States	Cross-sectional analysis from a longitudinal study	N = 190 Percentage of females = 51.6% Age range = Below 24 years	Took a subset from a larger study using entrants to residential shelters	**SA:** Sexual Risk Behaviour Assessment Schedule - Youth	**Alcohol use:** Items from a Drug and Alcohol Use Survey for Adolescents was used to assess current alcohol use during the previous 3 months	**Main effects of SA in non-abused, abused after age 13, and abused before age 13 on alcohol use in last 3 months (Table 1):** F or $\chi 2 = 11.7$, $p < 0.05$ for differences across the 3 groups **Alcohol use in past 3 months with SA history:** $F(2, 163) = 5.7$, $p < 0.01$	YES
Roy et al., 2011; Canada	Longitudinal; Prospective	N = 352 Percentage of females = 28% Age range = 14-23 years	Street youth	**Lifetime SA, and lifetime rape:** Questionnaire approved by the Institutional Review Board of the Faculty of Medicine at McGill University	**Injection drug initiation:** Questionnaire approved by the Institutional Review Board of the Faculty of Medicine at McGill University	**Univariate analysis:** **Lifetime SA and injection drug initiation:** $p < 0.05$ **Lifetime rape and injection drug initiation:** $p < 0.05$ **Multivariate analysis:** **Lifetime SA and injection drug initiation:** HR = 0.76, 95% CI = [0.27, 2.16], not significant **Lifetime rape and injection drug initiation:** HR = 1.24, 95% CI = [0.60, 2.55], not significant	NO

Russotti et al., 2021; The United States	Longitudinal; Prospective	N = 391 Percentage of females = 51.3% Age range = 10-22 years	Participants were an ethnically/ racially diverse sample of children (ages 10-12 years) that were involved in a summer camp research program and were followed until emerging adulthood (ages 18-22 years)	**CM (combined SA, PA, EA, and NEG):** The MCS was used to assess exposure, timing, and chronicity of CM from birth to 12 years based on DHS and CPS records	**Substance dependence (combined alcohol and marijuana symptoms):** The Diagnostic Interview Schedule for DSM-IV was used to assess the number of symptoms for marijuana dependence and alcohol dependence	**Direct associations using structural equation modeling between CM at wave 1 and substance dependence at wave 2:** not significant	NO
Schneiderman et al., 2016; The United States	Longitudinal; Prospective	N = 344 Percentage of females = 49.13% Age range = About 16-21 years	MAL group from active cases in a California child welfare department; comparison group from surrounding communities in California	**CM:** New substantiated referral to the child welfare department during the preceding month for any type of MAL	**Marijuana use:** Adolescent Delinquency Questionnaire (adapted); "One item that asked about frequency of marijuana or hashish use during the previous 12 months"	**Negative binomial regression predicting marijuana use: CM and marijuana use**: *b* = -0.13, SE = 0.21 (not significant)	NO

Shin et al., 2009; The United States	Cross-sectional analysis from a longitudinal study	N = 12,748 Percentage of females = 50.4% Age range = 12-21 years	A nationally representative sample of adolescents in grades 7 to 12	**SA:** "By the time you started 6th grade, how often had one of your parents or other adult caregivers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?" **PA:** "How often had slapped, hit, or kicked you?" **NEG:** "How often had not taken care of your basic needs, such as keeping you clean or providing food or clothing or how often had left you home alone when an adult should have been with you?"	**BD:** "During the past 12 months, on how many days did you drink five or more drinks in a row?"; Consumption of at least 5 consecutive drinks a minimum of 2 to 3 times each month over the last year was used to classify BD	**Percentage of participants with any MAL and BD:** 12.4%; **percentage of participants with no MAL and BD:** 9.9%; $p < 0.001$ based on the within subgroup analysis using a chi-square test **Logistic regression for BD as the outcome with any MAL:** **Any MAL:** AOR = 1.33, 95% CI = [1.13 1.57], $p < 0.05$ **Multivariable logistic regression for BD as the outcome with single types of MAL:** **Any NEG:** AOR = 1.15, 95% CI = [0.96, 1.37], p = not significant **Any PA:** AOR = 1.19, 95% CI = [0.96, 1.47], p = not significant **Any SA:** AOR = 1.42, 95% CI = [0.89, 2.25], p = not significant **Multivariable logistic regression for BD as the outcome with multiple types of MAL:** **NEG only:** AOR = 1.24, 95% CI = [1.00, 1.51], $p < 0.05$ **PA only:** AOR = 1.34, 95% CI = [1.02, 1.76], $p < 0.05$ **SA:** AOR = 2.26, 95% CI = [1.15, 4.43], $p < 0.05$ **NEG and PA:** AOR = 1.33, 95% CI = [1.00, 1.77], $p < 0.05$ **NEG, PA, and SA:** AOR = 1.79, 95% CI = [1.15, 2.78], $p < 0.05$	YES

Smith et al., 2005; The United States	Longitudinal; Prospective	N = 777 Percentage of females = 27.1% Age range = 13-22 years	Community-based sample consisting of urban youth	**Any MAL, NEG, PA, and SA:** CPS records of the Monroe County Department of Social Services which included information regarding age at substantiated MAL and MAL types	**DU:** Self-reported DU questions specifically regarding the use of "10 illicit drugs ranging from marijuana to cocaine/crack and heroin"	**Any adolescent MAL and late adolescent DU (16-18 years):** OR = 1.76, 90% CI = [1.05, 2.95], $p < 0.05$ (one-tailed) **Any adolescent MAL and early adult DU (20-22 years):** OR = 2.14, 90% CI = [1.22, 3.73], $p < 0.05$ (one-tailed) **Different types of adolescent MAL and DU in late adolescence and early adulthood:** **NEG and late adolescent DU:** OR = 0.96, 90% CI = [0.41, 2.25], p = not significant **NEG and early adult DU:** OR = 2.55, 90% CI = [1.10, 5.90], $p < 0.01$ (one-tailed) **PA and late adolescent DU:** OR = 3.66, 90% CI = [1.78, 7.52], $p < 0.01$ (one-tailed) **PA and early adult DU:** OR = 0.99, 90% CI = [0.41, 2.41], p = not significant **SA and late adolescent DU:** OR = 0.97, 90% CI = [0.35, 2.66], p = not significant **SA and early adult DU:** OR = 5.74, 90% CI = [1.68, 19.63], $p < 0.01$ (one-tailed)	YES
Solakoglu et al., 2018; Turkey	Cross-sectional	N = 2447 Percentage of females = 51% Age range = 14-16 years	Youth from high schools	**SA:** Asked whether or not they had experienced sexual abuse during the past 30 days, past 12 months, or more than 12 months ago	**Drinking alcohol:** Asked how often they had a drink of alcohol in the last 30 days **DU (including sleeping pills, cannabis, amphetamines, LSD, ecstasy, cocaine, mushroom, sniffing, anabolic steroids, and homemade brews/poteen):** Asked how often (if ever) they had used	**Logistic regression models predicting SU (Model 1):** **For SA:** **Drinking alcohol:** OR = 2.80, $p < 0.001$ **DU:** OR = 2.71, $p < 0.001$	YES

Thompson et al., 2015; The United States	Cross-sectional	N = 600 Percentage of females = 35.9% Age range = 18-24 years	Street youth receiving homeless services from nonprofit organizations	**PA:** 5 CTQ items related to PA **PN:** 5 CTQ items related to PN	**Alcohol addiction including alcohol use disorder:** Mini International Neuropsychiatric Interview investigating alcohol abuse and dependence over the past 12 months	**Bivariate analysis results:** **PN and alcohol addiction:** % with PN without alcohol addiction = 82.1%, % with PN and alcohol addiction: 91.0**%,** $\chi2 = 10.2$, $p < 0.01$ **PA and alcohol addiction:** % with PA without alcohol addiction = 75.7%, % with PA and alcohol addiction: 84.3**%,** $\chi2 = 6.8$, $p < 0.01$ **Hierarchical logistic regression results:** **PN and alcohol use disorder (Model 3):** Exp (B) = 1.64, CI = [0.87, 3.09] (not significant) **PA and alcohol use disorder (Model 3):** Exp (B) = 0.86, CI = [0.51, 1.45] (not significant) **PN and alcohol use disorder (Model 4):** Exp (B) = 1.68, CI = [0.87, 3.24] (not significant) **PA and alcohol use disorder (Model 4):** Exp (B) = 0.85, CI = [0.50, 1.46] (not significant)	NO
Tossone et al., 2018; The United States	Cross-sectional	N = 1307 Percentage of females = 100% Age range = 10-18 years	Youth from a diversion program with behavioural health issues	**SA:** Caregiver Information Questionnaire, "Has [name of child] ever been sexually abused?"	**Use of alcohol, marijuana, and other drugs (including cocaine, painkillers, heroin, tranquilizers, amphetamines, inhalants, etc. but excluding cigarettes or tobacco, and prescription drugs):** Adapted from the Substance Use Survey - Revised; measured lifetime, past 6-month, and past 30-day SU	**Logistic regression models predicting odds of SU according to presence of SA:** **Ever used alcohol:** B = 0.25, OR = 1.65, 95% CI = [1.20, 2.26], p = 0.002 **Ever used marijuana:** B = 0.20, OR = 1.48, 95% CI = [1.09, 2.02], p = 0.01 **Ever used other drugs:** B = 0.20, OR = 1.50, 95% CI = [1.10, 2.05], p = 0.01	YES

Tyler et al., 2013; The United States	Cross-sectional	N = 137 Percentage of females = 100% Age range = 14-21 years	Youth that were considered to be homeless or a runaway on the night prior to screening	**PA:** "Were you ever physically abused as a child (under age 18?)" **SA:** "Were you ever sexually abused as a child (under age 18?)"	**Alcohol use**: Asked respondents "how often they have drank beer, wine, or liquor in the past 6 months" **Marijuana use:** Asked respondents "how often they smoked marijuana in the past 6 months"	**Direct effects of MAL on alcohol use and marijuana use:** **Alcohol use:** **PA:** $\beta = 0.072$ (SE = 0.091), not significant **SA:** $\beta = -0.039$ (SE = 0.100), not significant **Marijuana use:** **PA:** $\beta = -0.013$ (SE = 0.085), not significant **SA:** $\beta = -0.020$ (SE = 0.093), not significant	NO

Valério et al., 2022; Brazil	Longitudinal; Prospective	N = About 3641 Percentage of females = 51.9% Age range = 15-22 years	Participants were adolescents and young adults from the city of Pelotas, Brazil	**EA, PA, SA, and PN:** A CTQ-based questionnaire was used to retrospectively assess 4 types of child MAL e.g., EA, PA, SA, and PN from birth to the age of 15 years	**Alcohol use:** The AUDIT was used to assess harmful alcohol use at 18 years and at 22 years; at 15 years, harmful alcohol use referred to alcohol use on at least 1 day during the past 30 days **Illicit DU:** Use of the following drugs during the past 30 days was assessed: "marijuana, cocaine, and solvents/inhalants at 15 years, and also ecstasy and hallucinogens at 18 and 22 years"	**Logistic regression of adjusted associations for child MAL and SU at different ages:** **Harmful alcohol use at 15 years:** **EA:** OR = 2.17, 95% CI = [1.80, 2.62], p < 0.001 **PA:** OR = 2.26, 95% CI = [1.72, 2.98], p < 0.001 **SA:** OR = 1.51, 95% CI = [0.83, 2.74], p = 0.175 (not significant) **PN:** OR = 1.22, 95% CI = [0.85, 1.75], p = 0.279 (not significant) **Harmful alcohol use at 18 years:** **EA:** OR = 1.61, 95% CI = [1.31, 1.97], p < 0.001 **PA:** OR = 1.68, 95% CI = [1.24, 2.26], p = 0.001 **SA:** OR = 1.00, 95% CI = [0.48, 2.05], p = 0.989 (not significant) **PN:** OR = 1.12, 95% CI = [0.77, 1.63], p = 0.555 (not significant) **Harmful alcohol use at 22 years:** **EA:** OR = 1.55, 95% CI = [1.22, 1.96], p < 0.001 **PA:** OR = 1.39, 95% CI = [1.00, 1.95], p = 0.006 **SA:** OR = 1.58, 95% CI = [0.72, 3.45], p = 0.254 (not significant) **PN:** OR = 0.99, 95% CI = [0.63, 1.56], p = 0.971 (not significant) **Illicit DU at 15 years:** **EA:** OR = 3.18, 95% CI = [1.46, 6.91], p = 0.004 **PA:** OR = 5.62, 95% CI = [2.43, 12.99], p < 0.001 **SA:** OR = 8.97, 95% CI = [2.76, 29.17], p < 0.001 **PN:** OR = 2.37, 95% CI = [0.77, 7.28], p = 0.132 (not significant) **Illicit DU at 18 years:** **EA:** OR = 1.59, 95% CI = [1.15, 2.20], p = 0.005 **PA:** OR = 0.95, 95% CI = [0.55, 1.65], p = 0.852 (not significant) **SA:** OR = 1.50, 95% CI = [0.52, 4.32], p = 0.456 (not	YES: EA, and PA with alcohol use; EA, PA, and SA with illicit DU NO: SA, and PN with alcohol use; PN with illicit DU

significant)
PN: OR = 1.20, 95% CI = [0.66, 2.20], p = 0.547 (not significant)
Illicit DU at 22 years:
EA: OR = 1.42, 95% CI = [1.08, 1.87], p = 0.012
PA: OR = 1.25, 95% CI = [0.82, 1.91], p = 0.297 (not significant)
SA: OR = 1.29, 95% CI = [0.48, 3.42], p = 0.613 (not significant)
PN: OR = 1.10, 95% CI = [0.66, 1.85], p = 0.710 (not significant)

Vaughn et al., 2007; The United States	Cross-sectional	N = 406 Percentage of females = 57% Age range = All 17 years	All youth turning age 17 in the foster care system among eight Missouri counties	**PA, SA, and PN:** CTQ	**Alcohol use, and SU (including use of marijuana, amphetamines, sedatives, opiates, cocaine, hallucinogens, and inhalants):** Diagnostic Interview Schedule for Children and Adolescents, modified portions of the Diagnostic Interview Schedule for DSM-IV, and the Comprehensive Addiction and Severity Index for Adolescents	**Logistic regression results:** **PA:** **Ever used illegal substances:** not significant **Polysubstance use:** not significant **Met substance abuse disorder criteria:** not significant **Current marijuana use (past year):** not significant **Current CNS stimulants use (past year):** OR = 0.2, CI = [0.1, 0.8], p = 0.0275 (protective factor) **Current CNS depressants use (past year):** not significant **Current alcohol use (last 6 months):** not significant **Current substance abuse (past year):** not significant **PN:** **Ever used illegal substances:** not significant **Polysubstance use:** OR = 0.4, CI = [0.2, 0.9], p = 0.03 (protective factor) **Met substance abuse disorder criteria:** not significant **Current marijuana use (past year):** not significant **Current CNS stimulants use (past year):** not significant **Current CNS depressants use (past year):** not significant **Current alcohol use (last 6 months):** not significant **Current substance abuse (past year):** not significant **SA:** **Ever used illegal substances:** not significant **Polysubstance use:** not significant **Met substance abuse disorder criteria:** not significant **Current marijuana use (past year):** not significant **Current CNS stimulants use (past year):** not significant **Current CNS depressants use (past year):** not significant **Current alcohol use (last 6 months):** not significant **Current substance abuse (past year):** not significant	NO

Wang et al., 2020; Taiwan	Longitudinal; Retrospective	N = 39,348 Percentage of females = 14.93% Age range = 9.2-19.0 years	The Taiwan National Health Insurance Research Database was the source of data for this study and consisted of a nationwide, population-based cohort in Taiwan	**CA:** The Taiwan Longitudinal Health Insurance Database was used to obtain data about CA; International Classification of Diseases (9th Revision, Clinical Modification) codes were used by clinicians to classify children based on whether or not they had experienced abuse	**Substance-related disorders:** The DSM-IV was used by board-certified psychiatrists to diagnose substance-related disorders including alcohol use disorder and illicit DU disorder	**Percentage of participants with CA and with a substance-related disorder:** 1.30%; **percentage of participants without CA and with a substance-related disorder:** 0.89%; p = 0.001 **Overall sensitivity test of CA exposure and the risk of substance-related disorder:** **Non-competing risks model:** Adjusted HR = 2.68, 95% CI = [2.40, 2.99], p < 0.001 **Competing risks model:** Adjusted HR = 2.70, 95% CI = [2.41, 3.01], p < 0.001	YES
Yen et al., 2008; Taiwan	Cross-sectional	N = 1684 Percentage of females = 50.9% Age range = 13-18 years	Junior high school-based sample from rural areas in Southern Taiwan	**PA:** Abuse Assessment Screen Questionnaire	**Problem drinking of alcohol:** Problem Drinking Experience Questionnaire involving the following questions: "'Have you ever drunk alcohol in the preceding month?' If the response was in the affirmative, responses were sought to two more questions, 'Have you ever been drunk in the preceding month?' and 'Have you ever experienced conflict with others after drinking or ever been blamed for drinking by your families?' Adolescents who answered yes to any of the latter two questions were considered problem drinkers during the preceding month"	**Correlates of problem drinking on univariate logistic regression:** **PA:** % with PA without problem drinking = 19.9% of those without problem drinking, % with PA and problem drinking: 45.5% of those with problem drinking **PA:** OR = 3.360, 95% CI = [2.389, 4.725] **Multivariate logistic regression results for PA and problem drinking:** **Model 1:** AOR = 3.351, 95% CI = [2.346, 4.787] **Model 2:** AOR = 2.918, 95% CI = [1.600, 5.322]	YES

Legend:

ACE = Adverse Childhood Experience; AOR = Adjusted Odds Ratio; AROR = Adjusted Relative Odds Ratio; AUDIT = Alcohol Use Disorders Identification Test; BD = Binge Drinking; CA = Child Abuse; CI = Confidence Interval; CIDI-SAM = Composite International Diagnostic Interview-Substance Abuse Module; CM = Childhood Maltreatment; CNS = Central Nervous System; CPS = Child Protective Services; CSA = Childhood Sexual Abuse; CTQ = Childhood Trauma Questionnaire; DHS = Department of Human

Services; DISC = Diagnostic Interview Schedule for Children; df = degrees of freedom; DSM = Diagnostic and Statistical Manual of Mental Disorders; DU = Drug Use; EA = Emotional Abuse; EN = Emotional Neglect; EV = Emotional Violence; gaRR = Gender-age adjusted Risk Ratio; HR = Hazard Ratio; LSD = Lysergic acid diethylamide; MAL = Maltreatment; MCS = Maltreatment Classification System; NEG = Neglect; NMPOU = Non-Medical Prescription Opioid Use; OR = Odds Ratio; PA = Physical Abuse; PEI = Personal Experience Inventory; PN = Physical Neglect; PV = Physical Violence; SA = Sexual Abuse; SE = Standard Error; SU = Substance Use; SV = Sexual Violence; UOR = Unadjusted Odds Ratio

Chapter 5: General Discussion

5.1 Summary of Findings

This thesis primarily investigated predictors and various associated factors of substance use/misuse among youth, including alcohol and other illicit substances. Youth, especially those between the ages of approximately 20 to 24 years, have the highest prevalence of substance use/misuse in comparison to other age groups or to all ages (IHME, 2019; Vasilenko et al., 2017). This is of particular significance since youth substance use/misuse is associated with detrimental outcomes such as deficits concerning brain function, structure, and cognition (Debenham et al., 2021; Lees et al., 2020; Squeglia et al., 2009), as well as numerous psychiatric conditions (Gobbi et al., 2019; Rioux et al., 2021; Tanaree et al., 2017; Welsh et al., 2017). While there is accumulating evidence of the high prevalences of various types of substance use/misuse and the associated adverse effects in youth, there is a lack of research regarding sociodemographic or clinical risk factors and effective strategies to prevent or mitigate youth substance use/misuse. The identification of predictors or other associated factors of substance use/misuse in youth is important to facilitate the prompt detection and early implementation of prevention or intervention methods among high-risk youth (Rampa et al., 2021).

In the first study, covered in Chapter 2, we used generalizable data from a nationwide, probability-sample household survey to determine the prevalence of underage alcohol use and its associated factors among Brazilian adolescents. We found a relatively high underage alcohol use prevalence of 22.2% for past 12-month use and 34.3% for lifetime use. Previous studies that estimated the prevalence of underage drinking in Brazil,

were limited in that they predominantly used less generalizable, school-based samples (Coutinho et al., 2016; Filho et al., 2012; Machado et al., 2018). Thus, we aimed to address this limitation and further expand on prior findings by investigating a variety of risk factors as well as alcohol-related problems associated with underage drinking among Brazilian adolescents.

Furthermore, this study determined that the most important risk factors associated with underage drinking over the past 12 months were lifetime tobacco use, self-reported depression, any history of illicit drug use, having no religion or religion other than Christianity, and residing in rural areas. This study also found that alcohol-related problems such as binge drinking, having an argument, relationship problems, and driving under the influence of alcohol, were more prevalent in adolescents with 12-month alcohol use than in the general adolescent population. Overall, the findings of this study demonstrate the severity of underage alcohol use in Brazil, as indicated by the high prevalence of underage drinking and associations with several alcohol-related problems. Importantly, the sociodemographic and clinical risk factors associated with underage alcohol use that were identified by this study are more feasible and inexpensive to assess from a clinical perspective than other physiological or behavioural risk factors. Such findings could aid in prevention or early intervention approaches by enabling the prompt detection and potential implementation of interventions or treatments for youth that are at the highest risk of underage alcohol use and its associated adverse outcomes (Rampa et al., 2021).

The alarming findings from Chapter 2 regarding the high prevalence of underage alcohol use and its associated factors among youth in Brazil, prompted us to conduct a

prospective cohort study analysis that used machine learning techniques to investigate predictors of illicit substance abuse/dependence in young adults from Pelotas, Brazil which is the focus of Chapter 3. We found that the strongest predictors of illicit substance abuse/dependence at baseline included alcohol abuse/dependence, tobacco abuse/dependence, being in a current major depressive episode, history of a lifetime manic episode, current suicide risk, and male sex. While at the 5-year follow-up period the strongest predictors of illicit substance abuse/dependence included tobacco abuse/dependence at baseline, history of a lifetime manic episode at baseline, male sex, alcohol abuse/dependence at baseline, and current suicide risk at baseline. Our study demonstrated that machine learning techniques are especially promising in the context of clinical outcomes, such as substance use/misuse, since we predicted illicit substance abuse/dependence at a high accuracy using sociodemographic and clinical characteristics coupled with machine learning approaches. Previous findings indicate that studies with machine learning models applied to substance use data were limited in that they predominantly investigated physiological or behavioural predictors which are more complicated to assess in clinical settings than the sociodemographic or clinical characteristics that were identified as predictors by our study (Barenholtz et al., 2020). Our study found a relatively high prevalence of current (past 3 months) illicit substance abuse/dependence among Brazilian young adults at baseline of 11.7% and at the 5-year follow-up period of 16.5%. This further demonstrates the need for employing advanced machine learning approaches to identify robust predictors of substance use/misuse,

particularly in youth that are at an elevated risk, since this can also better inform early intervention and prevention efforts (Rampa et al., 2021).

Finally, Chapter 4 presents a comprehensive systematic review and meta-analysis that examined whether childhood maltreatment is a predictor of substance use/misuse among youth. Altogether, the findings from this study indicated that various types of childhood maltreatment were significant predictors of various types of youth substance use/misuse. We found that sexual abuse and physical abuse were the most frequently investigated childhood maltreatment types, while alcohol was the most frequently investigated substance type. In contrast, few studies investigated neglect or emotional abuse, as well as other specific illicit substances (e.g., depressants, stimulants, opioids, and psychedelics), indicating a gap in the literature that should be addressed by future studies being conducted on this topic with a focus on these specific childhood maltreatment and substance types.

Our large systematic review and meta-analysis in Chapter 4 was novel in that it investigated a wide variety of physical and non-physical forms of childhood maltreatment (e.g., physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect) and a wide variety of youth substance use/misuse types (e.g., alcohol, cannabis, and other illicit drugs). We found that unspecified childhood maltreatment, physical abuse, and sexual abuse were predictors of alcohol use/misuse, cannabis use/misuse, and unspecified substance use/misuse among youth. Additionally, there was preliminary evidence to support that emotional abuse as well as emotional neglect predicted cannabis use/misuse in youth and that emotional abuse predicted unspecified substance use/misuse

in youth. However, there was not enough evidence to support such an association between emotional abuse, emotional neglect, physical neglect, and unspecified neglect with some of the other types of youth substance use/misuse. These findings show that several types of childhood maltreatment are important predictors of substance use/misuse in youth, highlighting the significance of identifying other preventable or modifiable predictors of youth substance use/misuse since this may further enhance prevention and intervention efforts in this area (Rampa et al., 2021; Teicher et al., 2016).

5.2 Significance and General Discussion

Overall, the findings of this thesis indicate the severity of substance use/misuse among youth and numerous predictors or other associated factors, thus, it is of utmost importance for suitable policy and prevention or intervention efforts aimed at addressing this problem to be developed. There is evidence to support that alcohol policies are important in preventing and minimizing underage alcohol use and alcohol-related harms among youth (Babor et al., 2022; Degenhardt et al., 2016; Livingston, 2024; Smith et al., 2024). The most promising policy measures to reduce alcohol consumption and its related harms in the general population include taxation, restrictions on physical availability, marketing restrictions or bans, and measures against driving while under the influence (Babor et al., 2022; Degenhardt et al., 2016). Prior findings also indicate that some youth-specific policies are effective, such as increasing the minimum legal purchasing age to a minimum of 18 years and enforcement of zero-tolerance policies regarding driving under the influence of alcohol for youth drivers (Babor et al., 2022; Smith et al., 2024). Regarding

interventions aimed at minimizing alcohol-related harms, there is accumulating evidence to suggest that behaviour or group therapy, family-based treatment programs, motivational enhancement, and specific types of pharmacotherapies are effective (Babor et al., 2022). In countries where recreational cannabis use has been legalized, similar policy measures to those implemented for alcohol, can be implemented to aid in the prevention and reduction of cannabis use and its associated harms among youth (Azofeifa et al., 2015). However, underlying sociodemographic and clinical factors associated with substance use/misuse in youth, such as the ones identified in Chapters 2-4 of this thesis, may limit the effectiveness of such policies or interventions (Livingston, 2024; Teicher et al., 2022).

In the case of illicit drugs, the aforementioned policy measures are unavailable (Stockings et al., 2016). There is some evidence of effective interventions to aid in the management of illicit substance use/misuse including individual or family therapy, school-based interventions, and medication-assisted treatment (Becker et al., 2023; Kulak & Griswold, 2019; Stockings et al., 2016). However, prior research into effective interventions for the management of illicit substance use/misuse has been limited in that it has predominantly been conducted in high-income countries and there is a lack of research into specific interventions for youth (Stockings et al., 2016). Thus, the identification of strong modifiable or preventable predictors for substance use/misuse among youth is important to better inform policy or intervention efforts (Livingston, 2024; Rampa et al., 2021; Teicher et al., 2022). For instance, since childhood maltreatment is a modifiable and preventable predictor of various different types of youth substance use/misuse, as discussed in Chapter 4 of this thesis, prevention or intervention efforts addressing childhood

maltreatment may further help to prevent or mitigate youth substance use/misuse (Teicher et al., 2016, 2022; Wekerle et al., 2019). Importantly, there is evidence indicating that home-visiting programs, parenting programs, school-based educational programs, and enhanced foster care placements help to prevent or mitigate childhood maltreatment and its associated consequences (MacMillan et al., 2009). Previous research has also found that childhood maltreatment is a predictor of executive functioning difficulties and deficits in executive functioning are also predictive of progression toward substance use disorders in youth with heightened reward sensitivity (Khurana et al., 2015; Letkiewicz et al., 2021; Lund et al., 2020; Peeters et al., 2017). Therefore, the identification of strong predictors of youth substance use/misuse, such as childhood maltreatment, may elucidate the underlying processes contributing to the risk of youth to use or misuse substances and the reinforcement or progression of such behaviours. This could prove to be especially beneficial in the facilitation of early intervention or prevention efforts since it provides additional modifiable targets, such as improving executive functioning among youth with a history of childhood maltreatment, which could still in turn lead to the prevention or mitigation of youth substance use/misuse. Interestingly, there is evidence to suggest that transcranial direct stimulation combined with a mindfulness-based treatment can significantly improve executive functioning and decrease craving among youth with a methamphetamine addiction (Alizadehgoradel et al., 2021). There is currently a lack of research into preventive or intervention-based measures for other potential modifiable and preventable risk factors of substance use/misuse such as poor nutrition or inadequate physical activity, thus further research on this topic may be a promising future direction to

inform additional strategies for protecting youth from using/misusing substances (Abrantes et al., 2023; Brellenthin & Lee, 2018; Schroeder & Higgins, 2017; Tremain et al., 2020).

Recreational cannabis use has been legalized in several countries and states often with a goal of regulating cannabis sales and distribution, especially among vulnerable populations including youth (Kourgiantakis et al., 2024; Stone, 2020). However, recent findings indicate that recreational cannabis legalization is associated with adolescent perceptions of acceptability regarding social norms related to youth cannabis use (e.g., youth perceiving parental acceptance of cannabis use, and decreases in youth perceptions of cannabis-related harms) (Ladegard & Bhatia, 2023; Stone, 2020; Young-Wolff et al., 2024). Precariously, youth perceptions of parental or other social acceptance pertaining to cannabis use are related to subsequent youth cannabis use (Ladegard & Bhatia, 2023; Stone, 2020; Young-Wolff et al., 2024). This is problematic considering the many associations of youth cannabis use with adverse outcomes such as subsequent cannabis dependence, other illicit drug use, psychosis, depression, suicide attempts as well as suicides, cognitive deficits, lung injury, and car crashes due to impairment (Kourgiantakis et al., 2024; O'Grady et al., 2024; Silins et al., 2014; UNODC, 2022). There is also evidence of associations between the legalization of recreational cannabis use and higher usage rates among youth, an increased prevalence of cannabis use among young adults, and an increase in cannabis-related emergency department visits among youth (Kourgiantakis et al., 2024; O'Grady et al., 2024; UNODC, 2022; Young-Wolff et al., 2024). More specifically, a recent scoping review by Kourgiantakis et al., 2024 reported that following the legalization of recreational cannabis use in Canada, the majority of studies investigating cannabis-related

emergency department visits found a rise among youth including for cannabinoid hyperemesis syndrome (Andrews et al., 2022), poisonings from recreational cannabis use (Zhang et al., 2022), and mental or behavioural effects due to cannabis use (Auger et al., 2021). There is an urgent need for policy efforts to focus on addressing the issue of cannabis use among youth in places where recreational cannabis use has been legalized, perhaps through the implementation of strategies involving public education programs, further restricting youth access, or increasing training for clinicians (Kourgiantakis et al., 2024; Ladegard & Bhatia, 2023; Silins et al., 2014; Young-Wolff et al., 2024).

Considering important risk factors associated with youth substance use/misuse that could be targeted with various interventions that have previously been found to be effective, may facilitate the process of preventing or reducing youth substance use/misuse. It is important to recognize that low- and middle-income countries often lack the capacity to implement health services and strategies for the prevention and treatment of mental disorders, including substance use/misuse, with cost-effectiveness as a considerable barrier (Babor et al., 2022; Erskine et al., 2015). There is an especially high need for health resources to be allocated to services or strategies focused on prevention and intervention efforts regarding substance use/misuse among youth in low- and middle-income countries (Erskine et al., 2015). Thus, the identification of predictors or other associated factors of youth substance use/misuse in low- and middle-income countries such as Brazil which was the focus of Chapters 2 and 3 of this thesis is especially relevant.

Depression, history of a manic episode, suicide risk, use or misuse of other substances (e.g., tobacco, alcohol, or illicit substances), having no religion or religion other

than Christianity, residing in rural areas, and male sex were identified as significant risk factors or predictors of underage alcohol use or illicit substance misuse among Brazilian youth (refer to Chapters 2 and 3 of this thesis). Standard first-line treatments for depression in youth include antidepressant monotherapy (e.g., fluoxetine, or escitalopram) and psychotherapy (e.g., cognitive behavioural therapy, affect-focused psychodynamic psychotherapy, family therapy, interpersonal therapy, and individual therapy) (Hazell, 2021; Selph & McDonagh, 2019). Notably, findings by Rohde et al., 2012 indicated that reduced rates of substance use for up to two years following the intervention resulted as a secondary benefit of a six-week group cognitive behavioural therapy depression prevention program in adolescents with high levels of depressive symptoms at baseline. Interventions that result in favourable effects for multiple youth mental health conditions, such as for depression and substance use, are especially advantageous for cost-effectiveness (Rohde et al., 2012). In the case of manic episodes among youth, suitable treatment options often involve both pharmacotherapy with a mood stabilizer or antipsychotic medication (e.g., lithium, aripiprazole, quetiapine, risperidone, or olanzapine) as well as psychotherapy (e.g., family-focused therapy, multifamily psychoeducational psychotherapy, or cognitive behavioural therapy) (Cichon et al., 2020; Elsayed et al., 2022). There is evidence that dialectical behavioural therapy for adolescents is effective in reducing suicidality among youth, while other interventions have shown promise (e.g., integrated cognitive behavioural therapy, the Safe Alternatives for Teens and Youths family intervention program, and various technology-based interventions) but need to be further investigated (Busby et al., 2020). Measures that have demonstrated effectiveness in preventing or reducing youth

substance use/misuse including alcohol, tobacco, or illicit substances are taxation, advertising restrictions or bans, minimum legal ages, school-based interventions, and individual or family therapy (Babor et al., 2022; Becker et al., 2023; Degenhardt et al., 2016; Jiloha, 2017; Kulak & Griswold, 2019; Stockings et al., 2016). Additionally, the US Preventive Services Task Force reported a moderate net benefit for primary care interventions involving education or counseling to prevent the initiation of tobacco use in youth, while recommending that further research studies focus on effective interventions to aid in the cessation of tobacco use among youth that use tobacco (Owens et al., 2020). These recommendations are especially important given that tobacco use among youth is a known predictor of subsequent use/misuse of other substances (Jiloha, 2017; Lewinsohn et al., 1999; Siqueira & Brook, 2003; Torabi et al., 1993). Sociodemographic risk factors or predictors of youth substance use/misuse such as having no religion, residing in rural areas, and male sex are useful to inform the development of further substance use/misuse prevention or intervention strategies and for identifying high-risk individuals. For example, prior findings suggest that involvement in religious organizations or other structured leisure activity programs protects against substance use/misuse in youth, thus encouraging youth to participate in such groups and programs may also help with substance use/misuse prevention efforts (MacKillop & Ray, 2017; Trucco, 2020; Woodward et al., 2023).

Chapter 4 of this thesis indicated that a variety of childhood maltreatment types are predictive of several different types of substance use/misuse among youth across the globe. Trauma-focused cognitive behavioural therapy is the leading treatment for youth with a history of childhood maltreatment with substantial evidence to support improvement in

trauma responses and related problematic behaviours or symptoms, including mental health conditions (MacMillan et al., 2009; Wekerle et al., 2019). Overall, the identification and consideration of risk factors or predictors of youth substance use/misuse has the potential to expedite more comprehensive prevention and intervention efforts.

5.3 Strengths

A more detailed account of the strengths pertaining to each of the studies included in this thesis, are presented in the corresponding chapters. Generally, the findings of these studies emphasize the problematic nature of substance use/misuse in youth as demonstrated by the high prevalences and numerous associated factors that were found. These novel findings are particularly relevant from a clinical perspective considering the various sociodemographic and clinical risk factors or predictors of youth substance use/misuse that were identified in Chapters 2-4.

The study in Chapter 2, used a nationwide, multi-stage, probability sample household survey which ensured that the results of this study are generalizable to the entire adolescent Brazilian population between the ages of 12 to 17 years. Prior studies assessing the prevalence of alcohol use among Brazilian adolescents were limited in that they focused on school-based samples (Coutinho et al., 2016; Filho et al., 2012; Machado et al., 2018). Associations between underage drinking over the past 12 months and a wide variety of sociodemographic and clinical factors were assessed using robust sampling methods and multivariate analysis considering survey weights and design.

The sophisticated machine learning techniques used in Chapter 3 are promising from a clinical perspective since our findings indicate the potential high accuracy of utilizing similar methods in the context of predicting diagnostic or prognostic outcomes, particularly related to substance misuse. Numerous sociodemographic and clinical predictors of illicit substance abuse/dependence were investigated, which are more feasible to assess in clinical settings than physiological or behavioural predictors that prior machine learning studies with substance use data had focused on (Barenholtz et al., 2020). Other strengths of this study include the prospective cohort design and the use of probabilistic sampling.

The systematic review and meta-analysis in Chapter 4 was the first to investigate a wide variety of non-physical and physical types of childhood maltreatment as predictors of a wide variety of substance use/misuse types among youth, in a comprehensive manner. This large systematic review included 58 different studies with a total of 170,749 participants across all studies. The results were first organized by substance type outcomes including alcohol, cannabis, unspecified substances, and other specific illicit substances. The results were further organized by maltreatment type exposures including unspecified childhood maltreatment, physical abuse, sexual abuse, emotional abuse, unspecified neglect, emotional neglect, and physical neglect. Just two recent systematic reviews on similar topics have been conducted, but they were both limited in that they looked at only physical or sexual abuse as maltreatment types and only cannabis as a substance type (De la Peña-Arteaga et al., 2021; Martínez-Mota et al., 2020).

5.4 Limitations

The specific limitations of each study are further discussed in the relevant chapters, while the main limitations are summarized below.

It is important to note that cross-sectional study designs preclude making inferences regarding causality, thus, longitudinal study designs are more suitable when investigating risk factors or predictors of outcomes such as substance use/misuse. The study in Chapter 2 had a cross-sectional design which was appropriate for its primary aim of estimating the prevalence of underage alcohol use in Brazilian adolescents. However, the cross-sectional design was limited in determining whether the various factors associated with underage drinking were risk factors or outcomes. Similarly, most of the studies that were included for our systematic review in Chapter 4, had a cross-sectional design which we decided to consider since childhood maltreatment was usually assessed retrospectively before substance use/misuse had occurred.

During the assessment of the main substance use/misuse outcomes, social desirability response bias may have contributed to underreporting of substance use/misuse by select study participants that had a high level of socially desirable responding (Latkin et al., 2017). This is a limitation for the studies in Chapter 2 and Chapter 3 which used a self-report questionnaire or validated screening test to assess the main substance use/misuse outcomes. Additionally, several of the studies included in the systematic review for Chapter 4 also used self-report measures to assess their substance use/misuse outcomes. Moreover, when assessing clinical outcomes such as substance use/misuse, structured clinical interviews are more robust methods that provide more detailed information than self-report questionnaires or screening tests, which should be considered for future studies.

The systematic review and meta-analysis in Chapter 4 was limited in that there was a lack of studies that investigated neglect or emotional abuse as childhood maltreatment types, and the use/misuse of other specific illicit substance types. Fortunately, our findings indicated this significant gap in the literature that future studies should aim to address. Additionally, a major limitation is that the relevant raw data was not reported by majority of the studies in our systematic review and therefore these studies could not be included in the meta-analyses. Thus, research studies should also ensure that they report all raw data, regardless of whether or not they find significant results in order to reduce publication bias in the meta-analyses.

5.5 Future Directions

Considering that most of the previous studies looking into factors associated with substance use/misuse in youth had cross-sectional study designs, future studies on predictors or risk factors of substance use/misuse among youth should consider using a longitudinal design which gives better insight into causal relationships. Additional studies on the topic of substance use/misuse in youth should be conducted in low- and middle-income countries since prior studies have predominantly focused on high-income countries, such as the United States (Livingston, 2024; Smith et al., 2024). The findings from the 2019 Global Burden of Disease Study also indicated that there is a lack of epidemiological data regarding mental disorders in youth from less privileged regions (Kieling et al., 2024).

Machine learning techniques are well-equipped to make diagnostic or prognostic predictions involving complex, multi-dimensional, clinical data (Barenholtz et al., 2020;

Squeglia et al., 2017). Therefore, future studies should be conducted using machine learning approaches to identify predictors of substance use/misuse among youth using more robust validation methods including external datasets for testing rather than a holdout dataset to increase generalizability.

While emotional abuse and neglect are among the most prevalent forms of childhood maltreatment (Stoltenborgh et al., 2015), a limited number of studies have investigated these maltreatment types and instead previous research tended to focus on physical forms of childhood maltreatment (De la Peña-Arteaga et al., 2021; Martínez-Mota et al., 2020). Thus, further studies on predictors of substance use in youth should investigate emotional abuse and neglect as predictors to determine whether these non-physical forms of maltreatment also predict substance use/misuse. The development and implementation of effective interventions for preventable or modifiable predictors of youth substance use/misuse such as childhood maltreatment (Teicher et al., 2016), or even potentially nutrition or physical activity (Abrantes et al., 2023; Brellenthin & Lee, 2018; Schroeder & Higgins, 2017; Tremain et al., 2020), is important for future research to focus on since the prevention of such predictors may in turn also aid with the prevention of substance use/misuse in youth.

Further research into early preventive or treatment-based interventions that are effective in youth is particularly important since once youth that are at the highest risk of substance use/misuse are identified by predictors or risk factors, such as the ones found in this thesis, these interventions can be promptly implemented to mitigate or prevent the associated adverse outcomes (Stockings et al., 2016). Studies focused on additional

interventions targeting significant clinical risk factors or predictors of youth substance use/misuse hold the potential to speed up prevention efforts. For instance, suicide risk was identified as a predictor of illicit substance abuse/dependence in Chapter 3 of this thesis. While there is some preliminary evidence to suggest that technology-based interventions and other programs aimed at reducing suicidality may be helpful, more robust studies are needed to confirm these findings (Busby et al., 2020). Similarly, further research should be conducted on sociodemographic predictors of youth substance use/misuse since this can also provide insight into other underlying factors for prevention and intervention efforts to address.

5.6 Conclusion

The research presented in this thesis demonstrates the numerous associations between substance use/misuse among youth and various predictors or other associated factors including sociodemographic or clinical characteristics. We identified several risk factors or predictors of youth substance use/misuse such as tobacco use/misuse, depression, manic episode history, other/no religion, residing in rural areas, and childhood maltreatment history. Overall, this thesis indicates the promising potential of identifying important predictors or other associated factors of substance use/misuse among youth in informing future prevention and intervention efforts.

5.7 References

Abrantes, A. M., Matsko, S., Wolfe, J., & Brown, R. A. (2023). Physical activity and alcohol and drug use disorders. *Routledge Handbook of Physical Activity and Mental Health*, 465–477. https://doi.org/10.4324/9781003423430-42/PHYSICAL-ACTIVITY-ALCOHOL-DRUG-USE-DISORDERS-ANA-ABRANTES-STEPHEN-MATSKO-JESSICA-WOLFE-RICHARD-BROWN

Alizadehgoradel, J., Imani, S., Nejati, V., Vanderhasselt, M. A., Molaei, B., Salehinejad, M. A., Ahmadi, S., & Taherifard, M. (2021). Improved Executive Functions and Reduced Craving in Youths with Methamphetamine Addiction: Evidence from Combined Transcranial Direct Current Stimulation with Mindfulness Treatment. *Clinical Psychopharmacology and Neuroscience : The Official Scientific Journal of the Korean College of Neuropsychopharmacology*, *19*(4), 653–668. https://doi.org/10.9758/CPN.2021.19.4.653

Andrews, C. N., Rehak, R., Woo, M., Walker, I., Ma, C., Forbes, N., Rittenbach, K., Hathaway, J., Wilsack, L., Liu, A., Nasser, Y., & Sharkey, K. A. (2022). Cannabinoid hyperemesis syndrome in North America: evaluation of health burden and treatment prevalence. *Alimentary Pharmacology & Therapeutics*, *56*(11–12), 1532–1542. https://doi.org/10.1111/APT.17265

Auger, N., Luu, T. M., Ayoub, A., Bilodeau-Bertrand, M., Lo, E., & Low, N. (2021). Cannabis-related Hospitalizations Among Youth in Canada Before and After Cannabis Legalization. *Journal of Addiction Medicine*, *15*(3), 245–247. https://doi.org/10.1097/ADM.0000000000000747

Azofeifa, A., Mattson, M. E., & Lyerla, R. (2015). Driving Under the Influence of

Alcohol, Marijuana, and Alcohol and Marijuana Combined Among Persons Aged 16-25 Years - United States, 2002-2014. *MMWR. Morbidity and Mortality Weekly Report*, *64*(48), 1325–1329. https://doi.org/10.15585/MMWR.MM6448A1

Babor, T. F., Casswell, S., Graham, K., Huckle, T., Livingston, M., Rehm, J., Room, R., Rossow, I., & Sornpaisarn, B. (2022). Alcohol: No Ordinary Commodity-a summary of the third edition. *Addiction (Abingdon, England)*, *117*(12), 3024–3036. https://doi.org/10.1111/ADD.16003

Barenholtz, E., Fitzgerald, N. D., & Hahn, W. E. (2020). Machine-learning approaches to substance-abuse research: Emerging trends and their implications. *Current Opinion in Psychiatry*, *33*(4), 334–342. https://doi.org/10.1097/YCO.0000000000000611

Becker, T. D., Castañeda Ramirez, S., Bruges Boude, A., Leong, A., Ivanov, I., & Rice, T. R. (2023). Interventions for prevention and treatment of substance use in youth with traumatic childhood experiences: a systematic review and synthesis of the literature. *European Child and Adolescent Psychiatry*, 1–20. https://doi.org/10.1007/S00787-023-02265-X/METRICS

Brellenthin, A. G., & Lee, D. (2018). Physical Activity and the Development of Substance Use Disorders: Current Knowledge and Future Directions. *Progress in Preventive Medicine*, *3*(3), e0018. https://doi.org/10.1097/PP9.0000000000000018

Busby, D. R., Hatkevich, C., McGuire, T. C., & King, C. A. (2020). Evidence-Based Interventions for Youth Suicide Risk. *Current Psychiatry Reports*, *22*(2). https://doi.org/10.1007/S11920-020-1129-6

Cichon, L., Janas-Kozik, M., Siwiecc, A., & Rybakowski, J. K. (2020). Clinical picture

and treatment of bipolar affective disorder in children and adolescents. *Psychiatria Polska*, *54*(1), 35–50. https://doi.org/10.12740/PP/ONLINEFIRST/92740

Coutinho, E. S. F., França-Santos, D., Da Silva Magliano, E., Bloch, K. V., Barufaldi, L. A., De Freitas Cunha, C., De Vasconcellos, M. T. L., & Szklo, M. (2016). ERICA: Patterns of alcohol consumption in Brazilian adolescents. *Revista de Saude Publica*, *50*(Suppl 1), 1s-9s. https://doi.org/10.1590/S01518-8787.2016050006684

De la Peña-Arteaga, V., Nogueira, S. O., Lynskey, M., & Hines, L. A. (2021). The Relationship Between Childhood Physical and Sexual Abuse and Adolescent Cannabis Use: A Systematic Review. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/FPSYT.2021.631245

Debenham, J., Birrell, L., Champion, K., Lees, B., Yücel, M., & Newton, N. (2021). Neuropsychological and neurophysiological predictors and consequences of cannabis and illicit substance use during neurodevelopment: A systematic review of longitudinal studies. *The Lancet. Child & Adolescent Health*, *5*(8), 589–604. https://doi.org/10.1016/S2352-4642(21)00051-1

Degenhardt, L., Stockings, E., Patton, G., Hall, W. D., & Lynskey, M. (2016). The increasing global health priority of substance use in young people. *The Lancet. Psychiatry*, *3*(3), 251–264. https://doi.org/10.1016/S2215-0366(15)00508-8

Elsayed, O. H., Pahwa, M., & El-Mallakh, R. S. (2022). Pharmacologic treatment and management of bipolar disorder in adolescents. *Expert Opinion on Pharmacotherapy*, *23*(10), 1165–1179. https://doi.org/10.1080/14656566.2022.2083954

Filho, V. C. B., De Campos, W., & Lopes, A. da S. (2012). Prevalence of alcohol and tobacco use among Brazilian adolescents: A systematic review. *Revista de Saude Publica*, *46*(5), 901–917. https://doi.org/10.1590/S0034-89102012000500018

Gobbi, G., Atkin, T., Zytynski, T., Wang, S., Askari, S., Boruff, J., Ware, M., Marmorstein, N., Cipriani, A., Dendukuri, N., & Mayo, N. (2019). Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *76*(4), 426–434. https://doi.org/10.1001/JAMAPSYCHIATRY.2018.4500

Hazell, P. (2021). Updates in treatment of depression in children and adolescents. *Current Opinion in Psychiatry*, *34*(6), 593–599. https://doi.org/10.1097/YCO.0000000000000749

IHME. (2019). *Global Burden of Disease Study (2019) – processed by Our World in Data. "All ages" [original dataset]*. https://ourworldindata.org/grapher/prevalence-of-drug-use-disorders-by-age

Jiloha, R. C. (2017). Prevention, early intervention, and harm reduction of substance use in adolescents. *Indian Journal of Psychiatry*, *59*(1), 111–118. https://doi.org/10.4103/0019-5545.204444

Khurana, A., Romer, D., Betancourt, L. M., Brodsky, N. L., Giannetta, J. M., & Hurt, H. (2015). Experimentation versus progression in adolescent drug use: A test of an emerging neurobehavioral imbalance model. *Development and Psychopathology*, *27*(3), 901–913. https://doi.org/10.1017/S0954579414000765

Kieling, C., Buchweitz, C., Caye, A., Silvani, J., Ameis, S. H., Brunoni, A. R., Cost, K.

T., Courtney, D. B., Georgiades, K., Merikangas, K. R., Henderson, J. L., Polanczyk, G. V., Rohde, L. A., Salum, G. A., & Szatmari, P. (2024). Worldwide Prevalence and Disability From Mental Disorders Across Childhood and Adolescence: Evidence From the Global Burden of Disease Study. *JAMA Psychiatry*, *81*(4), 347–356. https://doi.org/10.1001/JAMAPSYCHIATRY.2023.5051

Kourgiantakis, T., Vicknarajah, R., Logan, J., Edwards, T., Lee, E., Craig, S., Kaura, A., Williams, C. C., & Marshall, S. (2024). Understanding youth and young adult cannabis use in Canada post-legalization: a scoping review on a public health issue. *Substance Abuse Treatment, Prevention, and Policy*, *19*(1). https://doi.org/10.1186/S13011-024-00615-9

Kulak, J. A., & Griswold, K. S. (2019). Adolescent substance use and misuse: Recognition and management. *American Family Physician*, *99*(11), 689–696. https://pubmed.ncbi.nlm.nih.gov/31150174/

Ladegard, K., & Bhatia, D. (2023). Impact of Cannabis Legalization on Adolescent Cannabis Use. *Psychiatric Clinics*, *46*(4), 635–646. https://doi.org/10.1016/J.PSC.2023.03.008

Latkin, C. A., Edwards, C., Davey-Rothwell, M. A., & Tobin, K. E. (2017). The relationship between social desirability bias and self-reports of health, substance use, and social network factors among urban substance users in Baltimore, Maryland. *Addictive Behaviors*, *73*, 133. https://doi.org/10.1016/J.ADDBEH.2017.05.005

Lees, B., Meredith, L. R., Kirkland, A. E., Bryant, B. E., & Squeglia, L. M. (2020). Effect of alcohol use on the adolescent brain and behavior. *Pharmacology, Biochemistry,*

and Behavior, *192*. https://doi.org/10.1016/J.PBB.2020.172906

Letkiewicz, A. M., Funkhouser, C. J., & Shankman, S. A. (2021). Childhood maltreatment predicts poorer executive functioning in adulthood beyond symptoms of internalizing psychopathology. *Child Abuse & Neglect*, *118*. https://doi.org/10.1016/J.CHIABU.2021.105140

Lewinsohn, P. M., Rohde, P., & Brown, R. A. (1999). Level of current and past adolescent cigarette smoking as predictors of future substance use disorders in young adulthood. *Addiction*, *94*(6), 913–921. https://doi.org/10.1046/J.1360-0443.1999.94691313.X

Livingston, M. (2024). Declining Teenage Drinking: A Global Phenomenon? *Journal of Adolescent Health*, *74*(3), 395–396. https://doi.org/10.1016/J.JADOHEALTH.2023.12.009

Lund, J. I., Toombs, E., Radford, A., Boles, K., & Mushquash, C. (2020). Adverse Childhood Experiences and Executive Function Difficulties in Children: A Systematic Review. *Child Abuse & Neglect*, *106*. https://doi.org/10.1016/J.CHIABU.2020.104485

Machado, Í. E., Felisbino-Mendes, M. S., Malta, D. C., Velasquez-Melendez, G., Freitas, M. I. D. F., & De Andreazzi, M. A. R. (2018). Parental supervision and alcohol use among Brazilian adolescents: analysis of data from National School-based Health Survey 2015. *Revista Brasileira de Epidemiologia = Brazilian Journal of Epidemiology*, *21*(suppl 1). https://doi.org/10.1590/1980-549720180005.SUPL.1

MacKillop, J., & Ray, L. A. (2017). The Etiology of Addiction : A Contemporary

Biopsychosocial Approach. *Integrating Psychological and Pharmacological Treatments for Addictive Disorders*, 32–53. https://doi.org/10.4324/9781315683331-2

MacMillan, H. L., Wathen, C. N., Barlow, J., Fergusson, D. M., Leventhal, J. M., & Taussig, H. N. (2009). Interventions to prevent child maltreatment and associated impairment. *The Lancet*, *373*(9659), 250–266. https://doi.org/10.1016/S0140-6736(08)61708-0

Martínez-Mota, L., Jiménez-Rubio, G., Hernández-Hernández, O. T., & Páez-Martínez, N. (2020). Influence of the type of childhood violence on cannabis abuse and dependence among adolescents: a systematic review and meta-analysis. *Adicciones*, *32*(1), 63–76. https://doi.org/10.20882/ADICCIONES.1050

O'Grady, M. A., Iverson, M. G., Suleiman, A. O., & Rhee, T. G. (2024). Is legalization of recreational cannabis associated with levels of use and cannabis use disorder among youth in the United States? A rapid systematic review. *European Child & Adolescent Psychiatry*, *33*(3), 701–723. https://doi.org/10.1007/S00787-022-01994-9

Owens, D. K., Davidson, K. W., Krist, A. H., Barry, M. J., Cabana, M., Caughey, A. B., Curry, S. J., Donahue, K., Doubeni, C. A., Epling, J. W., Kubik, M., Ogedegbe, G., Pbert, L., Silverstein, M., Simon, M. A., Tseng, C. W., & Wong, J. B. (2020). Primary Care Interventions for Prevention and Cessation of Tobacco Use in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. *JAMA*, *323*(16), 1590–1598. https://doi.org/10.1001/JAMA.2020.4679

Peeters, M., Oldehinkel, T., & Vollebergh, W. (2017). Behavioral Control and Reward

Sensitivity in Adolescents' Risk Taking Behavior: A Longitudinal TRAILS Study. *Frontiers in Psychology*, *8*(FEB). https://doi.org/10.3389/FPSYG.2017.00231

Rampa, S., Molebatsi, K., & January, J. (2021). Aetiology and Early Developmental Influences on Substance Use Disorders. *Substance Use and Misuse in Sub-Saharan Africa: Trends, Intervention, and Policy*, 17–30. https://doi.org/10.1007/978-3-030-85732-5_2

Rioux, C., Huet, A. S., Castellanos-Ryan, N., Fortier, L., Le Blanc, M., Hamaoui, S., Geoffroy, M. C., Renaud, J., & Seguin, J. R. (2021). Substance use disorders and suicidality in youth: A systematic review and meta-analysis with a focus on the direction of the association. *PloS One*, *16*(8). https://doi.org/10.1371/JOURNAL.PONE.0255799

Rohde, P., Stice, E., Gau, J. M., & Marti, C. N. (2012). Reduced substance use as a secondary benefit of an indicated cognitive-behavioral adolescent depression prevention program. *Psychology of Addictive Behaviors : Journal of the Society of Psychologists in Addictive Behaviors*, *26*(3), 599–608. https://doi.org/10.1037/A0028269

Schroeder, R. D., & Higgins, G. E. (2017). You Are What You Eat: The Impact of Nutrition on Alcohol and Drug Use. *Substance Use & Misuse*, *52*(1), 10–24. https://doi.org/10.1080/10826084.2016.1212603

Selph, S. S., & McDonagh, M. S. (2019). Depression in Children and Adolescents: Evaluation and Treatment. *American Family Physician*, *100*(10), 609–617.

Silins, E., Horwood, L. J., Patton, G. C., Fergusson, D. M., Olsson, C. A., Hutchinson, D.

M., Spry, E., Toumbourou, J. W., Degenhardt, L., Swift, W., Coffey, C., Tait, R. J., Letcher, P., Copeland, J., Mattick, R. P., Allsop, S., Hall, W., Hayatbakhsh, R., Little, K., … Slade, T. (2014). Young adult sequelae of adolescent cannabis use: an integrative analysis. *The Lancet. Psychiatry*, *1*(4), 286–293. https://doi.org/10.1016/S2215-0366(14)70307-4

Siqueira, L. M., & Brook, J. S. (2003). Tobacco use as a predictor of illicit drug use and drug-related problems in Colombian youth. *Journal of Adolescent Health*, *32*(1), 50–57. https://doi.org/10.1016/S1054-139X(02)00534-7

Smith, L., López Sánchez, G. F., Pizzol, D., Oh, H., Barnett, Y., Schuch, F., Butler, L., McDermott, D. T., Ball, G., Chandola-Saklani, A., Shin, J. Il, & Koyanagi, A. (2024). Global Trends in the Prevalence of Alcohol Consumption Among School-Going Adolescents Aged 12-15 Years. *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine*, *74*(3), 441–448. https://doi.org/10.1016/J.JADOHEALTH.2023.10.007

Squeglia, L. M., Ball, T. M., Jacobus, J., Brumback, T., McKenna, B. S., Nguyen-Louie, T. T., Sorg, S. F., Paulus, M. P., & Tapert, S. F. (2017). Neural predictors of initiating alcohol use during adolescence. *American Journal of Psychiatry*, *174*(2), 172–185. https://doi.org/10.1176/APPI.AJP.2016.15121587/SUPPL_FILE/APPI.AJP.2016.15121587.PREVIOUSLY.PUBLISHED.PDF

Squeglia, L. M., Jacobus, J., & Tapert, S. F. (2009). The Influence of Substance Use on Adolescent Brain Development. *Clinical EEG and Neuroscience : Official Journal*

of the EEG and Clinical Neuroscience Society (ENCS), *40*(1), 31. https://doi.org/10.1177/155005940904000110

Stockings, E., Hall, W. D., Lynskey, M., Morley, K. I., Reavley, N., Strang, J., Patton, G., & Degenhardt, L. (2016). Prevention, early intervention, harm reduction, and treatment of substance use in young people. *The Lancet. Psychiatry*, *3*(3), 280–296. https://doi.org/10.1016/S2215-0366(16)00002-X

Stoltenborgh, M., Bakermans-Kranenburg, M. J., Alink, L. R. A., & van Ijzendoorn, M. H. (2015). The Prevalence of Child Maltreatment across the Globe: Review of a Series of Meta-Analyses. *Child Abuse Review*, *24*(1), 37–50. https://doi.org/10.1002/CAR.2353

Stone, A. L. (2020). Adolescent Cannabis Use and Perceived Social Norm Trends Pre- and Post-Implementation of Washington State's Liberalized Recreational Cannabis Policy: Healthy Youth Survey, 2008-2018. *Prevention Science : The Official Journal of the Society for Prevention Research*, *21*(6), 772–783. https://doi.org/10.1007/S11121-020-01136-0

Tanaree, A., Assanangkornchai, S., & Kittirattanapaiboon, P. (2017). Pattern and risk of developing alcohol use disorders, illegal substance use and psychiatric disorders after early onset of alcohol use: Results of the Thai National Mental Health Survey 2013. *Drug and Alcohol Dependence*, *170*, 102–111. https://doi.org/10.1016/J.DRUGALCDEP.2016.11.001

Teicher, M. H., Gordon, J. B., & Nemeroff, C. B. (2022). Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment,

research, prevention, and education. *Molecular Psychiatry*, *27*(3), 1331–1338. https://doi.org/10.1038/S41380-021-01367-9

Teicher, M. H., Samson, J. A., Anderson, C. M., & Ohashi, K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. *Nature Reviews. Neuroscience*, *17*(10), 652–666. https://doi.org/10.1038/NRN.2016.111

Torabi, M. R., Bailey, W. J., & Majd-Jabbari, M. (1993). Cigarette Smoking as a Predictor of Alcohol and Other Drug Use by Children and Adolescents: Evidence of the "Gateway Drug Effect." *Journal of School Health*, *63*(7), 302–306. https://doi.org/10.1111/J.1746-1561.1993.TB06150.X

Tremain, D., Freund, M., Wolfenden, L., Bowman, J., Dunlop, A., Bartlem, K., Bailey, J., McFadyen, T., Dray, J., Wye, P., Leigh, L., & Wiggers, J. (2020). The provision of preventive care for modifiable health risk behaviours by clinicians within substance use treatment settings: A systematic review. *Preventive Medicine*, *130*. https://doi.org/10.1016/J.YPMED.2019.105870

Trucco, E. M. (2020). A review of psychosocial factors linked to adolescent substance use. *Pharmacology, Biochemistry, and Behavior*, *196*. https://doi.org/10.1016/J.PBB.2020.172969

UNODC. (2022). *UNODC World Drug Report 2022 highlights trends on cannabis post-legalization, environmental impacts of illicit drugs, and drug use among women and youth*. UNODC. https://www.unodc.org/unodc/en/press/releases/2022/June/unodc-world-drug-report-2022-highlights-trends-on-cannabis-post-legalization--environmental-impacts-of-illicit-drugs--and-drug-use-among-women-and-

youth.html

Vasilenko, S. A., Evans-Polce, R. J., & Lanza, S. T. (2017). *Age trends in rates of substance use disorders across ages 18-90: Differences by gender and race/ethnicity*. https://doi.org/10.1016/j.drugalcdep.2017.08.027

Wekerle, C., Wolfe, D. A. ., Cohen, J. A. ., Bromberg, D. S. ., & Murray, L. (2019). *Childhood Maltreatment* (2nd ed.). Hogrefe Publishing.

Welsh, J. W., Knight, J. R., Hou, S. S. Y., Malowney, M., Schram, P., Sherritt, L., & Boyd, J. W. (2017). Association Between Substance Use Diagnoses and Psychiatric Disorders in an Adolescent and Young Adult Clinic-Based Population. *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine*, *60*(6), 648–652. https://doi.org/10.1016/J.JADOHEALTH.2016.12.018

Woodward, T. C., Smith, M. L., Mann, M. J., Kristjansson, A., & Morehouse, H. (2023). Risk & protective factors for youth substance use across family, peers, school, & leisure domains. *Children and Youth Services Review*, *151*, 107027. https://doi.org/10.1016/J.CHILDYOUTH.2023.107027

Young-Wolff, K. C., Does, M. B., Mian, M. N., Sterling, S. A., Satre, D. D., Campbell, C. I., Silver, L. D., Alexeeff, S. E., Cunningham, S. F., Asyyed, A., & Altschuler, A. (2024). Clinician perspectives on adolescent cannabis-related beliefs and behaviors following recreational cannabis legalization. *Addictive Behaviors*, *156*. https://doi.org/10.1016/J.ADDBEH.2024.108046

Zhang, E. W. J., Davis, A., Finkelstein, Y., & Rosenfield, D. (2022). The effects of COVID-19 on poisonings in the paediatric emergency department. *Paediatrics &*

Child Health, *27*(Suppl 1), S4–S8. https://doi.org/10.1093/PCH/PXAB100