

**SUBSTANCE USE AMONGST EMERGING ADULTS: REPERCUSSIONS OF
ADVERSE CHILDHOOD EXPERIENCES**

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ABSTRACT

Adverse Childhood Experiences (ACEs) have been identified as a pressing public health challenge that contributes to many of the top leading causes of death. Despite this, little is known regarding the relation between ACEs and substance use (SU) among emerging adults.

In Chapter II, a systematic review is presented of studies examining the relation between ACEs and SU among university students. This review describes the relation between ACEs exposure (cumulative and individual ACE types) and specific types of substance use. Next, in Chapter III, the association between ACEs and specific illegal drug types (hallucinogens, stimulants, marijuana) among a French sample of college students is evaluated while examining the cumulative exposure of ACEs and the respective contributions of different types of ACEs. Following, Chapter IV elucidates the relation between ACEs exposure and cigarette smoking, marijuana use, and binge drinking. The protective role of physical activity amongst persons with a history of ACEs are also examined in a nationally representative American sample of emerging adults.

This dissertation uses diverse approaches (e.g., systematic review, secondary data analysis, theoretical models) and samples (e.g., French, American) to comprehensively assess the relationship between ACEs and SU among emerging adults while demonstrating how protective factors (physical activity) promote resilience. These contributions are significant because they strengthen understanding of specific SU after ACE exposure and highlight the avenues for prevention in primary care and emerging adult settings.

TABLE OF CONTENTS

CHAPTER ONE: INTRODUCTION AND GENERAL INFORMATION	1
Substance Use and Emerging Adults.....	1
Adverse Childhood Experiences	3
Physical Activity and Resilience	5
Conclusion	7
CHAPTER TWO: ADVERSE CHILDHOOD EXPERIENCES AND SUBSTANCE USE AMONG UNIVERSITY STUDENTS: A SYSTEMATIC REVIEW	10
Introduction.....	10
Methods.....	12
Eligibility Criteria.	12
Search Strategy.	12
Data Extraction.	13
Quality Assessment.....	13
Results.....	13
Study Selection.	13
Study Characteristics.	14
ACE Instruments, Approach, and Prevalence.....	14
Substance Use.	15
Alcohol Use.	16
Tobacco Use.....	17
Marijuana Use.....	17
Prescription Drug Misuse.	17
Illicit Drug Use.	18
Quality Rating.....	18
Strength of Association Between Substances.	19
Mediators and Moderators.	19
Discussion.....	20
CHAPTER THREE: ADVERSE CHILDHOOD EXPERIENCES AND ILLEGAL DRUG USE AMONG COLLEGE STUDENTS: FINDINGS FROM A FRENCH SAMPLE.....	25
Introduction.....	25
Materials and Methods.....	27
Study Population.....	27
Measures	28
Adverse Childhood Experiences (ACEs).....	28
Cannabis.....	29
Stimulants and Hallucinogens.....	29
Illegal Drugs.....	30
Polydrug.....	30
Covariates.	30
Statistical Analyses.	31
Results.....	31
Participant Characteristics.	31

Associations between Cumulative ACEs and Lifetime Substance Use.....	32
Risky Substance Use.....	34
Associations between ACE types and lifetime illegal substance use.	34
Discussion	34
Conclusion	38
CHAPTER FOUR: BEATING TRAUMA: PHYSICAL ACTIVITY TO PROMOTE RESILIENCE AGAINST SUBSTANCE USE	39
Introduction.....	39
Methods.....	42
Study Population and Design.....	42
Analytic Strategy.	43
ACEs.	43
Frequent drug use outcomes.	45
Socio-demographics.....	45
Physical activity variables.....	45
Results.....	46
Participant Characteristics.	46
ACEs and Substance Use.....	47
Protective Factors.....	48
Discussion	49
CHAPTER FIVE: CONCLUSIONS AND RECOMMENDATIONS	56
Overview of Importance	56
Novel Findings and Innovative Approaches.....	56
Approach I	56
Approach II.....	57
Approach III.....	58
Future Directions	60
Add Health Dataset	60
i-Share Dataset.....	61
ACEs Measurement	62
Informed Framework and Prevention Strategies	63
Conclusion	65
LIST OF REFERENCES.....	67
APPENDICES	95
VITA.....	116

LIST OF TABLES

Table 1. Descriptive characteristics.	96
Table 2. Mediators, Moderators, and SU Outcomes.....	100
Table 3. ACE Type and SU.	103
Table 4. Demographic Characteristics and Other Risk Factors by ACE status.....	107
Table 5. The association between cumulative ACEs and illegal substance use.	108
Table 6. Analytic Sample Sociodemographic characteristics.....	110
Table 7. The association between cumulative ACEs and substance use in Waves III and IV.	112
Table 8. Association between physical activity modality and substance use amongst persons with ACEs.....	113

LIST OF FIGURES

Figure 1. PRISMA Flow Diagram of Literature Search.	95
Figure 2. Strength of Association of Exposure to 4+ ACEs and SU.	104
Figure 3. Dose Response Relationship between ACEs and SU.	105
Figure 4. Flowchart of i-Share Participants.	106
Figure 5. The association between ACE type and lifetime illegal drug use (cannabis, amphetamines, cocaine, hallucinogenic mushrooms, or ecstasy).	109
Figure 6. Cumulative ACEs and substance use in Waves III and IV.	111
Figure 7. Overview of Results: ACEs and Substance Use Risk.	114
Figure 8. Role of Physical Activity on Substance Use.	115

CHAPTER ONE: INTRODUCTION AND GENERAL INFORMATION

Substance Use and Emerging Adults

Over half of the world's population is affected by substance use (SU), the use of alcohol or drugs (SAMSHA, 2019). The vast and pervasive nature of SU pose tremendous societal, economic, and social burdens (Rehm & Shield, 2019), including an annual 740 billion dollars attributed to SU and substance use disorders in the United States alone ("Costs of Substance Abuse," 2020). Typically, SU is initiated in adolescence and peaks during emerging adulthood (18-29 years)(Johnson & Kaplan, 1990; Wisk & Weitzman, 2016). This time period is characterized by rapid shifts into diverse and new social environments often with less parental supervision (Arnett, 2005). During emerging adulthood, the brain is in a critical stage of development, with continued maturation of the prefrontal cortex, which contributes to higher-level cognitive abilities including adaptive, goal-directed behavior in complex situations (Kane & Engle, 2002). The combination of environmental shifts along with increased substance accessibility and neurological vulnerability contributes to emerging adults having the highest risk of SU and emerging SUDs (Arnett, 2005; Kessler et al., 2005).

Legal and illegal SU have considerable implications for emerging adults. Legal substances, typically consisting of tobacco, alcohol, and marijuana (note, the legality of marijuana differs globally) have the highest consumption patterns due to the greatest perceived easy availability and the lowest perceived risk, (United Nations, 2018). Individual differences, such as college attendance, can exacerbate the risk (Jang, Schuler, Evans-Polce, & Patrick, 2019), with 1 in 3 college students reporting recent binge

drinking (Krieger, Young, Anthenien, & Neighbors, 2018). Current contextual factors, such as the COVID-19 pandemic have demonstrated an increase in substance use (Roberts et al., 2021; Wei & Shah, 2020).

Legal SU is associated with deficiencies in psychological health, educational achievement, social competencies, financial difficulties, and physical health (Brook, Zhang, Leukefeld, & Brook, 2016; R. Hingson, Heeren, Winter, & Wechsler, 2005; R. W. Hingson, Zha, & Weitzman, 2009; Johnson & Kaplan, 1990; Mokdad, Marks, Stroup, & Gerberding, 2004; Wisk & Weitzman, 2016). Furthermore, female SU promotes increased risks to developing fetuses and children, as prenatal SU of tobacco, alcohol, and marijuana are associated with deleterious neonatal and child health outcomes, including but not limited to low birth weight, preterm birth, and fetal alcohol spectrum disorders (Woodward, McPherson, & Volpe, 2018).

Illegal SU, prohibited substance use due to unacceptable health and social consequences (Babor et al., 2010), is less prevalent than legal SU, however, the prevalence of current or last year illegal drug use among university students globally ranges from 5-17% (European Monitoring Centre for Drugs, 2018; Peltzer & Pengpid, 2016; Schulenberg et al., 2020; Yi, Peltzer, Pengpid, & Susilowati, 2017). Indeed, this prevalence range may be underestimated as it is challenging to have an accurate estimation of the prevalence of stigmatized and illegal behaviors (Degenhardt & Hall, 2012). Illegal SU is known to increase the risk of sexually transmitted diseases, intentional and unintentional injuries, cardiac problems, interpersonal violence, disability,

crime, and increased transmission of hepatitis B and C virus (Dube et al., 2003b; Peacock et al., 2018).

Adverse Childhood Experiences

Given the extensive breadth of SU worldwide and among emerging adults, it is critical to better understand risk and protective factors of SU to inform prevention policies, screening tools, treatment, and recovery. Early life experiences have also been related to the risk of SU and misuse. Adverse childhood experiences (ACEs), traumatic or stressful events that occur before age 18, are one such class of risk factors (CDC, 2019). ACEs are typically categorized in three groups of stressful or traumatic events, including: 1) abuse (emotional, physical, or sexual); 2) neglect (emotional or physical); and 3) household dysfunction (parental divorce, parental substance use, parental mental health challenge, domestic violence, parental death or separation, incarcerated family member). Recently, studies have expanded this original ACEs framework to consider other events that could occur in a child's social environment to impact child development (e.g., bullying, community violence, war).

The ACEs framework was originally discussed in a landmark study two decades ago, which found a relationship between adverse events during childhood and adolescence and impacts on several health outcomes (V. Felitti et al., 1998). ACEs are common, as a recent systematic review found up to 76% of college students reported having at least one ACE and up to 24% reported having four or more ACEs (Schwartz et al., 2022). ACEs, cluster, meaning children and adolescents who experience an ACE often experience several. Unfortunately, a dose-response pattern between ACEs exposure

and negative outcomes is found, whereby experiencing a higher number of ACEs is associated with many leading causes of death (CDC, 2019). ACEs negatively impact lifelong health and opportunities, spanning from chronic health diseases (e.g., heart disease, stroke cancer), mental health conditions (e.g., depression), social outcomes (e.g., unemployment, lower educational attainment), and health risk behaviors (e.g., suicidal thoughts, and substance use) (CDC, 2019; Hughes et al., 2017; Kalmakis & Chandler, 2015; Sonu, Post, & Feinglass, 2019).

The ACEs framework is supported by a biopsychosocial approach whereby in response to stress, ACEs biologically embed throughout the life course, and can contribute to disproportionate allostatic load and disrupted neurodevelopment (McEwen, 2016). Consequently, the ability to cope with challenging emotions may be impaired, which can lead to the adoption of SU. Thus, ACEs are associated with a 1.83 greater odds of a lifetime substance use disorder (alcohol, drug, or tobacco), compared to persons without such experiences (Choi, DiNitto, Marti, & Choi, 2016). Consequently, this predisposition is further magnified by early-life traumas. Emerging adulthood prepares individuals for later stages of adult development, but SU can interfere with developmental milestones. SU can have long-term negative effects on life-trajectories in association with injuries, academic problems, risky sexual behaviors, fighting, challenged relationships, financial instability, worsening mental health, and drug misuse, abuse, and dependence – emphasizing the critical need to better understand protective factors in early adulthood (Stone, Becker, Huber, & Catalano, 2012).

Physical Activity and Resilience

Physical activity (PA) may protect against the impact of early-life traumas, as it has demonstrated a dose-response relationship with primary and secondary prevention of 25 chronic medical conditions, whereby higher frequency of PA is related to enhanced health (Warburton & Bredin, 2017). Epidemiological studies have demonstrated that physical inactivity is associated with substance use disorders (Linke & Ussher, 2015). Psychological, behavioral, and neurobiological pathways have been suggested through which PA may exert positive impacts on SU.

Psychologically, PA has can alleviate cravings of SU (Baker, Japuntich, Hogle, McCarthy, & Curtin, 2006; Heilig, Egli, Crabbe, & Becker, 2010), is associated with positive mood and self-efficacy (Daley, 2008), and less mental health problems (Lavie, Milani, O'Keefe, & Lavie, 2011). Behaviorally, PA is typically an element of a healthy lifestyle that is associated with other positive health behaviors including good sleep and healthy diet (Berrigan, Dodd, Troiano, Krebs-Smith, & Barbash, 2003; Terry-McElrath & O'Malley, 2011). Neurobiologically, PA increases neurotransmitters, including dopamine, beta-endorphins, epinephrine, serotonin, and norepinephrine, which contribute to a reward circuitry (Boecker et al., 2008; Heitkamp, Schmid, & Scheib, 1993) and may explain the positive effects of PA on depression and anxiety (Greenwood & Fleshner, 2011). Further, PA creates hippocampal neurogenesis, which has demonstrated the ability to reduce the impact of stress (Yau, Lau, & So, 2011).

While PA may protect against SU, the optimal dose and modality needed is still being researched and may vary by individuals (Ekkekakis & Petruzzello, 1999; Williams,

2008). Studies have utilized unspecified terminology and measurements of PA, such as sport, and exercise interchangeably across studies (Khan et al., 2012; Lynch, Robinson, Abel, & Smith, 2017). While all are modes of PA there is much variability in each. For example, sports can differ from being team or individual, contact, or non-contact, or could be participated in at a recreational or elite level (Kwan, Bobko, Faulkner, Donnelly, & Cairney, 2014). A systematic review found that sport participation was typically associated with reduced illicit drug use and cannabis use but had increased likelihood of alcohol use (Kwan et al., 2014), illustrating there may be cultural aspects associated with sports participation that increase alcohol consumption. Thus more studies are needed to assess whether protection effects vary by type of PA and SU to inform prevention efforts (Brellenthin & Lee, 2018).

Resilience aims to understand how an individual develops healthfully regardless of being exposed to risk. Resilience refers to the process of three things: 1) overcoming the negative outcomes associated with risk exposure, 2) successfully coping with traumatic experiences, and 3) evading negative trajectories linked with risk (Fergus & Zimmerman, 2005). Resilience requires both risk and promotive factors which either reduce or avoid a negative event or assist in reaching a positive outcome (Fergus & Zimmerman, 2005). Three different models of resilience have been identified, compensatory, challenge, and protective (Fergus & Zimmerman, 2005; Rutter, 1987). These models describe how assets and resources work to positively change trajectories of individuals with risk (Fergus & Zimmerman, 2005). Chapter IV is guided by the

protective resilience model, whereby promotive factors decrease the effects of risk on a negative outcome (Fergus & Zimmerman, 2005).

Resilience can be fostered by promotive factors which lie within individuals, relationships, or environments, stressing the ecological nature of resilience models (R. Ortiz, 2019). Promotive factors are defined as either assets or resources. Assets lie within the individual, such as self-efficacy or competence, whereas, resources are external to the individual, including mentoring, parental guidance, or community support (Fergus & Zimmerman, 2005). Resilience theory, like the positive youth development model, emphasizes enhancing the strengths of youth through promotive factors, instead of a deficit approach, focusing on reducing risk (Zimmerman et al., 2013). PA is associated with enhanced resilience to stress and decreased SU across both human and animal species through psychological, behavioral, and neurobiological pathways (Brellenthin & Lee, 2018; Perez, Bravo, Rodgers, Khan, & Leasure, 2019; Sanchez, Lycas, Lynch, & Brunzell, 2015). PA may promote resilience as it is associated with increased self-efficacy (assets) (Daley, 2008) and many modalities of PA involve a community support and mentorship from coaches or trainers (resources). Thus, PA in early adulthood may contribute to a protective resilience model, mitigating future SU in the presence of ACEs.

Conclusion

Despite the high prevalence and potential impact of ACEs on SU, there are several gaps in the literature specific to emerging adults. Prior work is not specific by substance type, by the frequency of SU, the relative contribution of ACE types, or the capacity of different PA types to moderate the association of ACEs and SU (Griffin,

Bang, & Botvin, 2010; Kandel et al., 1997; Metrik, Caswell, Magill, Monti, & Kahler, 2016; Park, Lee, & Han, 2021). A dearth of information in this area prevents public health professionals from providing an informed framework to improve SU prevention strategies. Thus, this project aims to investigate gaps in the literature, specifically:

CHAPTER II: Provides a critical review of studies examining the relation between ACEs and SU among university students. This review presents the relation between ACEs exposure (cumulative and individual ACE types) and specific types of substance use.

CHAPTER III: Evaluates the association between ACEs and specific illegal drug types (hallucinogens, stimulants, marijuana) among a French sample of college students while examining the cumulative exposure of ACEs and the respective contributions of different types of ACEs.

CHAPTER IV: Elucidates the relation between ACEs exposure and frequent cigarette smoking, marijuana use, and binge drinking. The protective role of PA amongst persons with a history of ACEs are also examined in a nationally representative American sample of emerging adults. The quest of whether PA (modality) promotes resilience by moderating the relation between ACEs and SU is examined.

CHAPTER V: Conclusion and summarizes the dissertation in its entirety, including opportunities for future research.

This dissertation uses diverse approaches (e.g., systematic review, secondary data analysis, theoretical models) and samples (e.g., French, American) to comprehensively assess the relationship between ACEs and SU among emerging adults while demonstrating how protective factors (physical activity) promote resilience. These contributions are significant because they strengthen understanding of specific SU after ACE exposure and highlight the avenues for prevention in primary care and emerging adult settings.

CHAPTER TWO: ADVERSE CHILDHOOD EXPERIENCES AND SUBSTANCE USE AMONG UNIVERSITY STUDENTS: A SYSTEMATIC REVIEW

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Introduction

Substance use (SU), the use of alcohol or drugs, affects over sixty percent of the world's population (SAMSHA, 2019). SU can have long-term negative effects on life-trajectories in association with risky sexual behaviors, challenged relationships, and mental health decline (Stone et al., 2012). Further, SU can lead to substance use disorders (SUD), the continual use of a substance despite negative effects (Hasin et al., 2013), incurring grave societal, economic, and health costs (Rehm & Shield, 2019).

Emerging adulthood, characterized by rapid shifts into new social environments with less parental supervision and increased substance accessibility, is the population with the highest risk of SU and emerging SUDs (Arnett, 2005; Kessler et al., 2005). Attending college can exacerbate this risk, with 1 in 3 college students reporting recent binge drinking (Krieger et al., 2018). The brain is in a critical stage of development, increasing the severity of long-term consequences of SU (Arnett, 2005). As SU during

emerging adulthood is correlated with academic, economic, social, and behavioral challenges, it is important to consider early risk factors (Welsh, Shentu, & Sarvey, 2019).

Early life experiences have been related to the risk of SU (Leza, Siria, López-Goñi, & Fernández-Montalvo, 2021). Adverse traumatic or stressful events that occur before age 18, also named adverse childhood experiences (ACEs), are one such risk factor (CDC, 2019). ACEs refer to the cumulative exposure of childhood abuse, neglect, household dysfunction (e.g., parental divorce), and negative environmental experiences (e.g., bullying). Typically, as ACE exposure increases, so does the risk of negative health outcomes (Lee, Slack, Berger, Mather, & Murray, 2021). Worldwide, studies have reported 22-87% of emerging adults have experienced at least one ACE, indicating a high prevalence (Park et al., 2021).

Despite the high prevalence of ACEs and their potential impact, there is limited knowledge of how ACEs influence SU among university students. Two reviews have been conducted on the association between ACEs and emerging adult health outcomes and reported that ACEs were associated with increased SU (Park et al., 2021; Rogers et al., 2022). However, results were not distinct by university students (Park et al., 2021; Rogers et al., 2022) or substance type (Park et al., 2021) thus limiting our understanding. All substances present with differing risk and protective factors (SAMSHA, 2018), requiring unique social-ecological approaches for prevention, treatment, and recovery. Thus, understanding the relation between ACEs and each specific substance type among university students can aid in identifying and offsetting negative developmental cascades related to SU with a more specified lens. To date, no review has synthesized the available

evidence of the relation between ACEs and SU nor the relation between ACEs and substance type among university students specifically. Thus, we performed a systematic review to fill these gaps.

Methods

This systematic review was registered with the PROSPERO International prospective register of systematic reviews (CRD42021277882) and was conducted using an a-priori protocol following PRISMA guidelines (Shamseer et al., 2015).

Eligibility Criteria.

All studies had to meet the following inclusion criteria: (1) included data about ACE exposure, (2) SU during university attendance, (3) participants with a mean age of 18-30 years; and (4) self-reported or clinical SU outcome. There were no geographical restrictions, and filters for the search included limiting articles to human studies, 18 years or older, and the English language.

Search Strategy.

A literature search was conducted for studies of SU among university students with a mean age of 18-30 years and ACEs by searching the following electronic databases: CINAHL, PubMed, PsycINFO & ERIC, and Web of Science. The original CDC-Kaiser ACE study was published in 1998, thus the search included published articles starting January 1998 through September 2021 (V. Felitti et al., 1998). Systematic reviews and meta-analyses were excluded. The final search was run on September 17th, 2021. Relevant studies were identified by the following search terms: (1) adverse childhood experiences, (2) substance use, and (3) university or college students. Medical

Subject Headings terms were utilized to increase sensitivity of the search. After removing duplicates, studies were selected by the first author from titles, abstracts and full texts.

Lastly, reference lists of full text studies were reviewed.

Data Extraction.

A standardized data extraction excel chart was utilized to provide the following information when available: author, year of publication, study design, country, sample size, mean age of participant, types of ACE exposure, prevalence of ACEs, ACE measurement instrument, mediators, moderators, SU outcomes, and SU instrument.

Quality Assessment.

The checklist published by the US National Heart, Lung and Blood Institute for observational cohort and cross-sectional studies was used to assess the risk of bias in included studies (National Heart Lung and Blood Institute, 2019). All studies were assessed by the first author, with the second author reviewing a subsample that resulted in an overall agreement of Cohen's κ equaling 0.87. Disagreements were discussed between the first two authors to reach consensus. The checklist had 14 questions assessing internal validity, of which a final quality rating of good, fair, or poor was given. Articles were excluded if the quality was rated as poor (≤ 4 of the 14 criteria met).

Results

Study Selection.

Overall, 450 references were found by the algorithms. After removal of 49 duplicates, 401 articles were available for screening. Title and abstract review removed 371 articles and after full-text review, 13 articles were further removed. Methodological

quality assessment led to the exclusion of one article that was rated as poor (Brajović et al., 2019). As a result, 16 studies were included (Figure 1; All tables and figures are in appendices).

There were two instances where multiple reports were published on the same cohort with the same outcome variables (Forster, Grigsby, Rogers, & Benjamin, 2018a; M. Forster, C. J. Rogers, et al., 2019; Kameg, Lindsay, Lee, & Mitchell, 2020; Kameg & Mitchell, 2021). In these cases, only one study per primary outcome was included per cohort to avoid bias by summarizing the same participant more than once. The publication with the highest number of cases for primary outcomes was included (M. Forster, C. J. Rogers, et al., 2019; Kameg et al., 2020).

Study Characteristics.

Details regarding characteristics of eligible studies are summarized in Tables 1-2. The 16 studies included in total 53,433 university students from 17 countries, whose mean age ranged from 18-25. Sample sizes ranged from 292 to 16,370 university students. Over half of the studies were conducted in the United States or Canada (n=9), followed by Africa (n=4), Europe (n=2) and Asia (n=1). Studies were all cross-sectional, with exception to one cohort study (2 years, 6 waves of data) that reported ACEs and SU with just one wave of data for analyses (Windle, Haardörfer, et al., 2018). All included studies were published in the last 5 years (2015-2021).

ACE Instruments, Approach, and Prevalence.

Retrospective self-report measures that asked about early life adversities occurring before 18 years of age, identified ACE exposure (Table 1). The most common

instrument utilized was the ACE Questionnaire (n=8), originating from the landmark CDC-Kaiser Permanente study (V. Felitti et al., 1998). The ACE International Questionnaire (n=5) was also frequently used (World Health Organization, 2012).

ACE instruments captured 5 to 12 ACEs, with a larger focus on exposure to child abuse, neglect, and household dysfunction, and smaller emphasis on the social environment. The most commonly assessed ACE was sexual abuse (n=16), followed by emotional abuse (n=15), physical abuse (n=15), household violence (n=14), parental substance use (n=14), parental mental health (n=12), emotional neglect (n=10), incarceration (n=9), community violence (n=9), physical neglect (n=9), divorce (n=7), homelessness (n=1), financial problems (n=1), bullying (n=1), and caregiver absence (n=1; Table 1). The majority of studies used a cumulative ACE score (n=15), while fewer studies examined the individual ACE type (n=7). The prevalence of having at least 1 ACE ranged from 17.5- 76.2% and having four or more ACEs ranged from 0.3-24.6%.

Substance Use.

Studies with former references to substance abuse or alcoholism are referred to as problem SU, risky SU, SUD or the appropriate reference term to reduce the use of stigmatizing and outdated terminology (Grigsby, 2021). Among cross-sectional studies, problem SU was utilized to distinguish the negative consequences of SU, whereas risky SU referred to studies investigating the frequency and quantity of SU (Grigsby, 2021). Some studies investigated multiple types of SU outcomes; however, results are presented by substance type for clarification of the relationship between ACEs and specific SU. The most commonly assessed substance was alcohol (n=11), followed by tobacco (n=7), illicit

drugs (n=7), marijuana (n=2), and prescription drug misuse (n=2). Due to large heterogeneity, it was not possible to perform a meta-analysis; however we have provided a graphical description of the association between four or more ACEs and SU (Fig 2).

Alcohol Use.

Studies used retrospective survey questions about recent alcohol consumption (n=7) or validated measures, such as the Alcohol Use Disorder Identification Test-Consumption (AUDIT-C; n=3), the Brief Young Adult Alcohol Consequences Questionnaire/Daily Drinking Questionnaire (n=1), and Health Appraisal Questionnaire (n=1; Table 1).

Most studies found that ACEs were associated with current risky (Brett, Espeleta, Lopez, Leavens, & Leffingwell, 2018; Forster et al., 2019; Windle, Haardörfer, et al., 2018) or problem alcohol use (Hughes et al., 2019; Kameg & Mitchell, 2021; Schafer, 2021; Wiehn, Hornberg, & Fischer, 2018). The association between ACEs and risky alcohol use was not supported in one study (Krinner, Warren-Findlow, & Bowling, 2020). Students with four or more ACEs were more likely to report lifetime problem alcohol use (Hughes et al., 2019), potentially have alcohol use disorder (Kim, 2017), and report early alcohol initiation (Hughes et al., 2019) (Fig. 2). The relationship between ACE type and alcohol outcomes varied, with parental SU, sexual abuse, and physical abuse appearing to be more frequently associated with statistically significant relationships (Table 3).

Three studies assessed the risk of binge drinking. Four or more ACEs were associated with past 2-week binge drinking (Grigsby et al., 2020; Fig 2). Not all ACE

types were significantly associated with binge drinking (Table 3), however, sexual abuse had the strongest relations in two studies (Forster et al., 2019; Zhang et al., 2020).

Tobacco Use.

Seven studies analyzed the risk of tobacco consumption following ACE exposure. Most studies used retrospective survey questions to identify recent cigarette smoking and one study utilized the Fagerstorm Test for Nicotine Dependence (Table 1). In all studies, ACEs increased the likelihood of current cigarette smoking (Forster et al., 2019; T. J. Grigsby et al., 2020; Hughes et al., 2019; Wiehn et al., 2018; Windle, Haardörfer, et al., 2018). When measured by ACE type, the association wasn't always statistically significant (Table 3), however sexual abuse, parental SU, and collective and peer violence had the strongest relations (El Mhamdi et al., 2018; Zhang et al., 2020). Having four or more ACEs was found to increase odds of current or past 30-day tobacco use (Grigsby et al., 2020; Hughes et al., 2019; Wiehn et al., 2018) (Fig 2).

Marijuana Use.

Two studies measured the relation between ACEs and past 30-day marijuana use utilizing self-report retrospective survey questions (Table 1). Cumulated ACEs predicted risky past 30-day marijuana use (Windle, Haardörfer, et al., 2018) and were associated with past 30-day marijuana use (Forster et al., 2019). Parental SU, sexual abuse, and physical abuse were statistically significantly related to marijuana use (Table 3).

Prescription Drug Misuse.

The relation between ACEs and prescription drug misuse was assessed by two studies; one utilized a self-report retrospective survey question and the other used the

Tramadol Abuse Scale (Table 1). Results indicated that ACEs were associated with risky tramadol use among male university students (Onu, Ifeagwazi, Orjiakor, & Iorfa, 2021) and past year prescription drug use, including stimulant, antidepressant, opiate, and sedative use (Pakdaman et al., 2021) (Fig 3).

Illicit Drug Use.

Seven studies reported the link between ACEs and illicit drug use other than cannabis (e.g., cocaine, heroin, ecstasy). Four studies utilized survey questions to assess illicit drug use, two studies used the Drug Abuse Screening Test (DAST-10), and one utilized the Health Appraisal Questionnaire (Table 1). ACEs were associated with increased likelihood of lifetime and last year illicit drug use (Forster et al., 2019; Hughes et al., 2019), risky drug use, and SUDs (Kameg & Mitchell, 2021; Ramakrishnan, McPhee, Sosnowski, Rajasingam, & Erb, 2019). The association of ACEs with addictive behaviors, SUDs, and illicit drug use varied by ACE type, with parental SU, sexual abuse, and physical abuse having the most statistically significant relationships (El Mhamdi et al., 2017; Wiehn et al., 2018; Zhang et al., 2020; Table 3). Exposure to multiple ACEs was related to current illicit drug use (Fig. 2) (Wiehn et al., 2018) and increased risk of having a lifetime addictive behavior by 8-fold in females and 16-fold in males (El Mhamdi et al., 2017).

Quality Rating.

Overall, all included studies were rated with good or fair quality. Studies of lower quality typically did not recruit all subjects from the same population nor uniformly apply inclusion and exclusion criteria. This may have resulted in findings being less

representative of university students. All measurement of ACEs relied on retrospective self-report measures. While utilized frequently in the literature, this design introduces recall bias that may impact the association estimate. Most studies utilized 1-6 covariates in their statistical analyses (81%) to adjust for potential confounding factors (Table 2).

Strength of Association Between Substances.

When studies measured the strength of relations between ACEs and more than one substance type, differences in effect size emerged in diverging patterns. For example, among students who experienced four or more ACEs, there was a stronger association with problem alcohol use than tobacco use (Hughes et al., 2019), whereas, the opposite pattern was also demonstrated (T. J. Grigsby et al., 2020). Wiehn and colleagues (2018) indicated higher odds for cigarette use compared to illicit drug use among students with four or more ACEs. Reviewed together, persons with four or more ACEs have increased risk of binge drinking (adjusted odds ratio (aOR) (95%CI):1.5 (1.2,2.0)), problem alcohol use (aOR (95%CI) range: 4.32-4.57 (2.39,8.76)), illicit drug use (aOR (95%CI): 2.95 (1.94, 4.47)), and tobacco use (aOR (95%CI) range: 2.01-6.34 (1.7, 11.34)) (Fig 2). Two studies reported the dose response relationship between ACE exposure and SU (Forster et al., 2019; Pakdaman et al., 2021), demonstrating for every additional ACE experienced, there was a subsequent increase in odds of SU (Fig. 3), with illicit drug use having the largest increase per additional ACE.

Mediators and Moderators.

Fewer than half of the included studies (n=7) assessed mediators and moderators of the relationship between ACEs and SU. Mindfulness and sociosexual behaviors were

identified as mediators of the association of ACEs with past 30-day problem alcohol use (Brett et al., 2018) and tramadol use (Onu et al., 2021), respectively. Positive urgency, a facet of impulsivity, was found to partially mediate ACEs and SUDs (Ramakrishnan et al., 2019). Moderators of the relation between ACEs and SUDs were also identified, including supportive childhood relationships (Hughes et al., 2019), gender (El Mhamdi et al., 2018; El Mhamdi et al., 2017), and ethnicity (Forster, Grigsby, Rogers, & Benjamin, 2018b). Supportive childhood relationships moderated the risk of current smoking and lifetime problem alcohol use as related to ACEs (Hughes et al., 2019). Gender and the type of adversity modified the relationship between ACEs and past year and 30-day risky alcohol use (Schafer, 2021; Wiehn et al., 2018), past 30-day binge drinking (Zhang et al., 2020) past 30-day tobacco use (El Mhamdi et al., 2018; Zhang et al., 2020), lifetime addictive behaviors (El Mhamdi et al., 2018; El Mhamdi et al., 2017), and lifetime illicit drug use (Zhang et al., 2020). Statistically significant ethnic variation of the dose-response relationship between ACEs and SU existed, whereby Asian/Pacific Islanders had greater risk of past year stimulant and marijuana use and non-Hispanic White persons had greater likelihood of past year marijuana, sedative, and antidepressant use (Forster et al., 2019; Pakdaman et al., 2021).

Discussion

To our knowledge, this is the first systematic review summarizing the existing evidence and study characteristics about the relationship between ACEs and specific SU types among university students. This review identified 16 relevant articles, all published within the last five years, indicating an emerging research focus. Nearly all studies

reported a positive relation between ACEs and SU or risky SU, including alcohol, tobacco, marijuana, prescription-medication, and illicit drug use. The strength of association between ACEs and SU differed by substance, with the greatest strength for tobacco and illicit drug use. The relationship between ACE type and SU differed by substance and study, however, childhood sexual abuse and parental SU appeared to have the greatest number of statistically significant associations. A dose-response relationship emerged for every substance, whereby, as ACEs accumulate, there is a corresponding increased risk for SU. The findings demonstrated are similar to a review on the relation between ACEs and SU during emerging adulthood, however, add a unique perspective by focusing on university students and discussing the strength of association between ACEs and SU (Rogers et al., 2022). While students typically attend university during emerging adulthood, university students represent a different population with various contextual, social, and cultural factors that may increase accessibility to substance use. Further, these results are consistent with the research that has analyzed the association of ACEs and SU in older adults and the general population (Hughes et al., 2017; Kalmakis & Chandler, 2015; Petruccelli, Davis, & Berman, 2019). The majority of studies came from economically developed nations; thus, future research should be conducted globally to determine if this relationship is consistent across other cultural and economic contexts.

While strong associations of ACEs with SU were demonstrated, it is important to view these results with caution as there is heterogeneity in the classification of ACEs. Included studies ranged from assessing 5 to 12 ACEs from both household and social environments, which contributed to the diverse prevalence of ACEs reported across

studies. Since 1998, ACEs have encompassed childhood abuse, neglect, and household dysfunction. In the last decade, researchers have widened the spectrum of childhood adversities to also reflect traumas, such as community violence and bullying (D. Finkelhor, Shattuck, Turner, & Hamby, 2013). A consensus about the definition of ACEs would be beneficial, as well as standardization when measuring SU outcomes.

Several limitations within the literature and review exist. First, there was heterogeneity in the classification of ACEs and SU (e.g., time frame of SU, frequency of SU) among studies. Second, only manuscripts that used cumulative ACE measures were included for the review, thus, manuscripts that investigated the impact of single adverse event could be excluded. Nevertheless, this methodology has been commonly used to look at the relation between cumulative childhood trauma and SU (Kalmakis & Chandler, 2015; Leza et al., 2021; Park et al., 2021). Third, included studies utilized retrospective self-report measures of ACEs, potentially affected by recall bias. However, prospective ACE records have confirmed similar findings of negative life outcomes utilizing retrospective ACE measures (Reuben et al., 2016). Fourth, confounding variables were inconsistently included and reported. Fifth, the selection and extraction of information was made by a single reviewer. Despite this limitation, a subsample of quality reviews was completed by two reviewers and obtained high reliability. Further, this study adhered to PRISMA guidelines and is the first to systematically review and summarize studies that examined the relation between ACEs and specific SU types among university students.

Regardless of these methodological issues, there is convincing evidence that ACEs increase risk of SU among university students and this relation is complex. As such, resilience models that emphasize mediators and moderators in promoting healthy development regardless of ACE exposure should be explored. One identified mediator, mindfulness, is supported by a growing body of literature demonstrating its' role with resilience building and better behavioral health amongst persons with ACEs (Robin Ortiz & Sibinga, 2017; Whitaker et al., 2014). Among university students, mindfulness has been found to mediate the association between ACEs and SU and mental health outcomes (Brett et al., 2018; McKeen et al., 2021). Thus, interventions among university students that promote mindfulness may protect against future SU despite prior ACE trauma (Robin Ortiz & Sibinga, 2017).

Early screening of ACE exposure among university students, if feasible, might identify students at higher risk of SU and SUD and engage them in preventive or therapeutic strategies. As individuals with a history of ACEs are more likely to fail treatment for SUDs (López-Castro, Hu, Papini, Ruglass, & Hien, 2015; Najavits, Lande, Gragnani, Isenstein, & Schmitz, 2016), the challenges associated with treatment may be due to a lack of individualized and specific treatment. Thus, screening for ACEs and protective factors (The Positive and Adverse Childhood Events Survey (PACES)), combined with a nonjudgmental, trauma informed, person-centered screening approach may be well suited for university students (Chandler, Kalmakis, & Murtha, 2018; Leitch, 2015). While previously used among adult populations, this method intends to promote mindfulness and is believed to decrease the potential for further traumatization while

providing education and self-reflection on the link between ACEs and SU (Leitch, 2015). This knowledge may introduce self-awareness to university students regarding the pathway between ACEs and SU and build resilience and self-acceptance (Chandler et al., 2018; R. Ortiz, 2019).

CHAPTER THREE: ADVERSE CHILDHOOD EXPERIENCES AND ILLEGAL DRUG USE AMONG COLLEGE STUDENTS: FINDINGS FROM A FRENCH SAMPLE

Ashlyn Schwartz was involved in conceptualization, data analysis, writing, and editing of article. All authors contributed to the article which is currently under review for publication.

Introduction

Illegal drugs, prohibited substances due to unacceptable health and social consequences (Babor et al., 2010), pose tremendous risks to college students. While having an accurate estimation of the prevalence of stigmatized and illegal behaviors is challenging (Degenhardt & Hall, 2012), the prevalence of current or last year illegal drug use among university students globally ranges from 5-17%, with Europe having some of the highest estimates (European Monitoring Centre for Drugs, 2018; Peltzer & Pengpid, 2016; Schulenberg et al., 2020; Yi et al., 2017). France in particular has alarming illegal drug challenges, with the highest European Union prevalence of cannabis use (20%), a rising prevalence of cannabis and cocaine for two decades, and the highest quantity of amphetamines and methamphetamines seized (European Monitoring Centre for Drugs, 2018).

Emerging adults, typically adults 18-29 years, have an increased risk for substance use due to developmental and contextual factors. Emerging adulthood is categorized as a transitional stage, including instability, identify exploration, less parental support, self-focus, and greater availability of substances, all of which increase vulnerability to substance use (Arnett, 2005). College attendance further exacerbates this

risk, with higher rates of cannabis initiation (Miech, Patrick, O'Malley, & Johnston, 2017). Illegal substance use during university years can lead to negative legal, academic, and health consequences. Academically, illegal drug use has been associated with discontinuous enrollment (Arria et al., 2013), lower grade point average (Benson, Flory, Humphreys, & Lee, 2015; Boyd, McCabe, & d'Arcy, 2003) and drop out of college or delayed graduation (Suerken et al., 2016). Regarding health consequences, illegal drug use raises likelihood of risky behaviors, increased risk of injury, poorer relationships, substance use disorders, and death (Skidmore, Kaufman, & Crowell, 2016; Stone et al., 2012).

A growing number of studies have been examining how adverse childhood experiences (ACEs) impact lifelong health, health behaviors, and life potential, including illegal substance use (Dube et al., 2003a; Hughes et al., 2017; Leza et al., 2021; Villanueva & Gomis-Pomares, 2021). ACEs are typically conceptualized as traumatic or stressful events that occur before 18 years of age and can be analyzed independently or cumulatively. In the original ACEs study (V. Felitti et al., 1998), ACEs comprised three groups: 1) abuse (emotional, physical, or sexual), 2) neglect (emotional or physical), and 3) household dysfunction (mental illness in household, parental separation or divorces, incarcerated household member, substance abuse in household, or domestic violence). Recently, studies have expanded the original ACEs framework to consider other adverse events that could occur outside the home, such as bullying and community violence.

The results from a systematic review on ACEs exposure and substance use among college students summarizes that ACEs were associated with increased illegal drug use,

cannabis use, and substance use disorders (Schwartz et al., 2022). While these studies show consistent results, they are low in number and limited by their small sample sizes (Kameg et al., 2020; Ramakrishnan et al., 2019; Zhang et al., 2020). Plus only two studies were European sample (Hughes et al., 2019; Wiehn et al., 2018), only three studies considered ACEs by their subtype (El Mhamdi et al., 2017; Wiehn et al., 2018; Zhang et al., 2020), and no studies analyzed illegal drugs by drug categories (with exception to cannabis, which is illegal in France). As different categories of substances have distinct implications on the life course and prevention, it is important to understand how ACEs impact various types of illegal substance use. Thus, to fill these gaps, we have conducted the present study on a large sample of French university students. Our objective was to evaluate the association between ACEs and specific illegal drug types among college students, while examining the cumulative exposure of ACEs and the respective contributions of different types of ACEs.

Materials and Methods

Study Population.

This study used data from the internet-based Students Health Research Enterprise (i-Share) online prospective cohort (www.i-share.fr). Starting in 2013, this population-based cohort aims to explore the health of students in higher education institutions across France. Eligibility criteria included: 1) being 18 years or older, 2) enrolled at a university or higher education institution in France, and 3) able to understand French. After registering on the website, participants completed the baseline questionnaire. This study was approved by the National Commission for Information Technology and Liberties

(CNIL) [DR-2013-019]. The institution ethics review board (Comité de protection des personnes, Sud-Ouest et Outre Mer III, CPP) approved the i-Share protocol and all participants gave written informed consent to participate in the study. To be included in the present study, participants had to be between ages 18 and 30 and have available data on ACEs exposure and substance use.

Measures

Adverse Childhood Experiences (ACEs).

Self-reported, retrospective questions on traumatic childhood experiences before 18 years of age were utilized from the baseline questionnaire to create nine dichotomous measures of ACEs. The ACEs were defined as: 1) emotional abuse (adult caregiver ridiculed/criticized child often or child often had the feeling they had been mistreated emotionally by caregiver); 2) physical abuse (child had ever been beaten by an adult caregiver to the point of having bruises or having to see a doctor or child often had the feeling that they were physically abused by adult caregiver); 3) sexual abuse (adult caregiver ever touched, fondled child sexually or adult caregiver ever threatened to hurt child or to lie in order to touch or have sex with child); 4) emotional neglect (adult caregiver often ignored child or made them understand they did not matter or child often had the feeling that the adult caregiver did not want them to be born); 5) physical neglect (child's basic needs were often overlooked or there was rarely someone there to take care or protect child); 6) parental divorce (parents divorced or separated at or before 18 years of age); 7) parental substance use (either parent often had a problematic alcohol use or had alcohol use disorder or had a drug problem); 8) parental mental illness (child's

mother or father had problems with anxiety or depression); 9) bullying (child was often the victim of harassment by other children). ACEs were analyzed both separately by ACE type and by a cumulative ACEs score. For the cumulative score, the nine ACEs were summed and transformed into an ordinal variable representing 0, 1, 2, 3+ total traumas. Only cases with no missing data for all nine traumas were used in analyses (n=1174).

Cannabis.

Participants were asked if they had used cannabis within the last year and at which frequency (every day, several times a week, once a week, several times a month, once a month or less, and only once). Based on distributions in the data, we grouped the subjects into two classifications for analyses: lifetime (any use during lifetime) or monthly use (once a month or greater use during the last year) (reference: no use).

Stimulants and Hallucinogens.

In the baseline questionnaire, students were asked if they had taken amphetamines, cocaine, hallucinogenic mushrooms, or ecstasy in the course of their life and if so, how frequently (never, one time, two-five times, or more than six times). Participants who had taken any amount of cocaine and/or amphetamines were grouped into a lifetime stimulant category (reference: no use). Subjects who responded to taking any amount of ecstasy and/or hallucinogenic mushrooms were grouped into a lifetime hallucinogen category (reference: no use). If participants responded to taking stimulants or hallucinogens six or more times in their life, they were classified as risky stimulant or risky hallucinogen use (reference: no use) (Grigsby, 2021).

Illegal Drugs.

A composite variable was created for lifetime illegal drug use if a student had taken one of the following substances in their lifetime: cannabis, amphetamines, cocaine, hallucinogenic mushrooms, or ecstasy. If participants responded to taking any illegal drugs more than six times or taking cannabis monthly, participants were grouped into a risky illegal use variable (reference: no use). Lastly, participants were classified as multiple illegal drug use if during their lifetime they had consumed two or more types of drug categories: stimulants, hallucinogens, or cannabis (reference: no use).

Polydrug.

Participants were classified as polydrug use if a student reported using alcohol 2-3 times per week or 10 or more cigarettes a day and reported using any illegal drug during their lifetime. Due to the nature of the survey, polydrug use refers to the pattern of using several substances throughout the lifetime and does not represent current co-consumption of substances.

Covariates.

The covariates included were potential confounders of the relationship between ACEs and illegal drug use collected at baseline. Socio-demographic characteristics included: age (18-22 years or 23-30 years), gender, self-reported socio-economic status (SES) during adolescence (low or moderate/high), lifetime tobacco use (yes/no), lifetime binge drinking (e.g., at least 6 drinks on the same occasion) (yes/no), and anxiety and depression diagnoses from a medical doctor (yes/no).

Statistical Analyses.

Analyses were conducted in multiple steps. Firstly, the study sample was described and baseline characteristics between participants with and without ACEs were compared through chi-square tests. Secondly, the crude associations between cumulative and individual ACE types, sociodemographic characteristics, and substance use by using logistic regression models were examined. Thirdly, we adjusted for sex, adolescent SES, and age in multivariate logistic models. Fourthly, we adjusted for mental health (depression and anxiety diagnoses) and substance use (tobacco and binge drinking). Confirmation of the best model fit between multivariate models were executed by having the larger area under the curve and a Hosmer and Lemeshow Test $\geq .05$. SAS Enterprise Guide (version 8.3) and Microsoft Excel were used to conduct the analyses.

Results

A total of 1,157 out of 1,521 participants between 18 and 30 years of age completed questions within the baseline questionnaire on ACEs exposure, making them eligible for the present study. Among them, 1,052 had no missing data on lifetime illegal substance use (Figure 4).

Participant Characteristics.

Among the student sample, ACEs exposure was as follows: 0 ACEs (30.6%), 1 ACE (29.6%), 2 ACEs (19.2%), and 3+ACEs (20.7%). The most commonly reported ACEs were parental mental illness (38.0%) and divorce (34.6%), followed by bullying (18.1%), emotional neglect (14.3%), emotional abuse (12.5%), sexual abuse (11.0%), physical abuse (10.3%), parental substance use (9.7%), and physical neglect (6.6%). The

majority of participants were females (88.3%), with 20.4 (SD=2.3) years of age and had a moderate to high SES during adolescence (74.8%). Across the sample, 16.8% had a depression diagnosis and 16.6% had an anxiety diagnosis.

The most commonly reported substance used was lifetime cannabis use (52.2%), with one fifth of participants drinking alcohol weekly and using tobacco daily. Almost three quarters of the sample participated in binge drinking the last year (72.2%). A smaller portion of the sample reported illegal drug use (14.1%), comprised of stimulant use (8.0%) and hallucinogen use (11.9%). About one third of participants had lifetime polydrug use, one fifth of participants had consumed 2 or more illegal drugs in their lifetime, less had consumed 3 or more in their lifetime (12.4%), and even less students were classified as risky illegal drug use (10.0%).

Table 4 depicts baseline characteristics of the sample according to ACE status. In bivariate analyses, students with ACEs exposure had a higher likelihood of lifetime tobacco, cannabis, stimulant, illegal drug use (multiple and risky), having a low SES during adolescence, depression diagnosis, and anxiety diagnosis. There were no statistically significant differences between gender ($p=0.3078$) or age ($p=0.8864$) and having experienced ACEs.

Associations between Cumulative ACEs and Lifetime Substance Use.

After adjusting for sociodemographic variables, students with three or more ACEs were more likely to have lifetime hallucinogen, stimulant, cannabis, any illegal drug, polydrug, and multiple illegal drug use, compared to peers without ACE exposure (see Table 5). Final models adjusting for sociodemographic variables, substance use, and

mental health showed a dose response relationship between ACEs score and lifetime illegal drug use. Higher levels of ACEs exposure were associated with a greater likelihood of lifetime illegal substance use. Having three or more ACEs increased the risk of lifetime use of multiple illegal drugs (aOR:10.9; 95% CI: 4.6-26.0), stimulants (aOR: 3.6; 95% CI:1.7-7.7), hallucinogens (aOR: 2.0; 95% CI: 1.1-3.5), cannabis (aOR: 4.7; 95% CI: 2.7-8.0), illegal drugs (aOR: 2.7; 95% CI: 1.6-4.8), and polydrugs (aOR: 2.5; 95% CI: 1.6-3.9). Having a low SES during adolescence, being male, having an older age, lifetime binge drinking, tobacco use, and having an anxiety diagnosis increased the risk of lifetime substance use. Due to the high degree of cannabis use in the sample, a sensitivity analysis was performed that excluded cannabis from the illegal drug assessment. For every increase in ACE exposure there was a corresponding increase in use of illegal drugs (1 ACE aOR: 1.1; 95% CI: 0.7-1.6; 2 ACEs aOR: 2.6; 95% CI: 1.0-2.5; 3 ACEs aOR:2.8; 95% CI: 1.7-4.5).

There were no significant interactions for ACE exposure and anxiety diagnosis, depression diagnosis, sex, or SES during adolescence. We ran additional models to assess the relationship between ACEs and tobacco and binge drinking, as tobacco and alcohol are commonly available substances. There was no relationship found for 3+ACE exposure and risk of lifetime binge drinking (aOR: 0.4; 95% CI: 0.2-0.7) or last month binge drinking (aOR: 0.9; 95% CI: 0.6-1.4). Individuals with 3+ACEs were more likely to use tobacco daily (aOR: 1.6; 95% CI: 0.9-3.0) compared to lifetime use (aOR: 1.0; 95% CI: 0.6-1.6).

Risky Substance Use.

A dose-response relationship was found between ACEs and participants classified as risky substance users (e.g., used stimulants or hallucinogens more than six times during life or monthly cannabis use). Individuals with 3+ACEs had the greatest likelihood of risky stimulant use (aOR: 6.7; 95% CI: 1.4-16.1), hallucinogen use (aOR: 3.0; 95% CI: 0.9-10.2), cannabis use (aOR: 7.3; 95% CI : 2.5-11.2), and illegal drug use (aOR: 2.9; 95% CI: 1.5-5.8).

Associations between ACE types and lifetime illegal substance use.

In adjusted analyses, all ACE types but physical neglect demonstrated a consistent pattern of higher likelihood of lifetime illegal substance use. When analyzing the relation between ACE type and substance use, the estimates were highest for parental substance use (aOR: 2.6; 95% CI; 1.5-4.4), followed by sexual abuse (aOR: 2.3; 95% CI; 1.4-3.8), divorce (aOR: 1.9; 95% CI: 1.3-2.7), emotional neglect (aOR: 1.7; 95% CI: 1.1-2.8), physical abuse (aOR: 1.7; 95% CI: 1.0-3.0), parental mental health (aOR:1.5; 95% CI: 1.0-2.1), bullying (aOR: 1.5; 95% CI: 1.0-2.3), emotional abuse (aOR: 1.3; 95% CI: 0.8-2.3), and physical neglect (aOR: 0.8; 95% CI: 0.4-1.8) (see Figure 5).

Discussion

This study investigated the association of cumulative ACEs and ACE type with illegal drug use among French college students. Our study found that ACEs heighten the risk of illegal drug use among college students. A dose response relationship was found between ACE exposure and all types of illegal drug use, whereby higher ACE scores increased the risk of hallucinogen, stimulant, cannabis, polydrug use, illegal drug use,

and multiple illegal drug use. Compared to persons without ACE exposure, persons with 3+ACEs were anywhere from twice as likely to ten times as likely to use one of the categories of illegal drugs, highlighting the risk of clustered trauma. The same patterns were found with riskier substance use, whereby, individuals with 3+ACEs were more likely to use illegal drugs at a higher frequency during their lifetime.

Our analysis is one of the first to examine the risk of ACEs exposure on specific types of illegal drug use among college students. We demonstrated that individuals with 3+ACEs compared to none are 2.0, 3.6, and 4.7 times as likely to have used hallucinogens, stimulants, and cannabis, during their lifetime, respectively. While previous studies have found that ACEs increase the risk of illegal drug use among college students, no identified studies examined the the risk of stimulant or hallucinogen use (M. Forster, C. J. Rogers, et al., 2019; Hughes et al., 2019; Kameg et al., 2020; Ramakrishnan et al., 2019; Wiehn et al., 2018; Windle, Haardorfer, et al., 2018; Zhang et al., 2020) and very few investigated cannabis use (M. Forster, C. J. Rogers, et al., 2019; Windle, Haardorfer, et al., 2018). Consistent with our findings, higher ACE scores have been associated with cannabis use among college students, although these results have been in American samples (M. Forster, C. J. Rogers, et al., 2019; Windle, Haardorfer, et al., 2018). Understanding the drug-specific associations with ACE exposure is an essential step as prevention approaches for each illegal substance differs.

ACE exposure was found to be associated with much higher likelihoods of risky substance use, whereby, persons with 3+ACEs were 3, 6, and 7 times more likely to use hallucinogens, stimulants, cannabis at a higher lifetime frequency, respectively. Increased

frequency of illegal drug use is associated with heightened health risks, including risk of disease, substance use disorders, risky sexual behaviors, legal complications, and death (European Monitoring Centre for Drugs, 2018). This is especially relevant as research has indicated that ACEs are associated with a higher frequency of substance use disorders in adulthood (Leza et al., 2021). Thus, identifying risky substance use at an earlier developmental stage may reduce risk of future substance use disorders.

We found that ACEs are common, as over two-thirds of the sample has experienced an ACE and that this exposure is associated with illegal drug use. While removing all ACEs exposure may be unrealistic, these findings emphasize the importance of prevention of ACE exposure, utility of promoting parenting skills and healthy coping behaviors with persons at risk due to ACEs and allow us to grasp the impact of ACEs on emerging adult illegal drug use. As the brain is critically developing from continued prefrontal cortex maturation during emerging adulthood, the severity of consequences related to substance use increases (Arnett, 2005; Arnett, Žukauskienė, & Sugimura, 2014), highlighting the value of identification and screening efforts for ACEs.

We found that certain types of ACEs were associated with a higher risk of illegal drug use. Students who had experienced parental substance use, sexual abuse, and parental divorce had 2.6, 2.3, and 1.9 times the increased risk of illegal drug use, respectively. These results are consistent with the literature indicating parental substance (Wiehn et al., 2018; Zhang et al., 2020) and sexual abuse (El Mhamdi et al., 2017; Wiehn et al., 2018; Zhang et al., 2020) are associated with illegal drug use, although these were performed on smaller samples. We additionally found that childhood divorce heightened

the risk of college student illegal drug use. Thus, divorce may be an important risk factor for college student illegal drug use to consider in future research.

Several strengths of this study include adjustment on a wide variety of potential confounding factors, large sample size, and analyzing the relationship between ACEs exposure and illegal drug categories, frequency, and by ACE type. Regardless, some limitations should be considered. Firstly, the generalizability of our findings is somewhat limited as the i-Share cohort is not representative of the French student population. Further, although controlled for, there were a high proportion of females, which is expected as an overrepresentation of women in population studies based on voluntary participation is typical (Glass et al., 2015). Nevertheless, as only two European studies have been conducted on this topic, understanding how ACE exposure differs and impacts health in various countries and continents is important in our global understanding of ACEs and life course development. Secondly, illegal drug use was a lifetime drug use variable, impacting the ability to determine temporality in our data. However, this approach is used in the literature and has shown to be robust (Hughes et al., 2019; Zhang et al., 2020). Lastly, although we used ACEs commonly assessed in the literature, other stressful childhood experiences exist that were not included in our ACE assessment (e.g., parental intimate partner violence, parental incarceration, exposure to war, etc.) that should be considered as possible ACEs in future research (Ellis, MacDonald, Lincoln, & Cabral, 2008; Evans & Kim, 2007).

Consistently our results describe the significance of childhood trauma and stress on lifespan development. ACEs are a form of toxic stress that can change neurobiological

development (Bucci, Marques, Oh, & Harris, 2016; Nelson III & Gabard-Durnam, 2020; Robin Ortiz, Gilgoff, & Harris, 2022) and heighten vulnerability to substance use. While the pathways from ACEs exposure to illegal substance use are unclear, there is an urgent need to identify and screen for ACEs and childhood trauma among the pediatric and college population. Among pediatric populations, primary care settings offer an ideal avenue for ACE screening due to the regular contact with children and families (Barnes et al., 2020; Marie-Mitchell et al., 2019) and may afford opportunities for early identification and intervention. Among college populations, our findings suggest that university students with higher levels of childhood adversity may require additional support and services from clinical practitioners and university administrators. Adding screening of ACEs during university entrance and within university psychiatric services would enhance prevention, management, and treatment of illegal substance use. Due to the complexity and sensitivity of substance use and childhood trauma, providers should consider the impact of ACEs in relation to treatment, including trauma-based approaches (Booyesen & Kagee, 2020; Goddard, 2021; Mannarino, Cohen, & Deblinger, 2014; Oral et al., 2016; Wilson et al., 2018).

Conclusion

ACEs increase the risk for lifetime illegal drug use and risky drug use in a dose-responder fashion. These findings suggest that university students with higher levels of ACEs may benefit from additional support and services from clinical practitioners and university administrators.

CHAPTER FOUR: BEATING TRAUMA: PHYSICAL ACTIVITY TO PROMOTE RESILIENCE AGAINST SUBSTANCE USE

Ashlyn Schwartz was involved in conceptualization, data analysis, writing, and editing of article. All authors contributed to the article which is currently under review for publication.

Introduction

Substance use (SU) peaks during emerging adulthood (18-25 years) and has vast implications on lifelong health and opportunities for individuals, communities, and society (O'Connor et al., 2018; Wisk & Weitzman, 2016). Tobacco, alcohol, and cannabis are the most commonly used substances as they have the greatest perceived availability and the lowest perceived risk (SAMSHA, 2020). While perceived risk is low, tobacco is the top preventable cause of death worldwide (Samet, 2013), excessive alcohol consumption is a leading cause of premature mortality in the United States (O'Connor et al., 2018), and cannabis is linked with work challenges, poor school achievement, financial difficulties, and increased risk of psychiatric disorders (Brook et al., 2016). The high prevalence of SU among young adults (Baumer, Dennis, & Estrada, 2018) makes it imperative to better understand risk factors in emerging adulthood.

Some early life experiences can elevate risk of SU and misuse. Potentially traumatic or stressful events that occur before age 18 or adverse childhood experiences (ACEs) are one such risk factor (CDC, 2019). Nearly two-thirds of adults have one or more ACE (CDC, 2019). Findings from systematic reviews demonstrate that the number of ACEs has a moderate to strong association with SU in emerging adulthood (Park et al.,

2021) and as ACEs exposure increases so does the likelihood of SU (Rogers et al., 2022). Further studies indicate that ACEs may exert differing risks by specific substance types (Forster et al., 2019), as every additional ACE was associated with a corresponding 1.13, 1.38, and 1.28 increase for binge drinking, marijuana use, and smoking, respectively.

There remain several gaps in what is known about ACEs and SU. The majority of studies have utilized cross-sectional study design amongst university student populations, hindering understanding of how ACEs impact SU patterns after emerging adulthood and amongst persons with different educational backgrounds (T. J. Grigsby et al., 2020; Kim, 2017; Wiehn et al., 2018; Windle, Haardörfer, et al., 2018). Epidemiological studies have often utilized general classifications of substance use including lifetime use or within the last year, months, or weeks which may capture experimental or occasional substance users instead of frequent SU (Schwartz et al., 2022). As regular SU increases risk of developing substance use disorders (Moss, Chen, & Yi, 2012), it is imperative to investigate the association between ACEs and frequent SU.

Understanding protective factors on the pathway between ACEs and SU is critical as the impact of early life traumas may be buffered by protective factors, including physical activity (PA). PA has demonstrated a dose-response relationship with primary and secondary prevention of 25 chronic medical conditions (Warburton & Bredin, 2017) and is inversely associated with SU (Linke & Ussher, 2015). PA may act as a replacement for substance use as it increases neurotransmitters (e.g., epinephrine, serotonin, beta-endorphins, norepinephrine, and dopamine), which contributes to a reward circuitry similar to that of substance use (Boecker et al., 2008; Greenwood &

Fleshner, 2011; Linke & Ussher, 2015)). In addition, PA is associated with self-efficacy, positive mood, less mental health problems, and other positive health behaviors, including a healthy diet and good sleep, all of which are typically negatively associated with SU (Berrigan et al., 2003; Daley, 2008; Lavie et al., 2011; Terry-McElrath & O'Malley, 2011).

PA is also associated with enhanced resilience to stress and decreased SU across both human and animal species (Brellenthin & Lee, 2018; Perez et al., 2019; Sanchez et al., 2015). Resilience aims to understand healthy development of individuals regardless of risk exposure and can be nurtured through promotive factors (e.g., assets or resources) (Fergus & Zimmerman, 2005). PA could represent both an asset (e.g., increase self-efficacy) or a resource (e.g., social support from coaches, teammates), thus would contribute to a protective resilience model as a promotive factor, mitigating current or future SU in the presence of ACEs. The impact of PA on SU has differed by substance type and physical activity modality, highlighting the importance to analyze PA modality and SU separately (Brellenthin & Lee, 2018; Lynch et al., 2017). What is not known, however, is if PA has a protective effect in the presence of ACEs.

Using the National Longitudinal Study of Adolescent to Adult Health (Add Health) (<http://www.cpc.unc.edu/projects/addhealth>), we hypothesized that a higher number of ACEs would be associated with greater odds of frequent SU in emerging and early adulthood and that PA during emerging adulthood will lower current and prospective frequent SU. Guided by the protective resilience model, this study analyzed the potential moderating role of PA modalities on the association of ACEs with daily

cannabis and cigarette use and frequent weekly binge drinking. We progress the understanding of ACEs by utilizing a large, nationally representative sample to inform the impact on nine cumulative potentially traumatic events on frequent SU patterns in emerging and early adulthood and investigate the protective capacity of PA on current and prospective SU by analyzing several PA modalities (walking, strength training, team sports, and individual sports). Our study builds upon the existing literature by investigating several types of SU, having a longitudinal study design, examining frequent SU, and investigating the potential of PA to buffer the impact of ACEs on SU.

Methods

Study Population and Design.

The Institutional Review Board at The University of Tennessee-Knoxville and administrative process with the National Longitudinal Study of Adolescent to Adult Health data set (Add Health)(Bethell, Simpson, & Solloway, 2017) approved this study. Add Health is a nationally representative sample of adolescents in the United States who were 11-21 years in 1994-1995 (7-12th grade) and have been followed into adulthood (33-43 years) through five waves of data collection. Approximately 80% of participants were retained across the waves of data collection and when appropriate sample weights are utilized, the magnitude of bias due to attrition is small (Harris, 2013).

The analytical sample included participants (n=9,451) from the restricted-use dataset who had sample weights at each wave included in analysis: I (adolescence, 11-20 years), III (emerging adulthood, 18-27 years), and IV (early adulthood, 24-33 years). We characterized the relationships between the number of ACEs (Waves I, III, IV) and

frequent cannabis use, binge drinking, and cigarette smoking (Waves III, IV), by first adjusting for sociodemographic covariates (Waves III, IV) and then adjusting for protective factors in emerging adulthood (Waves III).

Analytic Strategy.

Survey procedures in SAS Enterprise Guide version 8.3 (SAS Institute Inc., Cary, North Carolina, USA) were utilized to account for the complex survey design. To describe the analytical sample, univariate, and bivariate analyses were conducted to estimate weighted prevalence of individual and cumulative ACEs (0, 1, 2, or 3+), sociodemographic characteristics, and SU in the sample and by sex. After meeting assumptions for statistical modeling, logistic regression models were run to estimate adjusted (aOR) odds ratios and 95% confidence intervals (CIs) for associations of ACEs and frequent cannabis use, binge drinking, and cigarette smoking at waves III and IV. Physical activity interactions with ACEs (walking*ACEs, strength training*ACEs, team sports*ACEs, and individual sports*ACEs) were added separately to the cannabis use, binge drinking, and cigarette smoking models in Wave III and IV. Next, the association between PA and frequent SU amongst ACEs exposure was assessed by adding PA variables to the adjusted regression models. Confirmation of the best model fit between multivariate models were executed by having the larger area under the curve and a Hosmer and Lemeshow Test $\geq .05$.

ACEs.

ACEs exposure was measured during Waves I, III, and IV through self-reported potentially traumatic experiences that occurred before 18 years of age (with exception to

parental binge drinking, which parents reported during Wave I). We created 9 dichotomous measures that have been previously used in Add Health research studies (Quinn et al., 2019; Scheidell et al., 2018): (1) *emotional abuse* (caregiver said things that really hurt one's feelings or made them feel not wanted or loved, ≥ 6 times); (2) *physical abuse* (caregiver hit one with a fist, kick one, or thrown one, ≥ 6 times); (3) *sexual abuse* (caregiver touch one in a sexual way, force one to touch him/her in a sexual way, or force one to have sexual relations, ≥ 1 time); (4) *neglect* (caregiver left one at home alone when an adult should have been with one, ≥ 6 times); (5) *witnessed violence* (see someone shoot or stab another person, ≥ 1 time); (6) *experience violence* (been shot or cut/stabbed, ≥ 1 time); (7) *parental binge drinking* ($\geq$ five drinks on one occasion in the past month), (8) *parental incarceration* (caregiver ever spent time in prison/jail), and; 9) *parental death* (death of biological mother or father).

Due to distributions in the data, we summarized the 9 dichotomous ACEs from Waves I, III, and IV to create an ordinal ACE score with a range of 0-3+ ACEs. Analyses included only cases with no missing data for all nine ACEs ($n=9,451$) with sample weights at each wave of analysis. We conducted two sensitivity analyses: 1) compare the associations of ACEs and SU in this subsample to the full sample and 2) compare the associations of ACEs and SU to those with a different ACEs classification, whereby the thresholds for emotional abuse, physical abuse, and neglect were 3 or more times instead of 6 or more times. Results followed the same patterns with no large differences that would change interpretation, thus, we present estimates for only the sample with

complete ACE data with the prior ACEs threshold values established by other researchers.

Frequent drug use outcomes.

During Waves III and IV, participants responded to various self-report questions regarding their SU; these questions were identical across waves. We used these questions to create dichotomous outcomes reflecting frequent SU in Waves III and IV. Outcomes were defined as follows with referent categories as no use: 1) daily cannabis use; during the past 30 days, on how many days did you use marijuana (persons who reported ≥ 1 per day were classified as daily cannabis use; 2) frequent weekly binge drinking: over the past 12 months, on how many days did you drink 5 or more drinks in a row; (persons who responded 3 days a week or higher were classified as frequent weekly binge drinkers); and 3) daily cigarette smoking: have you ever smoked cigarettes regularly, that is, at least 1 cigarette every day for 30 days.

Socio-demographics.

Adjusted models controlled for age from Wave III (18-20 years, 21-23 years, and 24-27 years) and several measures from Wave IV: sex (male, female), race/ethnicity (white, black, Hispanic, or other), adulthood educational attainment ($\leq$ high school education, some college or college degree, graduate education), and poverty (not having enough money to pay utility/housing bills).

Physical activity variables.

During Wave III participants were asked in the past seven days, how many times did they 1) walk for exercise, 2) participate in gymnastics, weightlifting, or strength

training, 3) participate in strenuous team sports such as football, soccer, basketball, lacrosse, rugby, field hockey, or ice hockey, and 4) participate in individual sports such as running, wrestling, swimming, cross-country skiing, cycle racing, or martial arts. For all categories (walking, strength training, team sports, and individual sports) the referent group was 0 times compared to any level of PA.

Results

Participant Characteristics.

The analytic sample had equal representation by sex (51.8% females), with a majority being white (69.4%), 14.7% living in poverty, a mean age of 22.0 years at Wave III and 27.8 years at Wave IV, and 63.4% having more than a high school education.

About half of the sample experienced no ACEs (50.4%) with 29.3% experiencing 1 ACE, 12.5% experiencing 2 ACEs, and 7.9% experiencing 3+ACEs (Table 6).

Cumulative ACE scores were similar across sex with no significant differences ($p=0.0763$). Individual ACE prevalence ranged from 1.1% (experienced violence) to 15.8% (emotional abuse). Females had increased exposure to emotional, sexual, and physical abuse than males, whereas males had increased exposure to witnessing and experiencing violence than females (Table 6).

In Wave III 12.4% of the sample used cannabis daily, 15.1% were frequent weekly binge drinkers, and 43.4% smoked cigarettes daily. Between Waves III and IV the percent of the sample that used substances dropped (cannabis, 11.7%; binge drinking, 3.9%) with exception to daily cigarette smoking which increased (46.8%). The majority of the sample had the same patterns of use over time, with, 15.9%, 13.4%, and 11.7%

either reducing or initiating cannabis use, binge drinking, or cigarette smoking, respectively between Waves III and IV. Chi-squared tests revealed that persons with any level of ACEs was more likely to report daily cannabis use and daily cigarette use at Waves III and IV ($p < .0001$) and there were no significant differences in frequent weekly binge drinking by ACEs exposure in Wave III ($p = 0.8416$) or Wave IV ($p = 0.0590$). Males were more likely to report frequent substance use (cannabis, cigarette smoking, and binge drinking) than females at all Waves (Table 6).

In Wave III, about half of the sample reported walking for exercise (47.1%), nearly a third participated in strength training activities (29.7%), a quarter participated in individual sports (25.1%), and a fifth participated in team sports (19.6%). Persons with ACEs exposure were less likely to engage in strength training (14.0% vs 15.7%; $p = 0.04$) and individual sports (11.1% vs 14.0%; $p < .0001$) than persons without ACEs. Females were more likely than males to walk for exercise, whereas males were more likely to strength train, engage in team sports, and participate in individual sports than females (Table 6).

ACEs and Substance Use.

At Wave III cumulative ACEs was strongly associated with daily cannabis use and daily cigarette use in a dose-responder fashion. Adjusted models demonstrated that for one, two, and three or more ACEs, respectively, the increase in odds of daily cannabis use were 40%, 80%, and 250% and daily cigarette smoking were 20%, 50%, and 214% (Figure 6). No level of ACEs was associated with frequent weekly binge drinking at Wave III.

In Wave IV, compared to persons with no ACEs, having two or three or more ACEs was associated with 2.0 and 2.1 times increase of daily cannabis use. As ACEs exposure increased, so did the risk of using cigarettes daily in early adulthood. Persons with one, two, or three or more ACEs had a 1.4, 1.6, and 2.3 times higher odds of reporting daily cigarette use compared to persons with no ACEs, respectively. Again, no significant association of cumulative ACEs with frequent weekly binge drinking was demonstrated (Figure 6).

Protective Factors.

In most models, education was a strong predictor of SU; individuals with a high school degree or less had increased odds of reporting frequent SU (Table 7). Relative to the non-Hispanic white group, in nearly all models, identifying as Hispanic, black, or other race was associated with lower odds of all SU outcomes. Males had increased risk for SU compared to females in most models. Persons in emerging adulthood with a higher economic status had consistently lower odds of frequent SU in Waves III and IV. Finally, older age was associated with decreased cannabis use and binge drinking.

The interaction terms between PA (walking, strength training, team sports, and individual sports) and ACEs were not statistically significant for current or prospective SU, indicating PA does not moderate the association of ACEs with SU. Although PA is not an effect modifier on the relation between ACEs and SU, certain PA modalities assert a significant protective effect on current and prospective SU (Table 8).

Walking for exercise was protective of current and prospective daily cannabis use. After adding walking to the logistic models with all adjustments, persons who walked for

exercise at Wave III had 40% lower odds of current daily cannabis use and 30% lower odds of prospective daily cannabis use. No other modalities of exercise were protective on current or prospective daily cannabis use (Table 8).

In adjusted models, team sport, individual sports, and walking were all protective against daily cigarette use in emerging adulthood, contributing to a 30%, 20%, and 20% lower odds of daily cigarette use, respectively. All PA modalities in Wave III were protective against prospective daily cigarette use in Wave IV (20-30% reduced odds) (Table 8).

Team sport and individual sport participation were significantly associated with increased odds of frequent weekly binge drinking at Wave III, but no significance emerged at Wave IV (Table 8).

Discussion

ACEs have been associated with adult SU, but little is known about the association with frequent SU among emerging and early adults and factors that may buffer this relation. We attempted to address this gap by assessing the relationship between ACEs and frequent cannabis use, cigarette smoking, and binge drinking among emerging and early adulthood and identifying protective factors on this pathway.

Cumulative ACEs was strongly associated with daily cannabis and cigarette use in a dose-respondent fashion in emerging and early adulthood. Having just two ACEs strongly predicated increased odds of daily cannabis or cigarette use in emerging and early adulthood. Our findings align with several studies and systematic reviews demonstrating that ACEs are associated with increased SU risk in emerging or early

adulthood (Ford et al., 2011; Forster et al., 2019; Scheidell et al., 2018; Schwartz et al., 2022). However, these previous studies typically classified SU as lifetime or any current SU, which may capture experimental SU. Therefore, our unique findings are one of the first to look at the risk of cumulative ACEs on frequent SU.

The Add Health dataset allows comparing the odds of frequent SU across emerging and early adulthood and extend the literature by describing the relationship between ACEs and the most commonly used substances over time. Our results demonstrate that experiencing ACEs has continuous impacts across emerging and early adulthood with a persistent dose-response relationship between ACEs and SU. Having three or more ACEs was associated with at least a two times higher risk of daily cannabis and cigarette use, highlighting the duration of the consequences of ACEs. As emerging adulthood is the developmental period with highest SU (Wisk & Weitzman, 2016), these results underscore the combined risk for emerging adults and the increased risk for early adults, who typically have decreasing SU frequency.

The literature has shown conflicting relationships between ACEs exposure and binge drinking among emerging and early adulthood. Some studies have showed moderate risk of binge drinking (Campbell, Walker, & Egede, 2016; M. Forster, Vetrone, Grigsby, Rogers, & Unger, 2019; T. J. Grigsby et al., 2020; Jung et al., 2020), whereas other studies have shown no association (Laurinaitytė, Assini-Meytin, & Čunichina, 2022) or only found associations by certain ACEs types (Fang & McNeil, 2017; Zhang et al., 2020). In this study, no level of ACEs was associated with frequent weekly binge drinking at either time point. Results from our study suggest that the effect of cumulative

ACEs may not be as profound as that for other SU and may be explained by other contextual factors. One out of three college students report recent binge drinking, indicating individual factors such as college attendance may explain this finding (Jang et al., 2019; Krieger et al., 2018) and the lack of association could indicate normative behavior for this age group.

This study identified protective factors that reduce the impact of ACEs on current and prospective frequent SU. While PA did not moderate the association with ACEs and SU, PA was identified as a protective factor that may promote resilience against current and prospective daily cannabis and cigarette use. These results align and build upon the work of two relevant longitudinal analyses who identified that PA is associated with lower SU and the protection of prospective SU (cigarette smoking, marijuana use, illegal drug use), with exception to alcohol (Henchoz et al., 2014; Terry-McElrath & O'Malley, 2011). A systematic review examining the relationship between sport participation and SU indicated that sport participation was associated with reduced illicit drug use 80% of the time, reduced cannabis use half of the time, and was never protective against alcohol consumption (Kwan et al., 2014). The same positive association between sports participation and alcohol use was found in another systematic review (Sønderlund et al., 2014). Thus, in line with the literature, our results demonstrated that no PA modality was protective against current or prospective binge drinking and in fact individual and team sports participation were both associated with increased risk of frequent weekly binge drinking in Wave III. These findings demonstrate that binge drinking amongst emerging and early adults may be more related to social or cultural factors than ACEs (Lynch et al.,

2017). Our study extends previous work by testing if the association between PA and SU remains significant for persons with ACEs exposure. Further, previous studies utilized generalized terminology, such as sport and exercise, instead of analyzing by specific types of PA. Our approach found PA's protective capacity to SU varied by PA type and should be explored by researchers to better understand which PA circumstances are necessary to have beneficial outcomes for SU.

Walking is the most accessible form of aerobic activity in the United States and has established health benefits ("Centers for Disease Control and Prevention. More People Walk to Better Health," 2012). Walking was associated with reduced risk of current and future daily cannabis and cigarette use. According to persons with substance use disorders, walking is one of the most preferred exercise activities (Abrantes et al., 2011; Linke et al., 2015; Neale, Nettleton, & Pickering, 2012; Stoutenberg, Warne, Vidot, Jimenez, & Read, 2015), indicating this PA type may have promise to inform prevention and treatment of SU. PA guidelines recommend 3-5 days of aerobic activity for best health outcomes (*Physical Activity Guidelines for Americans, 2nd edition*, 2018), thus, the threshold of walking needed to see protective effects among persons with ACEs should be investigated by future researchers. The promise of PA to protect against current and prospective SU appears to differ by PA type.

Muscle strengthening, walking, team sports, and individual sports were protective against future daily cigarette use, indicating PA may be most efficacious for tobacco smoking prevention. Indeed, physical inactivity is a leading risk factor for tobacco use (Kramer, 2020). PA has an association with the primary and secondary prevention of

many chronic medical conditions; including decreased depressive episodes (Hamer, Stamatakis, & Steptoe, 2009; Warburton & Bredin, 2017), which are commonly found among persons with ACEs (De Venter, Demyttenaere, & Bruffaerts, 2013). PA may moderate the association between ACEs and depression, as a review found associations between ACEs and poor mental health outcomes among persons with less frequent PA activity (Hadwen, Pila, & Thornton, 2022). Regular physical activity has been demonstrated as an effective way to improve mental health and has little costs while supporting several health outcomes at once (Kramer, 2020). Considering the multifaceted consequences ACEs present across the lifespan (V. J. Felitti et al., 2019), walking for prevention of current and future SU among emerging adults ACEs is a cost-effective, accessible, intervention that may support not only SU prevention but enhanced mental health amongst young adults.

Our study clarifies the relationship between ACEs and frequent cigarette smoking, marijuana use, and binge drinking in emerging and early adulthood and suggests that walking for exercise amongst persons with ACEs may promote the effectiveness of SU prevention strategies. Expanding our current understanding, this analysis has several strengths including utilization of a large nationally representative sample, investigating the impact of ACEs on the most commonly used substances, adjustment on a wide variety of potential confounding factors and biological variables, comprehensive utilization of 9 ACEs , analyzing the protective capacity of four modalities of PA on current and prospective SU, and conducting several sensitivity analyses.

Despite the strengths of this study, certain limitations should be considered when interpreting results. First, given ACEs and SU are both linked with dropping out of school, the sample may be limited to selection bias and attrition. While these limitations exist, they are inherent to the study design. Second, data on sensitive topics may be influenced by social desirability and recall bias. To account for this, Add Health utilized a suitable and robust computerized survey tool that is more reliable and valid for collecting information on sensitive topics compared to other methodologies (Cooley, Miller, Gribble, & Turner, 2000). Third, the PA variables asked about PA during the last week which may not be representative of PA levels over time and the questionnaire didn't assess duration of activity. The sample was asked if they were generally more or less active in the last week and less than 5% of the sample was less active, thus the level of self-reported PA is unlikely to impact results. To understand the dose of PA needed for prevention efforts, researchers should include assessments of frequency, intensity, time and type of PA (Ainsworth et al., 2012). Fourth, parental binge drinking was assessed by one parent and may not be indicative of cumulative exposure to binge drinking. Lastly, the measurement of daily cigarette smoking asks about lifetime cigarette consumption, thus we cannot ascertain the exact timing of ACEs and daily cigarette smoking. However, the mean age of regular cigarette smoking was 18 years of age within the analytical sample, thus most SU likely occurred after ACEs exposure.

ACEs may represent a form of chronic stress that contributes to disproportionate allostatic load and disrupted neurodevelopment which can consequently impact healthy coping strategies and lead to SU (McEwen, 2016). Early adoption of SU can negatively

impact long-term health trajectories and has significant implications during emerging adulthood as brain development is continuing (Arnett, 2005). These colliding risks make it imperative to understand factors that may promote resilience and reduce the intensity of the relation between ACEs and SU in emerging and early adulthood. Our results indicate ACEs exposure is common in a nationally representative sample of Americans and cumulative ACEs are associated with increased risk of daily cigarette and cannabis consumption. Our analyses support the inclusion of walking as a protective factor that may promote resilience amongst persons with ACEs to lower risk of current and future substance use. These findings should be investigated further to understand if walking for exercise can promote SU prevention strategies for persons with ACEs.

CHAPTER FIVE: CONCLUSIONS AND RECOMMENDATIONS

This chapter will conclude the dissertation by summarizing the key research findings in relation to the research aims and discussing the value and contribution thereof. It will also propose opportunities for future research.

Overview of Importance

Adverse childhood experiences (ACEs), traumatic or stressful events that occur in the first 18 years of life, have been linked to various negative health outcomes, including many of the leading causes of death for adults (V. J. Felitti et al., 2019; Hughes et al., 2017). Persons with ACE traumas have an increased likelihood of substance use (SU) and substance use disorders (Leza et al., 2021). SU peaks in emerging adulthood and is associated with health consequences, challenged relationships, and academic consequences (Skidmore et al., 2016; Stone et al., 2012). As this is a period of continued neurodevelopment and developmental transitions, having exposure to ACEs compounds existing risks (Arnett, 2005). While both ACEs and SU represents public health concerns, limited research on this topic has been conducted among the emerging adult population with several gaps in the literature. This dissertation investigated these limitations by using diverse approaches and samples to contribute to an informed framework to improve SU screening and prevention strategies.

Novel Findings and Innovative Approaches

Approach I.

The objective of Chapter II was to critically review studies that examined the relation between ACEs and SU among university students. Systematic reviews are

considered to provide one of the highest levels of evidence for research questions, as they are based on the findings of a group of studies and are conducted in an a-priori, comprehensive, and systematic manner. Of 450 articles screened, 16 met inclusion criteria, including 53,433 university students with and without ACEs exposure from 17 countries. While other reviews had been conducted on similar topics, no review had focused on university students with ACEs exposure or specified outcomes by substance type. Results demonstrated that university students reporting ACEs had an increased risk of alcohol, tobacco, marijuana, prescription-medication, and illicit drug consumption compared to students not reporting ACEs and that this relationship varied by substance type, with ACEs having the greatest association with illicit drug use and tobacco. Thus, the review demonstrated the importance of analyzing the relationship between ACEs and SU by substance type, especially as all substances present with differing risk and protective factors and require unique social-ecological approaches for prevention (SAMSHA, 2018). Emerging adults with ACEs exposure had the highest risk for illegal drug and tobacco use, thus Chapters III and IV focused on these outcomes, respectively.

Approach II.

Building upon Chapter II, Chapter III examined data from a French sample of college students to investigate the consequences of ACEs on illegal drug use. Collaborating with the University of Bordeaux, I examined how ACEs are associated with specific illegal drug types (hallucinogens, stimulants, marijuana). The analytic sample was part of the Internet-based Students Health Research Enterprise [i-Share] cohort project (<https://www.i-share.fr/>). I-Share uses surveys to evaluate the health of

thousands of college students over ten years and, as such, it is the largest and most comprehensive dataset of its kind in France. Similar to the systematic review findings, ACEs exposure was common in France with 70% of the analytical sample reporting one or more ACEs. Students with three or more ACEs had a higher likelihood of using illegal drugs than persons with no trauma exposure and a dose-response relationship also emerged between ACEs and illegal SU. Unlike other studies in the field that categorized illegal drug use into one category, this analysis described the association between ACEs and several types of illegal drugs. This analysis also described the relationship between nine ACE types and illegal drug use and revealed exposure to parental substance use, sexual abuse, and divorce were associated with the highest risk of illegal SU.

As discussed in Chapter II, most research on ACEs exposure and SU has been conducted in the United States and no French data were available for the systematic review. As France has a different healthcare system, policies, and cultural practices than the United States related to illegal drug use, understanding the impact of ACEs in the French context was an important next step to understanding if the threats of ACEs were similar in other cultural contexts. Our results indicate that the burden of ACEs on illicit substance use are indeed similar between the United States and France. Thus, these findings indicate despite cultural and legal differences, ACEs may represent a form of toxic stress that exert similar risks across various contexts.

Approach III.

The last approach taken to address the dissertation's aim was an analysis of a nationally representative American dataset (National Longitudinal Study of Adolescent to

Adult Health data set (Add Health; <https://addhealth.cpc.unc.edu/>)). The two prior studies focused on risk factors for SU among emerging adults; this study took a turn by using a theoretical model of resilience and examining protective factors of the pathway between ACEs and SU. Understanding both risk and protective factors is vital to enhance prevention efforts.

As the systematic review highlighted a substantial risk between ACEs exposure and tobacco consumption, the last approach focused on understanding the relation between ACEs and commonly used substances in the United States, including tobacco. While other studies had investigated the link between ACEs and commonly used substances (Forster et al., 2019; T. J. Grigsby et al., 2020; Hughes et al., 2019; Windle, Haardörfer, et al., 2018; Zhang et al., 2020), these studies investigated the risk of lifetime use or any quantity of use. Previous approaches may have therefore captured occasional users. To understand ACEs contribution with higher risk substance use, Chapter IV investigated the risk of ACEs on frequent substance use, defined as daily cannabis use, daily cigarette smoking, and weekly binge drinking (≥ 3 times a week). The design of the Add Health study allowed us to compare the odds of frequent SU across emerging and early adulthood and extend the literature by portraying the relationship between ACEs and the most commonly used substances over time. Our results demonstrate the aftermath of trauma has continuous impacts across emerging and early adulthood with a persistent dose-response relationship between ACEs and SU. In analyzing potential protective factors that could reduce the impact of childhood trauma on current and prospective

frequent SU, the results demonstrated that walking in emerging adulthood reduced risk of current and prospective daily cigarette and cannabis use.

Future Directions

Through the dissertation's diverse approaches and analyses, several opportunities for future research have been identified.

Add Health Dataset

ACEs increase SU risk among emerging adults. This is the same time period where mental health challenges emerge and in addition to SU, childhood traumas have been highly associated with anxiety and depression (Thompson, Kingree, & Lamis, 2019). Although ACEs increase risk for both mental health challenges and substance use, the pathway between ACEs and these outcomes is not well understood. Some studies have found that mental health challenges, including depression and anxiety mediate the pathway between ACEs and SU. Existent studies have focused almost exclusively on legal drug use or behavioral addictions (e.g., social media, gambling) (Lim, Cheung, Kho, & Tang, 2020; Quinn et al., 2019; Walsh & Cawthon, 2014), providing the opportunity to test whether such relations hold true for illegal drug use. Longitudinal datasets, such as Add Health, present an occasion to further investigate this pathway with mediation analyses. This approach could yield critical information to inform screening and prevention efforts amongst adolescents and young adults.

In addition, some studies have indicated that physical activity may moderate the association between ACEs and mental health outcomes (Hadwen et al., 2022). Regular physical activity has been shown to be an effective way to enhance mental health

(Kramer, 2020), however, it's unclear if this relation remains amongst persons with ACEs exposure. The ability of physical activity to protect against depression, anxiety, ADHD, or suicidal ideation amongst persons with ACEs could be a next step that would further inform prevention efforts for persons with childhood traumas.

i-Share Dataset

Several studies have documented that childhood trauma is associated with alterations in brain development, typically reduced hippocampus and amygdala volumes (Dannlowski et al., 2012; Herzog & Schmahl, 2018; Oshri et al., 2019). These studies are hampered by small sample sizes (average $n=40$), limited analyses controlling for gender, inclusion of only one type of ACE (physical or sexual abuse) and reflecting populations with psychopathologies. The i-Share dataset also includes a subsample of individuals with MRI data ($n\sim 1,000$). This rich dataset is much larger than earlier studies and more extensive with a comprehensive assessment on 9 ACE types. Thus, this dataset provides an alternate approach to understand which ACE types and how cumulative ACEs contribute to brain structure in emerging adulthood.

On a similar note, studies have reported a relationship between ACEs and decreased gray matter in various brain regions (Gorka, Hanson, Radtke, & Hariri, 2014; Kirsch et al., 2021; Rinne-Albers et al., 2017). Substance use has also been associated with gray matter alterations, usually gray matter loss (Harro, 2015; Weinstein, Livny, & Weizman, 2016). However, the same limitations of small sample sizes exist, thus it is unclear how ACEs exposure is associated with variations in gray matter volume and their links with substance use. Analyzing this question would demonstrate if there were

differences in brain volume by ACEs exposure among young adults and whether these differences relate to substance use. Decreased gray matter, hippocampal, and amygdala volume can inhibit academic performance, social relationships, and healthy development. Thus, this project would provide insight on the brain structure and development of young adults and enhance prevention efforts.

ACEs Measurement

Beyond opportunities for future research, it is important to note some limitations within the conceptualization of ACEs for researchers to consider. Although ACEs are considered one homogenous term, ACEs are in fact diverse and as the list of ACEs continues to expand, researchers should consider if these various early life exposures are indeed similar and comparable. For example, the original ACEs study and scale focused on abuse, neglect, and household dysfunction. In the last decade several new types of ACEs from the child's social environment are being included in studies, including exposure to bullying, war, terrorism, poverty, etc. To compare the impact of ACEs across studies there is a need to standardize ACEs terminology so meta-analyses can be conducted to see more consistent and accurate effects of the same ACEs exposures. Further, within ACEs measurements, scales utilize different thresholds for what consists of an ACE. For example, certain studies say an individual must have experienced abuse more than 6 times whereas other studies say individuals must have experienced this exposure often. Again, standardizing this terminology and classification is urgently needed to increase understanding of ACEs and their impacts.

Informed Framework and Prevention Strategies

From this dissertation, several key factors have been identified on the relation between ACEs and SU that can inform a framework and prevention efforts. First, there is strong evidence that cumulative ACEs (3 or 4 or more ACEs) drastically increase the risk of SU, indicating not only the importance of screening for ACEs exposure but also of identifying individuals with multiple ACEs. Second, ACEs exposure doesn't exert uniform risks across all substances, with the highest risk of illicit drug use and inconsistent associations with binge drinking (Figure 7). Third, not all physical activity modalities are protective against current or future substance use (Figure 8). Caution should be employed when considering exercise prescription in the form of team or individual sport participation until further research is conducted and understood, however, walking for exercise may demonstrate a promise to protect against SU in the presence of ACEs.

Future interventions should investigate the role of walking amongst various levels of ACEs exposure. As SU risk is the largest amongst cumulative ACEs exposure, it is vital to understand if walking exerts similar influences amongst persons with high levels (3+) or low lower levels of ACEs (1-2). Attention to walking prescription (frequency, intensity, and time) should be controlled for to understand how the dose of physical activity may relate to substance use prevention. Heart rate or activity monitors can be utilized to have detailed descriptions of the exercise load. Further attention should be given to individual, relationship, and community-level factors that may explain the protective role of walking, including walking alone versus walking with a friend and the

safety of the community. While there are several neurobiological pathways that may explain walking as a protective factor, it is important to consider relationships and environments drastically influence behavior and may act as protective or risk factors.

Given the relationship between ACEs exposure and SU, enhanced screening efforts for ACEs among college students should be an important consideration at universities. These efforts would enhance evaluation, diagnosis, management, and delivery of care (Brown et al., 2017). Professionals who work with college students with SU or mental health challenges should consider the role of ACEs before developing their treatment plans and be prepared to discuss these sensitive topics using a trauma informed approach (Goddard, 2021; Oral et al., 2016). Exposure to ACEs involves potential exposure to traumatic stress and may result in a complex presentation of posttraumatic stress disorder (PTSD), as well as self-regulatory emotional disturbances and impulsivity (Cloitre et al., 2009), leading to the recognition of a developmental trauma disorder diagnosis or complex PTSD in ICD-11 (Brewin et al., 2017; Van der Kolk & d'Andrea, 2010). Thus, emerging adults with both ACEs exposure and SU may need a different treatment, as a classical treatment of SU alone might not be sufficient to address the effects of trauma and the various manifestations of co-morbid PTSD and SU. In this regard, there is a need to increase access to therapies specifically designed to target underlying trauma, such as trauma-focused cognitive behavioral therapy (Mannarino et al., 2014), eye movement desensitization and reprocessing (Wilson et al., 2018), or prolonged exposure therapy (Booyesen & Kagee, 2020). These same considerations and

approaches should be considered with primary care doctors, incarceration facilities, or substance use clinics treating emerging adults.

Even more importantly, our findings highlight the importance of identifying and screening for ACEs and childhood trauma among the pediatric population as a major public health need with implications for adulthood. Considering risk factors at early stages and screening in pediatric and primary care settings provides an opportunity for early identification, and intervention while preventing the development of SU and complex trauma. Primary care is the best setting for ACEs screening because of the regular intervals of interaction with children and their families (Barnes et al., 2020; Marie-Mitchell et al., 2019). Several questionnaires have been developed in the pediatric setting to screen and assess for ACEs, despite limitations regarding their use and psychometric reliability (McLennan, MacMillan, & Afifi, 2020), which points to the need for further understanding of the nature of ACEs and their impact for a better screening (David Finkelhor, 2018).

Conclusion

The results of the overall dissertation are significant because they strengthen understanding of specific SU after ACEs exposure and highlight the avenues for prevention in primary care settings and amongst emerging adults. The dissertation utilized high levels of evidence including a systematic review and secondary data analysis with nationally representative populations, large sample sizes, and samples from different world regions (France, USA). This multifaceted approach filled gaps in the literature by analyzing the risks of ACEs on a large spectrum of SU types (e.g., alcohol,

tobacco, cannabis, stimulants, and hallucinogens) utilized at different frequencies (e.g., lifetime, year, month, week, and day). In addition, a comprehensive assessment of nine types of ACEs were incorporated in analyses to enhance understanding of long-term consequences of cumulative ACEs and the respective contributions of different ACE types. Beyond demonstrating the relationship between risk factors and SU amongst emerging adults, this dissertation elucidates how protective factors, such as physical activity can promote resilience. Taken together, this dissertation strengthens existing knowledge of the association between ACEs and SU amongst emerging adults and highlights strategies to inform screening and prevention efforts.

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APPENDICES

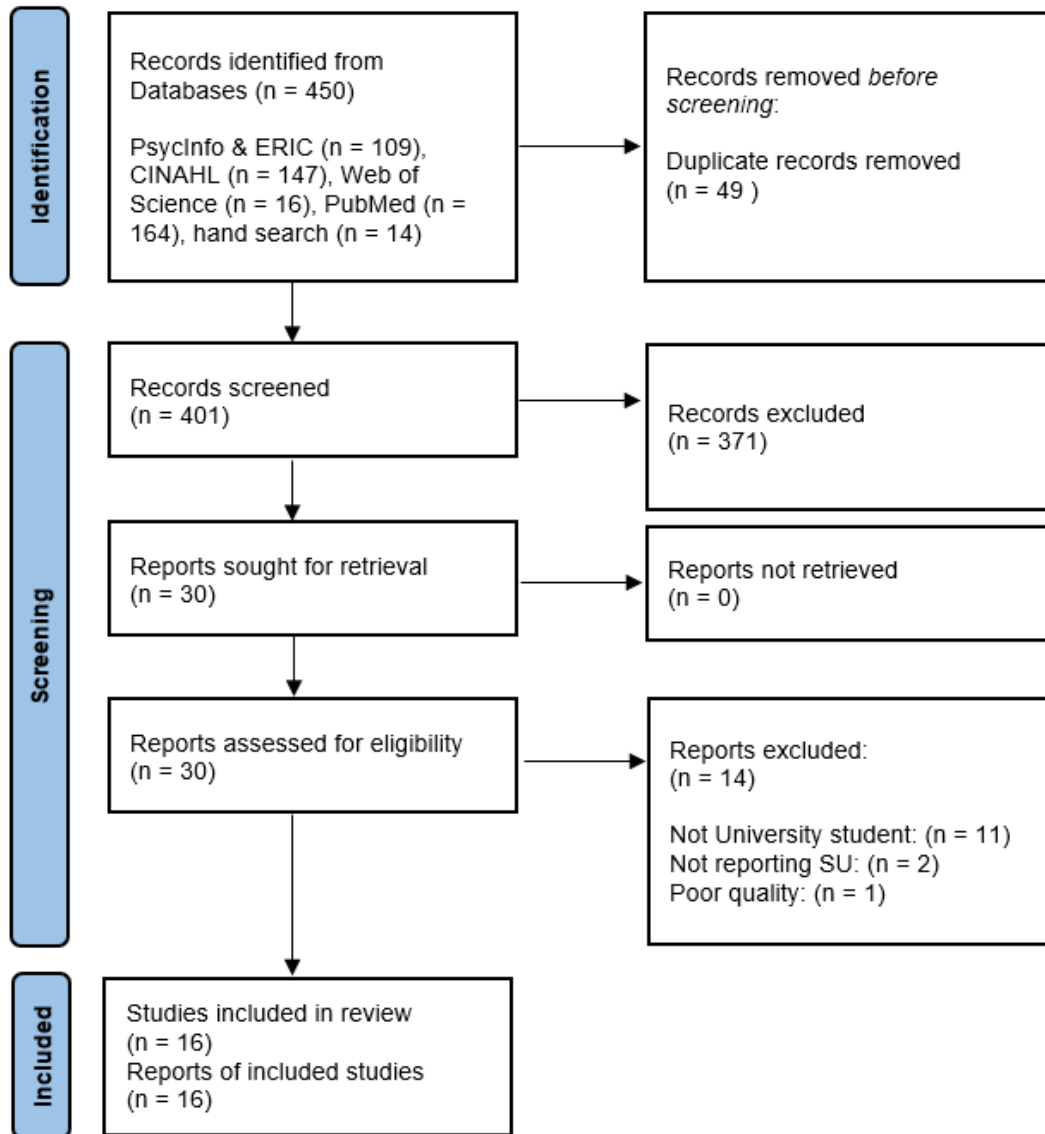


Figure 1. PRISMA Flow Diagram of Literature Search.

Table 1. Descriptive characteristics.

Study and Country	Types ACEs	ACE instrument/ cumulative or individual ACEs	Prevalence (%)		N	Male (%)	Mean Age (SD)	Outcome/ Measure
			1 ACE	4+ ACE				
<i>Brett et al., 2018, USA</i>	EA, PA, SA, EN, VH, SU, MH, IN	ACES-SF/ cumulative	19.2	8.4	385	16.1	20.09 (3.01)	Alcohol consumption and consequences/ Daily Drinking Questionnaire, Brief Young Adult Alcohol Consequences Questionnaire
<i>El Mhamdi et al., 2018, Tunisia</i>	VC, PN, EN, PA, SA, EA, PR, CV	ACE-IQ/ cumulative and individual	76.2	NR	1200	24.5	22.00 (2.1)	Current tobacco smoking/ Fagerstrom Test for Nicotine Dependence
<i>El Mhamdi et al., 2017, Tunisia</i>	VC, PN, EN, PA, SA, EA, PR, CV	ACE-IQ/ cumulative and individual	74.8	9.8	1200	24.5	22.00 (2.1)	SU (tobacco, alcohol, and street drugs)/ Health Appraisal Questionnaire
<i>Forster et al., 2019, USA</i>	SU, EA, PA, VH, SA	Items from org. ACE/ cumulative and individual	45.0	NR	7148	40.0	22.27 (4.06)	Alcohol, marijuana, tobacco, binge drinking, illicit drugs, polysubstance / Survey

Table 1 continued

<i>Study and Country</i>	Types ACEs	ACE instrument/ cumulative or individual ACEs	Prevalence (%)		N	Male (%)	Mean Age (SD)	Outcome/ Measure
			1 ACE	4+A CEs				
<i>Grigsby et al., 2020, USA</i>	EA, PA, SA, VH, IN, SU, MH	Items from org. ACE/ cumulative	51.7	8.62	16370	33.4	21.52 (2.83)	Recent tobacco smoking, binge drinking, and e-cigarette use/ Survey
<i>Hughes et al., 2019, Europe</i>	PA, EA, SA, DIV, VH, MH, SU, IN	Family health questionnaire/ cumulative	46.2	5.6	14661	39.6	18-25	Early alcohol initiation, problematic alcohol use, smoking, drug use/ Survey
<i>Kameg et al., 2020, USA</i>	PA, EA, SA, EN, PN, MH, SU, IN, DIV, VH	Org. ACE/ cumulative	56.2	NR	616	11.2	18-21	Risky alcohol use and risky drug use/ AUDIT-C; DAST-10
<i>Kim, 2017, South Korea</i>	PA, EA, SA, EN, PN, MH, SU, IN, DIV, VC, BU	ACE-IQ/ cumulative and individual	49.9	7.8	939	NR	21.83 (NR)	Alcohol use disorder (problem alcohol use and potential alcohol use disorder)/ AUDIT-K
<i>Krinner et al., 2020, USA</i>	PN, PA, EN, EA, SA, SU, MH, VH	ACE-IQ/ cumulative	NR	NR	568	28.0	21.00 (NR)	Risky alcohol use / Survey

Table 1 Continued

Study and Country	Types ACEs	ACE instrument/ cumulative or individual ACEs	Prevalence (%)		N	Male (%)	Mean Age (SD)	Outcome/ Measure
			1 ACE	4+A CE				
<i>Onu et al., 2021, Nigeria</i>	PA, SA, EA, EN, PN, SU, MH, VH, DIV, IN	Org. ACE / cumulative	NR	NR	301	96.0	22.60 (NR)	Risky tramadol use/ Tramadol Abuse Scale
<i>Pakdaman et al., 2021, USA</i>	SU, MH, PA, EA, HOM, SA	Org. ACE / cumulative	17.5	9.1	3899	29.3	24.55 (7.65)	Risky prescription use (opiates, antidepressants, sedatives, and stimulants)/ Survey
<i>Ramakrishnan et al., 2019, Canada</i>	EA, PA, SA, MH, VH, DIV, IN, SU, EN, PN	Org. ACE/ cumulative	NR	NR	292	21.2	18.85(2.23)	Substance use disorder (excluding alcohol and tobacco)/DAST-10
<i>Schafer, 2021, USA</i>	SA, MH, VH, SU	CPICS/ cumulative and individual	24.0	0.3	795	100	18.56 (0.51)	Risky alcohol use/ Survey
<i>Wiehn et al., 2018, Germany</i>	EA, PA, SA, MH, VH, DIV, IN, SU, EN, PN, FP, CA, BU	ACE-IQ/ cumulative and individual	22.9	24.6	1466	19.3	24.09 (4.49)	Risky alcohol use, tobacco use, illegal drugs/ AUDIT-C; Survey

Table 1 Continued

Study and Country	Types ACEs	ACE instrument/ cumulative or individual ACEs	Prevalence (%)		N	Male (%)	Mean Age (SD)	Outcome/ Measure
			1 ACE	4+A CE				
Windle <i>et al.</i> , 2018, USA	PA, EA, SA, EN, PN, DIV, MH, SU, IN, VH	Org. ACE / cumulative	21.3	12.4	2969	NR	18-25	Alcohol, tobacco, marijuana/ Survey
Zhang <i>et al.</i> , 2020, Zambia	PA, EA, SU, SA, VH	Org. ACE/ individual	27.6	NR	624	48.3	22.90 (2.2)	Tobacco, binge drinking, and illicit drug/ Survey

Abbreviations. EU=European Union; USA=United States of America, PN=physical neglect, EN=emotional neglect, PA=physical abuse, EA=emotional abuse, SA=sexual abuse, SU=household or parental SU, MH=household or parental mental health, IN=incarceration, CV=collective violence; VH=violence household, VC=violence community, DIV=divorce, BU=bullying; HOM=homelessness; FP=financial problems; CA=caregiver absence; PR=parental/caregiver relationship; PS=parental separation/divorce; PD=parental death; NR=not reported; The Adverse Childhood Experiences Questionnaire- Short Form=ACES-SF; Adverse Childhood Experiences-International Questionnaire=ACE-IQ; Children's Perception of Interparental Conflict Scale= CPICS; Original ACE Scale= Org. ACE; Drug Abuse Screening Tool=DAST-10; AUDIT=Alcohol Use Disorder Identification Test Consumption

Table 2. Mediators, Moderators, and SU Outcomes.

<i>Study</i>	Mediators/ Moderators	Covariates in Adjusted Models	Substance Type	Main Findings (related to SU)
<i>Brett et al., 2018</i>	Mindfulness	Sex and age	Alcohol	-Higher ACE score and lower levels of mindfulness predict risky alcohol use. -Mindfulness mediates the relationship between ACEs and problem alcohol use.
<i>El Mhamdi et al., 2018</i>	Gender	Anxiety, depression, and intrafamilial ELA	Tobacco	-Prevalence of current smoking is higher among emerging adults who report early life adversities
<i>El Mhamdi et al., 2017</i>	Gender	Age, marital status, edu., and anxiety, depression	Tobacco, alcohol, and street drugs	-Students with ≥ 1 ACE had significantly higher odds of SU compared to counterparts without ACE exposure. -The odds of SU increased with increased ACE exposure.
<i>Forster et al., 2019</i>	Ethnicity	Age, sex, state, and depressive symptoms,	Alcohol, marijuana, tobacco, and illicit drugs	-Every additional ACE was associated with a corresponding increase in odds of alcohol, binge drinking, tobacco, marijuana, illicit drugs, and polysubstance use. -Significant ethnic variation of the dose-response relationship between ACEs and tobacco, marijuana, and binge drinking existed.
<i>Grigsby et al., 2020</i>	NA	Sex, age, race/ethnicity, and site	Tobacco and alcohol	-Graded relationship between ACE exposure and cigarette use, and e-cigarette use. -ACEs did not yield gender-specific SU trajectories.

Table 2 Continued

Study	Mediators/ Moderators	Covariates in Adjusted Models	Substance Type	Main Findings (related to SU)
<i>Hughes et al., 2019</i>	Supportive childhood relationships	Age, gender, and childhood SES	Alcohol, smoking, and drug use	-Strong association between ACE and SU outcomes. -Supportive childhood relationships were associated with moderating risk of smoking and problem alcohol use.
<i>Kameg et al., 2020</i>	NA	NA	Alcohol and drugs	-No significant association between ACE score and risky alcohol use, however a statistically significant association between ACEs and risky drug use.
<i>Kim, 2017</i>	NA	Sex, region, parental edu., and family income	Alcohol	-Significant correlation between ACEs and alcohol use disorder -Graded associations of cumulative ACE exposure and alcohol use disorder.
<i>Krinner et al., 2020</i>	NA	Age, sex, race/ethnicity, and health behaviors,	Alcohol and tobacco	- ACE exposure was not associated with risky alcohol use.
<i>Onu et al., 2021</i>	Sociosexual behavior	Age	Tramadol use	-ACEs were positively associated with tramadol use. -The relationship between ACEs and tramadol use was mediated by sociosexual behaviors and desires.
<i>Pakdaman et al., 2021</i>	NA	School year, sex, race/ethnicity	Prescription drugs	-ACEs were significantly related to increased opiate, antidepressant, sedative, and stimulant use. -Race/ethnicity interaction was significant in prediction of stimulant misuse.

Table 2 Continued

Study	Mediators/ Moderators	Covariates in Adjusted Models	Substance Type	Main Findings (related to SU)
<i>Ramakrishnan et al., 2019</i>	Positive urgency	NA	Substance use disorder	-Positive urgency partially mediated the relationship between ACEs and substance use disorders.
<i>Schafer, 2021</i>	NA	NA	Alcohol	- A dose-response relationship between ACEs and risky alcohol use emerged. -Household substance use was significantly associated with risky alcohol use.
<i>Wiehn et al., 2018</i>	NA	Sex, age, parental age and edu., migration bkgd, and family SES	Alcohol, tobacco, and illegal drugs	-Experiencing four or more ACEs was associated with current smoking and substance use disorders. -A dose response relationship between ACEs and health risk behaviors was found.
<i>Windle et al., 2018</i>	NA	Age, sex, and race/ethnicity	Alcohol, tobacco, and marijuana	-Higher ACE scores significantly predicted risky cigarette, alcohol, and marijuana use.
<i>Zhang et al., 2020</i>	NA	Age, sex, and maternal edu.	Tobacco, alcohol and illicit drugs	-ACEs were associated with increased risk of smoking, binge drinking, and illicit drug use

Abbreviations: education=edu.;early life adversities=ELA; background=bkgd; NA=not assessed; significant=statistical

significance

Table 3. ACE Type and SU.

ACE TYPE	Alcohol use	Potential AUD	Risky alcohol use			Binge drink		Tobacco use					Marijuana use	Illicit drug use		
Par substance use	*	*			*	*		* ²	* ¹	*		*	*	*		*
Par interpersonal violence								* ²	* ¹							
Par relationship	NA	NA	NA	NA	NA	NA	NA	* ²	* ¹	NA	NA	NA	NA	NA	NA	NA
Divorce	NA	*			NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	*
Incarcerated par	NA	*		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Par mental illness	NA				*	NA	NA	* ²	* ¹	NA	NA		NA	NA	NA	*
Financial problems	NA	NA	NA	*	NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	
Par death	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA		NA	NA	NA	*
Physical	NA			*	NA	NA	NA		* ¹	NA	NA		NA	NA	NA	
Emotional	NA				NA	NA	NA	NA	NA	NA	NA	*	NA	NA	NA	
Sexual	*	*			*	*	*	* ²	* ¹	*	*		*	*	*	*
Emotional		*			NA			NA	NA	*				*		*
Physical	*	*			NA	*		* ²					*			
Bullying	NA				NA	NA	NA	* ²	* ¹	NA	NA		NA	NA	NA	*
Community vio	NA			NA	NA	NA	NA	* ²	* ¹	NA	NA	NA	NA	NA	NA	NA
Collective vio	NA	NA	NA	NA	NA	NA	NA	* ²	* ¹	NA	NA	NA	NA	NA	NA	NA

Abbreviations: par=parental; vio=violence; AUD=alcohol use disorder; Statistically significant odds ratio=*; statistically non-significant odds ratio=blue color; NA=not assessed; female=¹; male=²; Data presented from the following studies: (El Mhamdi et al., 2018; El Mhamdi et al., 2017; Forster et al., 2019; Kim, 2017; Schafer, 2021; Wiehn et al., 2018; Zhang et al., 2020)

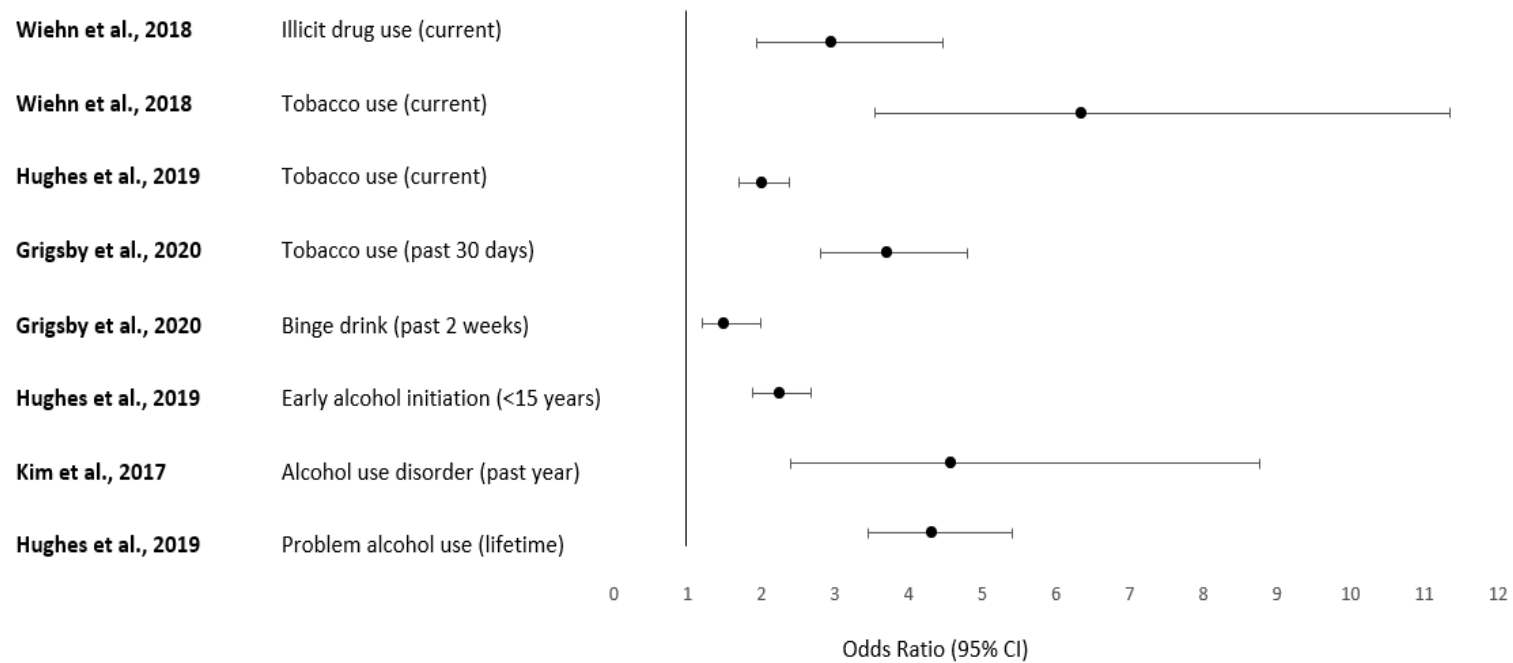


Figure 2. Strength of Association of Exposure to 4+ ACEs and SU.

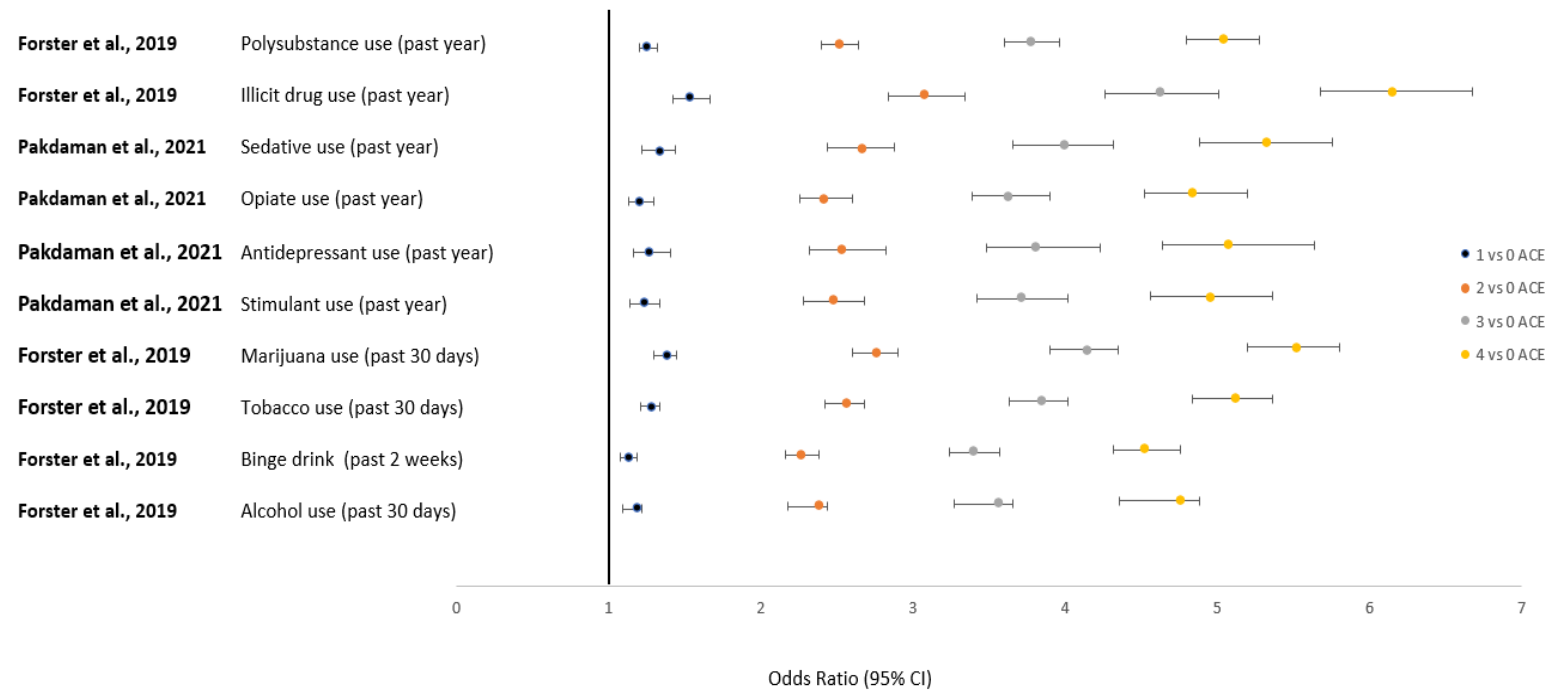


Figure 3. Dose Response Relationship between ACEs and SU.

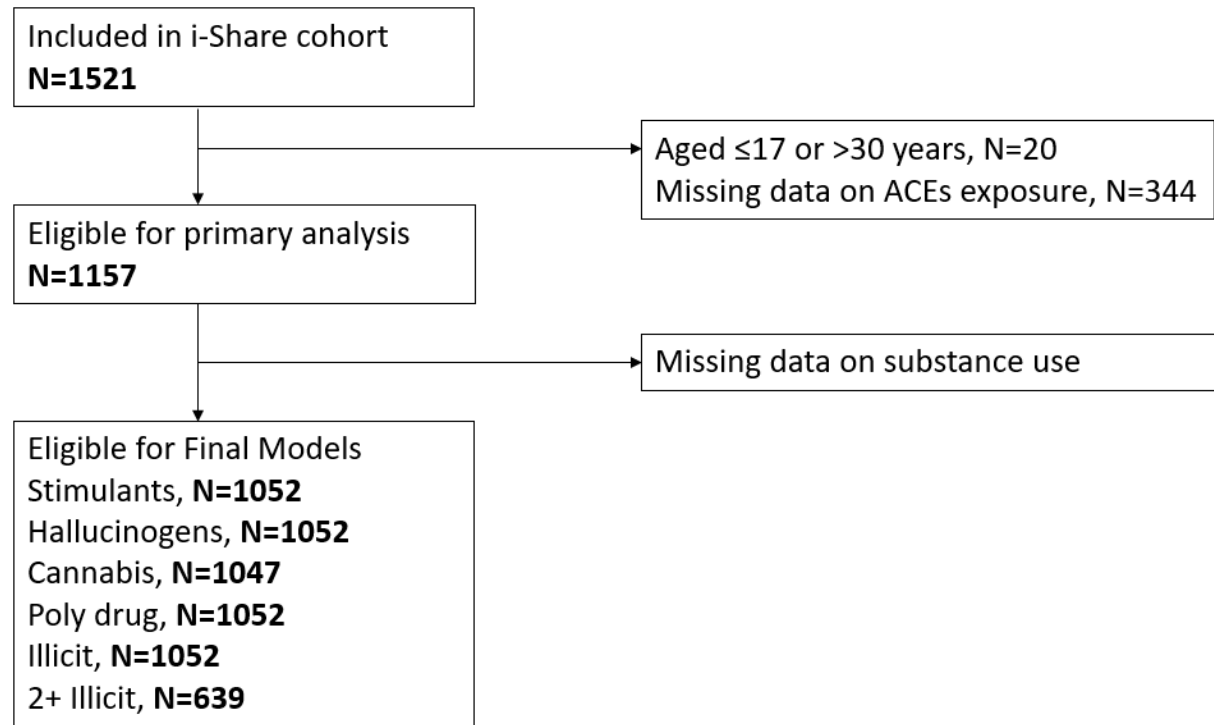


Figure 4. Flowchart of i-Share Participants.

Table 4. Demographic Characteristics and Other Risk Factors by ACE status.

Variable	Level	No ACEs		ACEs		Chi-square p-value
		N	%	N	%	
Gender	Female	282	79.7	660	82.2	0.3078
	Male	72	20.3	143	17.8	
SES Adolescence	Moderate-high	335	94.6	686	85.4	<.0001
	Low	19	5.4	117	14.6	
Age	18-22 years	254	75.4	578	74.9	0.8864
	23-30 years	83	24.6	193	25.1	
Depression Diagnosis	No	333	94.1	630	78.5	<.0001
	Yes	21	5.9	173	21.5	
Anxiety Diagnosis	No	328	92.7	637	79.3	<.0001
	Yes	26	7.3	166	20.7	
Weekly Alcohol Use	No	248	78.2	578	78.6	0.8830
	Yes	69	21.8	157	21.4	
Lifetime Binge Drink	No	43	15.1	140	21.2	0.0295
	Yes	242	84.9	521	78.8	
Daily Cigarette Use	No	232	97.9	514	95.0	0.0625
	Yes	5	2.1	27	5.0	
Lifetime Tobacco Use	No	204	64.2	411	55.7	0.0105
	Yes	114	35.9	327	44.3	
Monthly Cannabis Use	No	242	96.0	524	92.9	0.0856
	Yes	10	4.0	40	7.1	
Lifetime Cannabis Use	No	174	55.2	327	44.7	0.0017
	Yes	141	44.8	405	55.3	
Lifetime Hallucinogen Use	No	287	90.5	640	87.1	0.1114
	Yes	30	9.5	95	12.9	
Lifetime Stimulant Use	No	303	95.6	665	90.5	0.0050
	Yes	14	4.4	70	9.5	
Lifetime Illegal Drug Use	No	288	90.9	622	84.6	0.0067
	Yes	29	9.2	113	15.4	
Lifetime Polydrug Use	No	230	72.6	513	69.8	0.3673
	Yes	87	27.4	222	30.2	
Multiple Illegal Drug Use	No	170	85.4	327	74.3	0.0018
	Yes	29	14.6	113	25.7	
Risky Illegal Drug Use	No	299	94.3	651	88.6	0.0038
	Yes	18	5.7	84	11.4	

Table 5. The association between cumulative ACEs and illegal substance use.

All results report the adjusted odds ratio (aOR) and (95% confidence interval, CI). N=986 for all models except Multiple illegal

N=639.

Level	Stimulant (lifetime)	Hallucinogen (lifetime)	Cannabis (lifetime)	Illegal (lifetime)	Polydrug (lifetime)	Multiple illegal (lifetime)
Model 1*						
0 ACE	-	-	-	-	-	-
1 ACE	0.9 (0.4-1.9)	1.0 (0.6-1.8)	1.1 (0.8-1.5)	1.0 (0.6-1.6)	0.8 (0.6-1.2)	1.1 (0.7-2.0)
2 ACEs	2.3 (1.1-4.6)	1.1 (0.6-2.0)	1.5 (1.1-2.2)	1.4 (0.8-2.4)	1.2 (0.8-1.8)	1.9 (1.1-3.3)
3 ACEs	4.6 (2.4-8.8)	2.3 (1.4-3.8)	2.5 (1.7-3.6)	2.6 (1.6-4.2)	1.6 (1.1-2.3)	4.3 (2.6-7.4)
Model 2**						
0 ACE	-	-	-	-	-	-
1 ACE	0.9 (0.4-2.2)	1.0 (0.6-1.8)	1.2 (0.9-1.6)	1.0 (0.6-1.7)	0.9 (0.6-1.3)	1.2 (0.7-2.1)
2 ACEs	2.9 (1.4-6.2)	1.4 (0.7-2.5)	1.8 (1.2-2.6)	1.7 (1.0-3.0)	1.6 (1.1-2.5)	2.4 (1.3-4.4)
3 ACEs	5.6 (2.8-11.3)	2.9 (1.7-4.9)	2.9 (1.9-4.2)	3.1 (1.9-5.2)	2.2 (1.5-3.3)	5.5 (3.1-9.9)
Model 3***						
0 ACE	-	-	-	-	-	-
1 ACE	0.9 (0.4-2.1)	1.1 (0.6-2.0)	1.3 (0.9-2.0)	1.0 (0.6-1.8)	0.9 (0.6-1.4)	1.5 (0.7-2.9)
2 ACEs	2.4 (1.1-5.3)	1.2 (0.5-2.1)	2.0 (1.2-3.2)	1.5 (0.9-2.7)	1.6 (1.0-2.4)	2.3 (1.1-4.8)
3 ACEs	3.6 (1.7-7.7)	2.0 (1.1-3.5)	4.7 (2.7-8.0)	2.7 (1.6-4.8)	2.5 (1.6-3.9)	10.9 (4.6-26.0)

**Model 1- univariate analyses presented as OR and 95% CI*

***Model 2- multivariate analyses adjusted on sex, SES during adolescence, and age, presented as aOR and 95% CI*

****Model 3- multivariate analyses adjusted on sex, SES during adolescence, age, anxiety and depression diagnosis, lifetime binge drinking, and lifetime tobacco use, presented as aOR and 95% CI*

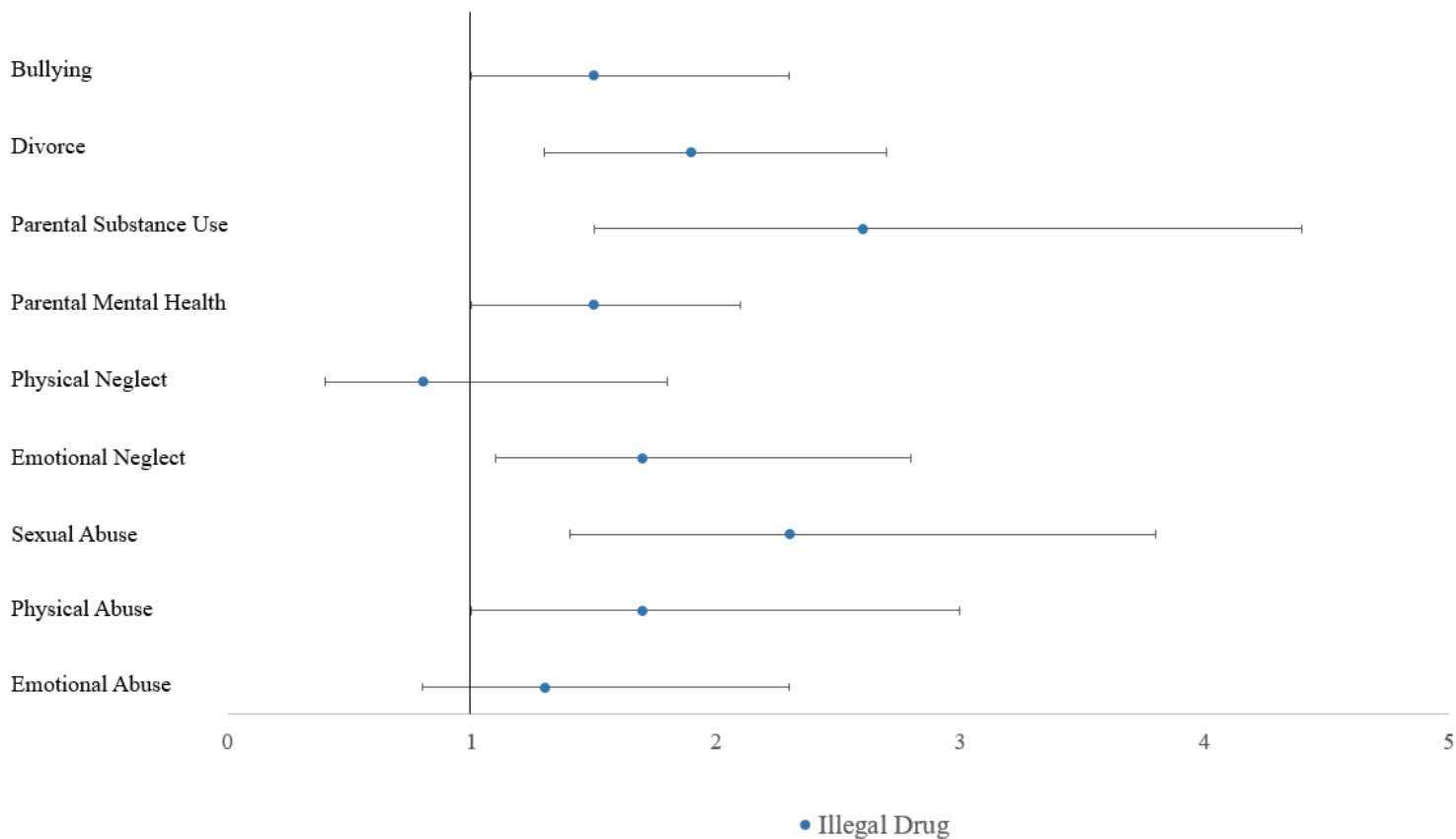


Figure 5. The association between ACE type and lifetime illegal drug use (cannabis, amphetamines, cocaine, hallucinogenic mushrooms, or ecstasy).

All results report the adjusted odds ratio (aOR) and (95% confidence interval, CI); adjusted for sex, adolescent SES, age, lifetime binge drinking, lifetime tobacco use, and depression and anxiety diagnosis. N=986 for all models.

Table 6. Analytic Sample Sociodemographic characteristics.

Variable	Total		Male		Female		p
	N	M	N	M	N	M	
18-20 years	2103	28.1	872	13.0	1231	15.0	0.0528
21-23 years	5265	50.7	2353	24.3	2912	26.4	
24-27 years	2083	21.2	995	10.8	1088	10.4	
White	5415	69.4	2450	33.4	2965	36.1	0.2060
Black	1818	13.6	724	6.2	1094	7.4	
Hispanic	643	4.8	308	2.4	335	2.4	
Other	1571	12.2	738	6.2	833	5.9	
Poverty	1341	14.6	495	6.1	846	8.5	0.0004
≤high school graduate	2059	23.9	1114	14.0	945	9.9	<.0001
Some college/ degree	6085	63.4	2672	29.3	3413	34.1	
≥graduate school/degree	1306	12.7	433	4.9	873	7.8	
Neglect	1051	10.6	501	5.3	550	5.3	0.3790
Emotional abuse	1510	15.8	547	6.3	963	9.6	<.0001
Physical abuse	826	8.2	386	3.9	440	4.2	
Sexual abuse	751	7.8	256	3.0	495	44.8	0.0005
Parental incarceration	1025	10.6	439	5.0	586	5.6	
Parent binge drink	1120	13.1	504	6.8	616	6.3	0.0497
Parent deceased	490	4.5	202	2.1	288	2.5	0.3414
Witness violence	1066	9.9	587	5.7	479	4.1	<.0001
Experience violence	109	1.1	88	0.9	21	0.2	
0 ACEs	4682	50.3	2074	23.7	2608	26.5	0.0763
1 ACE	2802	29.3	1281	14.9	1521	14.4	
2 ACEs	1253	12.5	561	5.9	692	6.6	
3 ACEs	761	7.9	322	3.6	439	4.3	
Daily cannabis use	1054	12.4	667	8.0	387	4.4	<.0001
≥3 days/week binge drink	1246	15.1	855	10.6	391	4.5	
Daily cigarette smoking	3714	43.4	1802	21.9	1912	21.5	0.0072
Daily cannabis use	962	11.7	601	7.8	361	4.0	<.0001
≥3 days/week binge drink	331	3.9	233	2.9	98	0.9	
Daily cigarette smoking	4010	46.8	1964	24.1	2046	22.7	<.0001
Walk	5343	54.7	1990	21.8	3353	32.9	
Strength training	2776	29.3	1677	18.1	1099	11.1	<.0001
Team sports	1166	11.7	909	9.4	257	2.4	
Individual sports	2415	25.2	1270	14.2	1145	11.0	<.0001

*p values represent chi-squares test between sexes.

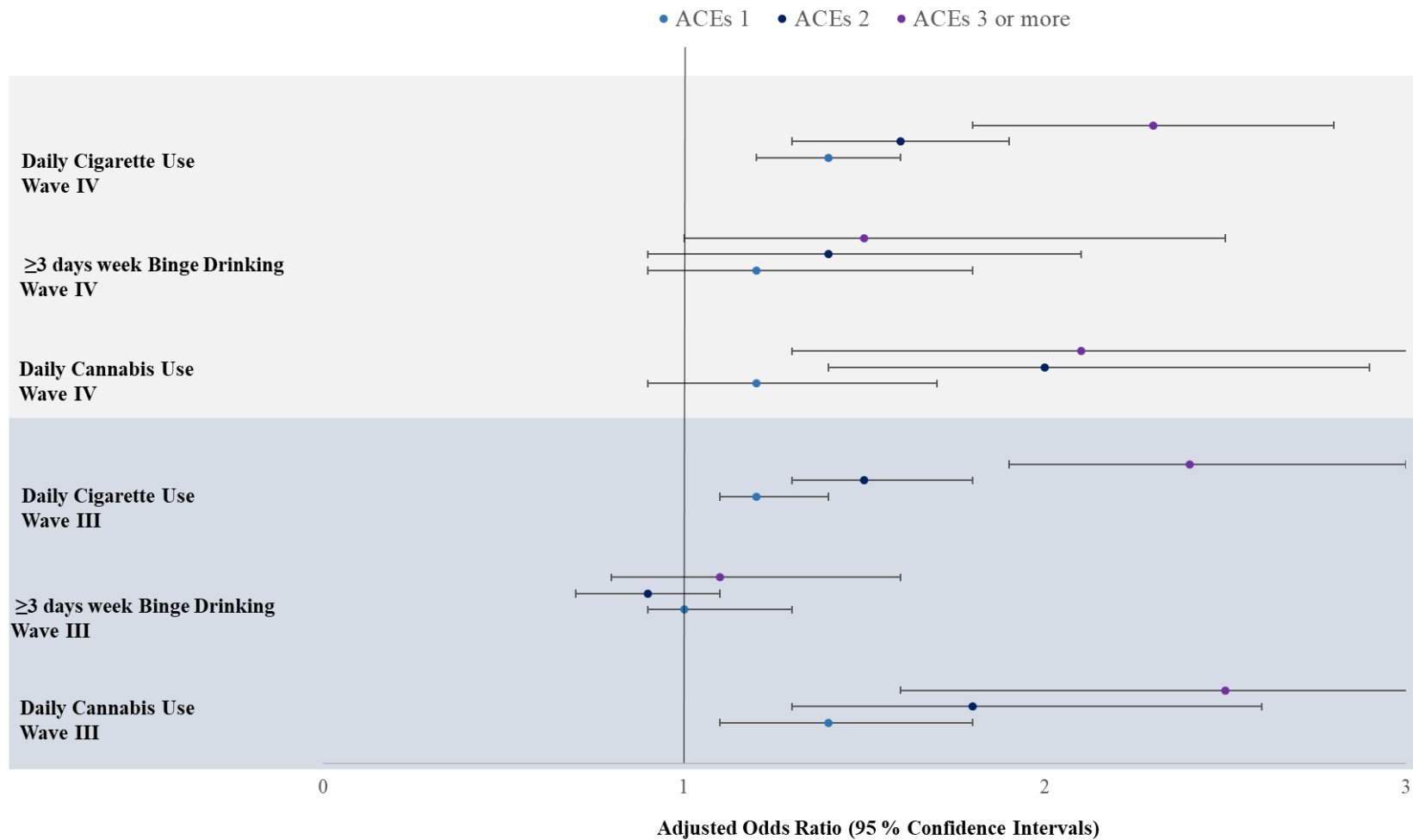


Figure 6. Cumulative ACEs and substance use in Waves III and IV.

Multivariate analyses adjusted on ACEs, education, race, SES adulthood, sex, and age presented as aOR (95% CI).

Table 7. The association between cumulative ACEs and substance use in Waves III and IV.

Level	WAVE III									WAVE IV								
	Daily Cannabis			≥3 days week Binge Drink			Daily Cigarette			Daily Cannabis			≥3 days week Binge Drink			Daily Cigarette		
	N=9,411			N=9,416			N=9,427			N=8,354			N=9,423			N=9,434		
0 ACE	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1 ACE	1.4	1.1	1.8	1.0	0.9	1.3	1.2	1.1	1.4	1.2	0.9	1.7	1.2	0.9	1.8	1.4	1.2	1.6
2 ACEs	1.8	1.3	2.6	0.9	0.7	1.1	1.5	1.3	1.8	2.0	1.4	2.9	1.4	0.9	2.1	1.6	1.3	1.9
3 ACEs	2.5	1.6	3.6	1.1	0.8	1.6	2.4	1.9	3.0	2.1	1.3	3.3	1.5	0.9	2.5	2.3	1.8	2.8
Graduate School	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
College	2.0	1.1	3.6	1.1	0.8	1.5	3.0	2.3	3.8	1.9	1.1	3.5	2.4	1.1	5.0	2.5	2.0	3.1
High School	2.9	1.5	5.8	0.9	0.6	1.3	4.6	3.4	6.1	3.2	1.8	5.7	3.4	1.5	7.6	4.4	3.4	5.6
White	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other	0.5	0.3	0.8	0.7	0.5	0.8	0.6	0.5	0.7	0.7	0.4	0.9	1.0	0.6	1.7	0.6	0.4	0.7
Hispanic	0.6	0.3	1.2	0.5	0.3	0.8	0.5	0.4	0.7	0.6	0.3	1.1	0.5	0.2	1.3	0.4	0.3	0.6
Black	0.3	0.2	0.4	0.3	0.2	0.5	0.3	0.2	0.4	0.8	0.5	1.2	0.5	0.3	0.7	0.3	0.2	0.4
No Poverty adult	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Poverty adult	1.4	1.0	1.9	1.1	0.9	1.4	1.4	1.1	1.7	2.8	2.0	3.8	0.9	0.6	1.4	1.7	1.4	2.2
Female	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Male	2.5	1.9	3.3	3.1	2.6	3.6	1.1	0.9	1.2	2.6	2.0	3.4	3.3	2.4	4.5	1.2	1.1	1.4
24-27 years	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
21-23 years	1.4	0.9	1.9	1.3	1.1	1.6	1.0	0.9	1.3	1.3	0.9	1.8	0.9	0.6	1.3	1.1	0.9	1.3
18-20 years	1.8	1.2	2.8	1.5	1.1	1.9	1.0	0.8	1.2	2.0	1.3	3.0	1.2	0.8	1.8	1.1	0.9	1.4

Table 8. Association between physical activity modality and substance use amongst persons with ACEs.

Level	WAVE III									WAVE IV								
	Daily Cannabis			≥3 days week Binge Drink			Daily Cigarette			Daily Cannabis			≥3 days week Binge Drink			Daily Cigarette		
	N=9,411			N=9,416			N=9,427			N=8,354			N=9,423			N=9,434		
No Walk	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Walk	0.6	0.5	0.8	0.7	0.5	1.0	0.8	0.7	0.9	0.7	0.5	0.9	0.7	0.5	1.0	0.8	0.7	0.9
No strength train	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Strength train	0.9	0.7	1.1	1.2	1.0	1.5	0.8	0.7	1.4	0.9	0.7	1.1	0.9	0.7	1.4	0.8	0.7	0.9
No team sport	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Team sport	0.9	0.7	1.2	1.3	1.1	1.6	0.7	0.6	0.8	0.9	0.6	1.2	0.9	0.7	1.3	0.7	0.6	0.8
No individual sport	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Individual sport	0.8	0.6	1.1	1.3	1.1	1.5	0.8	0.6	0.9	0.9	0.7	1.2	0.8	0.5	1.1	0.7	0.6	0.8

* Multivariate analyses adjusted on ACEs, education, race, sex, SES adulthood, and age presented as aOR (95% CI).

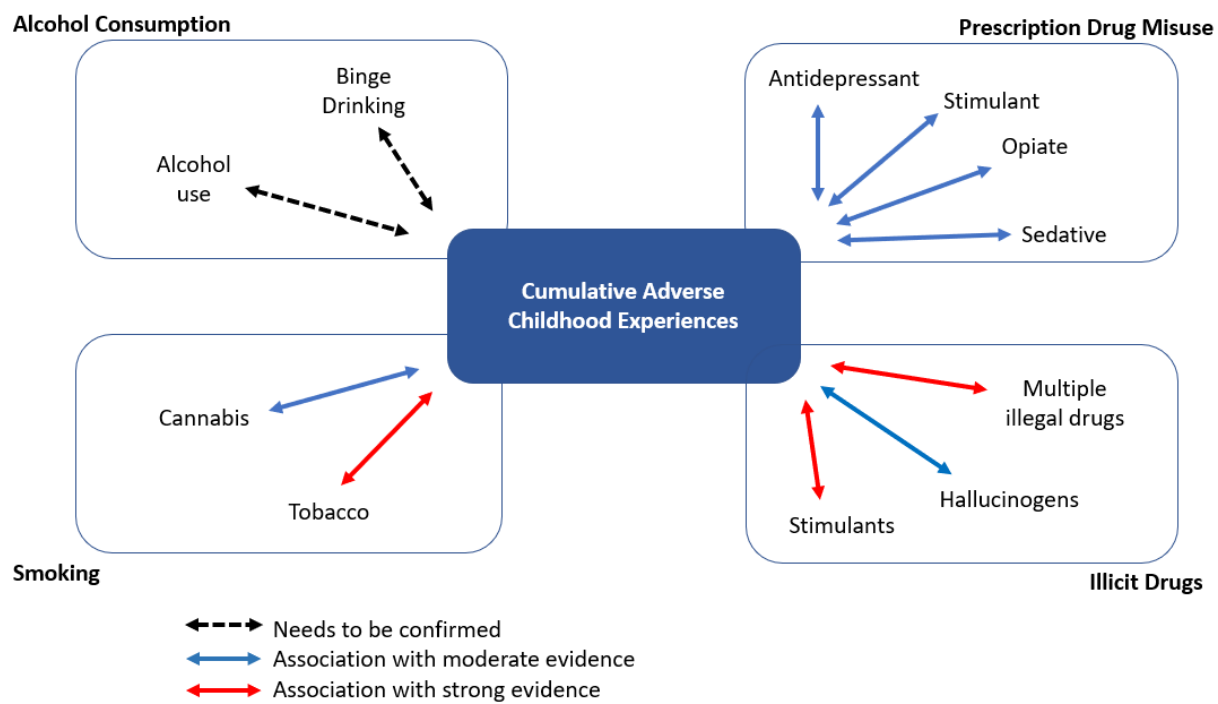


Figure 7. Overview of Results: ACEs and Substance Use Risk.

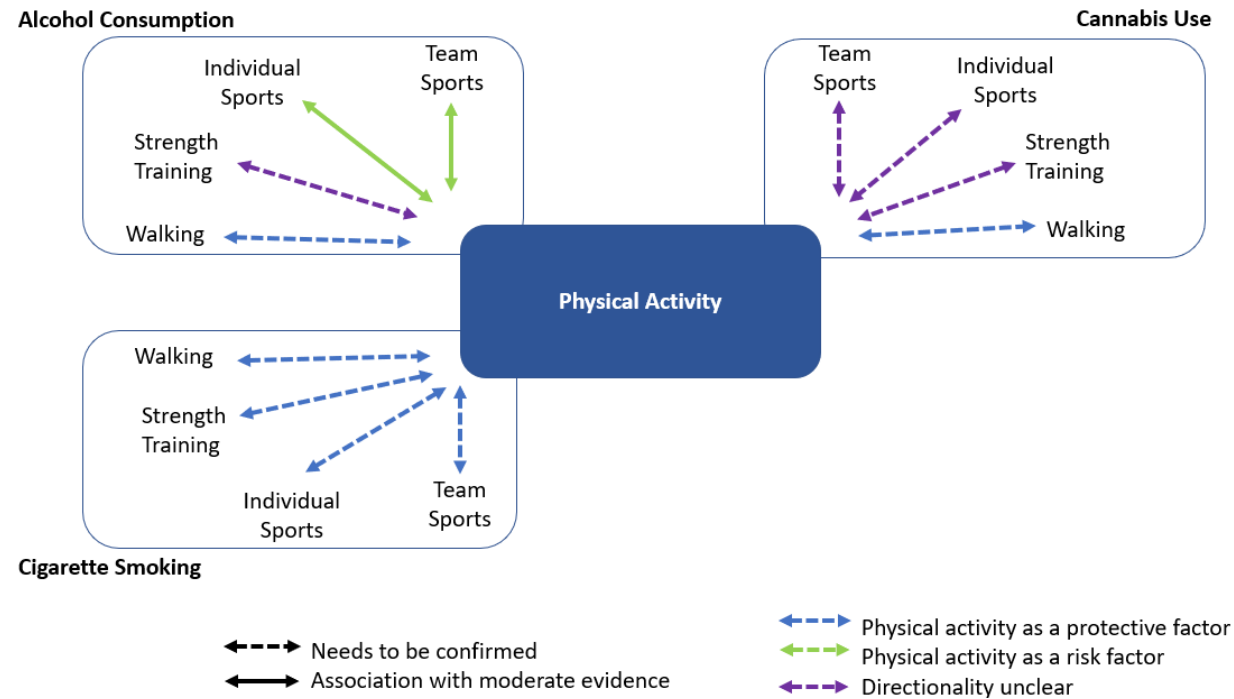


Figure 8. Role of Physical Activity on Substance Use.

VITA

Ashlyn Nicole Schwartz was born to parents Jay and Deborah Schwartz in Marietta, Georgia. Ashlyn played soccer for 20 years, where she represented the state of Georgia and Southeastern Region Olympic Developmental Team. Ashlyn joined Kennesaw State University as a senior in high school and stayed there for her Bachelor's degree in Exercise Science. Ashlyn was highly involved as president of the women's club soccer team where she created an international charity soccer tournament and was the head of the exercise science club. This led her to pursue her Master's degree in Kinesiology then Doctoral degree in Public Health Sciences at The University of Tennessee, Knoxville where she continued her involvement in volunteering and leadership positions. After the tragic loss of her brother in 2016 to an opioid overdose, Ms. Schwartz dedicated her research to substance use disorders. Ashlyn developed productive collaborations with local health centers for investigating developmental outcomes of opioid-exposed infants and served as project director for two years on a community based opioid disorder research grant. Ashlyn is an outdoor enthusiast who enjoys to hike and kayak, plays piano, and write poetry. Her love to travel and commitment to studying substance misuse led her to apply for a Fulbright scholarship, of which she received in 2021. Upon receiving an extension, Ashlyn finished her doctoral degree whilst living in France and learning French. Ashlyn has a heart for community health and helping persons with substance use and mental health challenges.