

University of Nevada, Reno

**Substance use and drug overdose: Role of individual and environmental factors**

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## ABSTRACT

Studies have explored risk and protective factors for substance use in adolescent and maternal populations. However, even with this increased understanding of risk and protective factors, trends continue to remain the same or worsen in vulnerable populations such as sexual minority youth, pregnant people, and those who die by drug overdose. The general aims of this dissertation are to: 1) Investigate protective environmental factors among sexual minority youth for nonmedical use of prescription opioids (NMUPO); 2) Explore the direct and interactive effects of stressful life events (SLEs) and adverse childhood experiences (ACEs) among pregnant people on marijuana use; and 3) Identify social and contextual factors associated with substances used among drug overdose decedents.

To achieve these aims, I first used representative data from 156,149 youth from 24 states in the U.S. and assessed environmental protective factors (state equality laws and LGBTQ supportive school environment) among sexual minority youth for NMUPO using generalized linear mixed models. In the second study, I explored individual risk factors of ACEs and SLEs and their direct and interactive effects on marijuana use among a population-based sample of 2,483 pregnant people in Nevada using generalized estimating equations. In the third study, I explored the social and contextual factors related to drug overdose deaths among 1,948 decedents in Nevada to identify potential opportunities that could have prevented their death using latent class analysis, multinomial logistic regression, and Chi-squared tests.

The first study found that the school environment was associated with a reduced odds of NMUPO, while this finding did not hold up with state equality laws. The second study found that ACEs and SLEs were associated with marijuana use during pregnancy, and there was evidence of additive interaction when assessing both exposures jointly. The third study identified four distinct groups of people who die by drug overdose and several social and contextual factors associated with these groups. Collectively, these findings highlight the need for advancing research of protective factors in vulnerable populations, and finding ways to prevent drug overdose.

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## **Chapter 1: Introduction**

Over thirty years ago, Hawkins and colleagues established the risk and protective factor framework to determine causes and ways to prevent substance use (Hawkins et al., 1992). Risk factors are defined as an indicator that increases the likelihood of substance use, while protective factors are defined as an indicator that reduces the likelihood of substance use (Hawkins et al., 1992). Since then, there has been an abundance of research published identifying risk and protective factors for substance use in a variety of populations, mostly adolescent populations and less so on maternal populations (Bond et al., 2007; Cleveland et al., 2008; Harrison et al., 2008; Havens et al., 2009). For example, for adolescents, risk factors for substance use include feeling disconnected from school and their peers, as well as parental substance use (Bond et al., 2007; Cleveland et al., 2008). Protective factors for adolescent substance use include resiliency, strong bonds with family, school, and community (Cleveland et al., 2008; Sloboda et al., 2012). Risk factors for substance use among maternal populations include such things as depression, psychosocial stressors, and experiencing intimate partner violence (Harrison et al., 2008). Protective factors for substance use include being married, having a higher level of education, and being employed (Havens et al., 2009). However, even with this increased understanding of risk and protective factors, the prevalence of substance use among sexual minority youth is still much higher than their non-sexual minority peers, and substance use trends among pregnant people have increased (CDC, 2020; SAMHSA, 2022).

Additionally, one potential outcome of substance use is drug overdose death, which has increased the past two decades in the United States and is of great concern (CDC, 2021).

### Life course perspective

Drawing from a life course perspective, adolescence and pregnancy represent two sensitive periods in a person's life that can be negatively impacted by substance use that can have profound health effects across the life course (Iser et al., 2007; Louw, 2018; Mereish, 2019). For adolescence, those who use substances are more likely to misuse substances or be diagnosed with a substance use disorder in adulthood than those who do not use substances (Volkow & Wargo, 2022). It is well-established that SMY are at greater risk of substance use compared to their heterosexual peers (Mereish, 2019). SMY are also limited in protective factors for substance use that have been researched, so it is imperative that a special focus of substance use prevention be on SMY (Mereish, 2019). Additionally, pregnant people (and their infants) are more susceptible to the harms of substance use (Louw, 2018; Volkow & Wargo, 2022). Substance use during pregnancy is associated with many negative birth and developmental outcomes on the infant (i.e. premature birth, low birth weight), which can make it difficult for the infant to live a healthy, fulfilling life (Ross et al., 2014). The time beginning from conception to the first few years of life are critical for long-term development and health, and prenatal substance use may deter this growth (Louw et al. 2018). SMY and pregnant people will be highlighted as two populations of interest to further explore the role of risk and

protective factors since they can benefit most from these interventions, then attention will be focused on people who died by drug overdose and factors associated with their death.

### Sexual minority youth

SMY are those identifying as gay, lesbian, or bisexual, and report a higher prevalence and earlier initiation of substance use compared to their heterosexual peers (Capistrant & Nakash, 2019; Kecojevic et al., 2012). These disparities can be explained in part by the minority stress theory, which posits that SMY face unique stressors such as prejudice and discrimination, and these stressors can in turn have a negative impact on their health (Meyer, 2003). According to the minority stress theory, distal factors in the social environment may contribute to discrimination and may influence proximal stressors, which are internal responses to negative experiences such as self-stigmatization or concealment (Meyer, 2003). Such stressors are cumulative and may lead to unhealthy coping habits, such as substance use (Hatzenbuehler, 2009; Kelleher, 2009; Meyer, 2003). A recent review of risk and protective factors for substance use among sexual and gender identity minority youth found most studies to date have focused on individual-level minority stress factors (i.e. stigma), with limited studies addressing protective factors at the community or environmental level (Kidd et al., 2018).

### State equity laws

Environmental protective factors at the state-level and school-level may influence substance use behaviors among SMY. At the state-level, research has explored protective factors for LGBTQ youth in the form of state equity laws, which include such things as nondiscrimination and anti-bullying laws that prohibit discrimination and bullying on the basis of sexual orientation and gender identity (Chien et al., 2022; Watson et al., 2021). Recent studies have found that SMY living in states with more equitable laws for LGBTQ persons were less likely to engage in tobacco use and reported mixed findings for binge drinking, with no studies having explored NMUPO (Chien et al., 2022; Watson et al., 2021).

#### LGBTQ Supportive School Environments

At the school-level, recent research explored the role of supportive school environments for LGBTQ youth, encompassing a range of several school practices, which include such things as presence of gay straight alliances (GSAs), prohibiting harassment, having safe spaces, and facilitating access to fulfill physical and psychosocial health needs for LGBTQ youth, and found that fostering supportive environments within schools was associated with a reduced odds of alcohol use and illicit substance use for SMY compared to non-SMY (Coulter et al., 2016; Kaczowski et al., 2022). Although two studies have explored NMUPO using this supportive school environment for LGBTQ youth indicator, they found no associations (potentially due to low sample size of sexual minority youth), and were limited in the effects of state-level confounding variables assessed (Kaczowski et al., 2022; Watson et al., 2021).

## Pregnant people

Pregnancy can be a vulnerable time period in a person's life where negative life exposures may have a worse effect on a person compared to if exposures happened outside this period (Kuh et al., 2003). For example, the effects of emotional stressors such as fighting more with a partner, may affect pregnant people more than when they were not pregnant due to the changes involved during pregnancy, which may lead them to engage in self-medicating behaviors, such as substance use (Mishra et al., 2010). According to the 2021 National Survey on Drug Use and Health, 19.6% of pregnant people reported using illicit or non-illicit substances in the past month (SAMHSA, 2022). Most notably, 7.7% of pregnant people reported using illicit drugs, and 9.8% reported alcohol use in the past month (SAMHSA, 2022). This is concerning since certain substances, for example alcohol and opioids, are known to be associated with negative birth outcomes on the infant, such as fetal alcohol syndrome and neonatal abstinence syndrome, respectively (CDC, 2022a; CDC, 2022b). However, it has been reported that marijuana use during pregnancy has increased (4.7% in 2018 to 8% in 2020), which is concerning since the evidence of the effects of marijuana use during pregnancy on the infant (i.e. premature birth, low birth weight, and other developmental problems) are still inconclusive (Grzeskowiak et al., 2020; Mark et al., 2016; Nashed et al., 2020; Sarrafpour et al., 2020).

### Adverse childhood experiences

Adverse childhood experiences (ACEs) are potentially traumatic events occurring before the age of 18, and include such things as childhood abuse and household challenges (Testa et al., 2022). Recent research suggests that ACEs are associated with marijuana use during pregnancy, with studies finding that pregnant people reporting higher ACE scores are more likely to use marijuana compared to those reporting no ACEs (Jasthi et al., 2021; Klasner et al., 2022; Osofsky et al., 2021; Testa et al., 2022a). However, most of these studies focused on smaller, specific populations of pregnant people, such as those receiving prenatal care, receiving care at one hospital, or were low-income (Jasthi et al., 2021; Klasner et al., 2022; Osofsky et al., 2021). One recent population-based study also reported that pregnant people reporting higher ACE scores are more likely to use marijuana compared to those reporting No ACEs, but did not adequately control for confounding variables such as pregnancy intention, health insurance during pregnancy, and prenatal cigarette use (Testa et al., 2022a).

### Antenatal stressful life events

Antenatal stressful life events (SLEs) are major life events that commonly occur among pregnant people prior to birth that may cause harm or stress to an individual such as having financial issues, divorce or difficulties with a partner, and death of a spouse (Allen et al., 2020). Little attention has been placed on studying the relationship between SLEs and substance use during pregnancy, with recent studies finding associations between SLEs and substance use

during pregnancy in the form of alcohol, cigarettes, e-cigarettes, opioids, and marijuana (Allen et al., 2019; Allen et al., 2020; Esper et al., 2019; Testa et al., 2021; Testa et al., 2022b). One recent study found that pregnant people reporting high cumulative SLE scores were more likely to use marijuana during pregnancy compared to those who reported no SLEs (Allen et al., 2020). However, this study did not adjust for pregnancy intention, and adjusted for marital status, which is an SLE (Allen et al., 2020).

Although research has found that ACEs and SLEs are associated with marijuana use among pregnant people, limited research has assessed the effect of these factors jointly in analyses for substance use behaviors (Buehler et al., 2022). Consideration of recent SLEs within the context of childhood adversity is important to prevent substance use during pregnancy since prior traumas play a pivotal role in shaping how individuals cope with current stress (Osofsky et al., 2021). Since pregnancy is a sensitive life period, assessing the joint effects of ACEs and recent SLEs on marijuana use can identify people who may benefit from early interventions that address these exposures.

### Drug overdose

Substance use is a strong risk factor for drug overdose, which is when someone takes a substance in excess, which is typically accompanied by respiratory depression and unresponsive in the case of opioid overdose (Bohnert et al., 2012). Since the beginning of the modern overdose epidemic in 1999, there has been over a million people who have lost their lives to

drug overdose (CDC, 2022c). The first wave of the modern overdose epidemic began in the early 2000s with an increase in deaths due to the explosion in prescription opioid use, which was followed by a second wave with an increase in deaths due to heroin use in 2010, and a subsequent third wave beginning in 2013 with increases in overdose deaths involving synthetic opioids such as fentanyl (CDC, 2021). Emerging research suggests a fourth wave of the epidemic involving multiple substances, referred to as polysubstance use, fueled by an increase in stimulant use (Ciccarone, 2021; Han et al., 2021; Hoots et al., 2020). The number of drug overdose deaths have continued to increase, most recently by 20% from 2020 to 2021, and show little signs of slowing down (Tanz et al., 2022).

#### Circumstances surrounding overdose

Among drug overdose decedents, the circumstances surrounding the overdose are factors that include events that were related to the decedent's overdose and may have contributed to it, and are typically documented as part of the death investigation, but are typically not used often due to the time involved to put it in a usable form (Ropero-Miller et al., 2020). These factors have strong parallels to the social determinants of health (i.e. social and community context) and may shed more light on areas where interventions can be placed to prevent overdose death (Barocas et al., 2019; Holland et al., 2021). Research has looked at a few circumstances such as naloxone administration, previous overdose, recent release from treatment or incarceration, mental health diagnosis, and location of overdose, but have

focused on opioid-involved and/or stimulant-involved overdose deaths only (Mattson et al., 2018; O'Donnell et al., 2020). They did not assess relationships between circumstances and substances, which would have provided more depth to their findings by identifying which circumstances would be most beneficial for intervention (Mattson et al., 2018; O'Donnell et al., 2020). To account for polysubstance use, prevention should focus on targeting factors or circumstances that differ amongst multiple substances to prevent polysubstance overdose death (Compton et al., 2020). The loss of life and the effect of substance use and drug overdose on those closest to those effected has led to considerable costs in the U.S. (Florence et al., 2021).

#### Burden of substance use and drug overdose

Substance use and drug overdose have led to large societal and economic costs in the U.S. (Florence et al., 2021). In 2021, in the past month, over half of people (57.8%) over the age of 12 in the United States used tobacco, alcohol, or an illicit substance, while 1 in 6 people reported a substance use disorder in the past year (SAMHSA, 2022). A recent report from CDC estimates that opioid use disorder and fatal opioid overdose cost the U.S. over \$1 trillion in 2017 alone for health care, criminal justice, and lost productivity (Florence et al., 2021). Most of this burden is related to reduced quality of life as a result of opioid use disorder and the value of lives lost (Florence et al., 2021). Due to the great burden associated with substance use and drug overdose, there is a clear need to identify ways to prevent or intervene, especially in

vulnerable populations that have a higher risk of substance use and overdose, by delving deeper into understudied risk and protective factors.

#### Dissertation aims

This dissertation will first explore environmental protective factors (state equality laws and LGBTQ supportive school environment) among sexual minority youth for nonmedical use of prescription opioids. Second, I will assess individual risk factors (ACEs and SLEs) and their interactive effects on marijuana use among pregnant people. Third, attention will be turned to people who died by drug overdose, where I will explore the social and contextual factors related to those deaths to identify potential opportunities that could have prevented their death. This dissertation will explore the following three aims: 1) Investigate protective environmental factors among sexual minority youth for nonmedical use of prescription opioids; 2) Explore the direct and interactive effects of stressful life events and adverse childhood experiences among pregnant people on marijuana use; and 3) Identify social and contextual factors associated with substances used among drug overdose decedents.

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## Chapter 2

### **Protective environmental factors and nonmedical use of prescription opioids among sexual minority youth**

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### Abstract

**Purpose:** Nonmedical use of prescription opioids (NMUPO) is a pressing public health concern, and affects sexual minority youth at greater rates compared to heterosexual youth. We investigated whether two protective environmental factors, 1) the Human Rights Campaign's state equality index (SEI), which reviews statewide laws and policies that affect lesbian, gay, bisexual, transgender, and questioning (LGBTQ) people, and 2) supportive school environments for LGBTQ youth, which include such things as gay straight alliances and safe spaces, influenced NMUPO among sexual minority and heterosexual high school students.

**Methods:** We combined data from the 2017-2019 Youth Risk Behavior Surveillance System, 2016-2018 School Health Profiles, state-level socio-demographic and SEI data across 24 states (n=156,149 students). Generalized linear mixed models were used to examine associations between 1) SEI and 2) supportive school environments for LGBTQ youth, with NMUPO, accounting for the clustering at the school- and state-levels.

**Results:** Before adjustment, we found that youth in states with a higher SEI were less likely to engage in NMUPO compared to students in states with lower SEI, but this was no longer significant after adjustment. After adjusting for individual- and state-level indicators, SMY in states with supportive school environments for LGBTQ youth were less likely to engage in NMUPO.

**Conclusions:** Supportive school environments for LGBTQ youth may play an important role in the health of SMY. Establishing more inclusive policies and supportive environments within schools may reduce NMUPO among SMY.

## **Introduction**

Nonmedical use of prescription opioids (NMUPO), defined as using prescription pain medicine without a prescription or differently than prescribed, is associated with a greater risk of overdose morbidity and mortality among youth. Currently, 1 in 7 high school students report NMUPO (Hadland et al., 2021; Jones et al., 2020) and sexual minority youth (SMY), which includes youth that report their sexual identity as being lesbian, gay, or bisexual, have significantly higher rates of NMUPO (Morgan et al., 2020) and are more likely to initiate use at younger ages compared to heterosexual youth (Capistrant & Nakash, 2019; Kecojevic et al., 2012).

These disparities can be explained in part by the minority stress theory, which posits that SMY face unique stressors such as prejudice and discrimination, and these stressors can in turn have a negative impact on their health (Meyer, 2003). According to the minority stress theory, distal factors in the social environment may contribute to discrimination and may influence proximal stressors, which are internal responses to negative experiences such as self-stigmatization or concealment (Meyer, 2003). Such stressors are cumulative and may lead to unhealthy coping habits, such as substance use (Hatzenbuehler, 2009; Kelleher, 2009; Meyer,

2003). Distal stressors can operate at the structural-level, specifically the state SMY live in and the school they attend (Hatzenbuehler, 2009; Meyer, 2003). For example, a state climate that makes it difficult to install laws that may put protections in place for harassment and victimization on the basis of sexual identity, may lead SMY to engage in NMUPO as a coping mechanism (Watson et al., 2021). The school environment may also contribute as a distal stressor, especially if there are no practices in place that prohibit bullying or harassment on the basis of sexual identity (Hatzenbuehler, 2009). However, drawing from the positive youth development framework (PYDF), specifically the aspect of the enabling environment, state- and school-level environmental factors may be able to reduce negative health outcomes such as NMUPO by helping develop, support, and encourage SMY to thrive in the face of adversity (Poteat et al., 2014).

At the state-level, research has explored protective factors for LGBTQ youth in the form of state equity laws, which include such things as nondiscrimination and anti-bullying laws that prohibit discrimination and bullying on the basis of sexual orientation and gender identity (Chien et al., 2022; Watson et al., 2021). Recent studies have explored the relationship of these laws and substance use, and found that SMY living in states with more equitable laws for LGBTQ persons were less likely to engage in tobacco use, but found mixed findings for binge drinking (Chien et al., 2022; Watson et al., 2021). No studies to our knowledge have explored the influence of these state-level environmental protective factors and NMUPO among youth.

At the school-level, recent research explored the role of supportive school environments for LGBTQ youth, encompassing a range of several school practices, which include such things as presence of gay straight alliances (GSAs), prohibiting harassment, having safe spaces, and facilitating access to fulfill physical and psychosocial health needs for LGBTQ youth, and found that fostering supportive environments within schools was associated with a reduced odds of alcohol use and illicit substance use for SMY compared to non-SMY (Coulter et al., 2016; Kaczowski et al., 2022). Two recent studies, one in the U.S. and one in Canada, looked at the relationship between supportive school environment indicators for LGBTQ youth and NMUPO, and found no association between these two factors (Kaczowski et al., 2022; Watson et al., 2020). These studies used similar metrics to define a supportive school environment for LGBTQ youth, with the U.S. study using characteristics that include such things as presence of GSAs, prohibiting harassment, and having safe spaces, while the Canada study included GSAs, anti-bullying policies, and community features surrounding schools such as events that promoted inclusivity among LGBTQ persons (Kaczowski et al., 2022; Watson et al., 2020). These studies had small samples of SMY which limited their ability to find statistically significant associations (Kaczowski et al., 2022; Watson et al., 2020). They were also limited in controlling for the effects of state-level socio-demographic factors that are associated with substance use such as socio-economic status, income inequality, and urbanicity (Galea et al., 2007; Kaczowski et al., 2022; Lynch et al., 2001; Rand & Pacey, 2021; Watson et al., 2020). The U.S. study did not control for any factors beyond the individual-level, while the Canada study controlled for just a

few general community environment factors such as population size and alcohol sales per capita (Kaczowski et al., 2022; Watson et al., 2020).

To address the gaps in previous research and to better understand the role of environmental factors and NMUPO, the purpose of this study is to explore the association between 1) a comprehensive measure of state climate in the form of the Human Rights Campaign's state equality index (SEI), which reviews statewide laws and policies that affect LGBTQ persons, and 2) supportive school environments for LGBTQ youth and NMUPO, among SMY and non-SMY students, using high school survey data from 24 states across the United States.

## **Methods**

### Participants and procedures

The Youth Risk Behavior Survey (YRBS) is conducted in 44 states in the U.S. and collects information on health-related risk behaviors in high school students in grades 9-12 attending public schools (Underwood et al., 2020). This survey is designed to be a representative sample of high school students within the states it is conducted in (Underwood et al., 2020).

The School Health Profiles is conducted in 43 states every two years and monitors trends in school health education, bullying and sexual harassment practices, school health policies, school-based health services, family engagement and community involvement, and

health coordination within schools, and is completed by principals and lead health education teachers (Centers for Disease Control and Prevention, 2019).

We merged the YRBS and SHP for 24 states that 1) had representative and weighted data for the 2017-2019 YRBS and 2016-2018 SHP and 2) asked the survey questions about sexual identity and nonmedical prescription opioid use (N=164,420). We then omitted students who had missing data on sexual identity (N=5,993) or missing data for the outcome (N=2,278). The final analytical sample was comprised of 156,149 students from 24 states (Alabama, Arizona, Arkansas, California, Connecticut, Florida, Hawaii, Illinois, Kentucky, Maine, Michigan, Nebraska, Nevada, New Mexico, North Carolina, North Dakota, Ohio, Pennsylvania, Rhode Island, South Carolina, Utah, Vermont, and West Virginia, and Wisconsin). This study was approved by the University of Nevada, Reno's Institutional Review Board.

Measures

Exposures

#### *State Equality Index*

The 2019 Human Rights Campaign's (HRC) State Equality Index (SEI) summarizes statewide laws and policies impacting LGBTQ persons and their families (Warbelow et al., 2020). This index provides an assessment of several different types of laws, including non-discrimination laws, anti-bullying laws, hate crime laws, and anti-conversion therapy laws for each state in the U.S. (Warbelow et al., 2020). States were assigned into the following four

categories based on a scoring of statewide laws and policies that impact LGBTQ people: 1) High priority to achieve basic equality (focus on raising support for basic LGBTQ equality with non-discrimination protections in employment and housing); 2) building equality (building upon initial advancements with safer school policies, protection in healthcare); 3) solidifying equality (ensuring broad implementation of basics laws and advancing laws concerning parenting, youth, and healthcare); and 4) working toward innovative equality (having a range of protections such as safer school policies, non-discrimination laws, and working on advancing innovative legislation) (Warbelow et al., 2020). This categorization considers the presence or absence of laws, the scope of protections offered, and the positive or negative impact to LGBTQ persons (Warbelow et al., 2020). Since the final analytical sample only contained 24 states that were primarily split between the highest and lowest categories, we dichotomized this into low SEI (categories 1 and 2) or high SEI (categories 3 and 4), to account for state-level differences in state's progress toward achieving policies demonstrating equality for LGBTQ persons. This dichotomized measure was also used in a previous study using the SEI to explore multi-level predictors at the state-level among LGBTQ persons (Rodriguez et al., 2020).

### *Supportive School Environment for LGBTQ Youth*

The following measures were assessed individually and summed up to create the supportive school environment for LGBTQ youth: 1) having a GSA or related club; 2) identifying safe spaces; 3) prohibiting harassment; 4) encouraging staff to attend professional

development; 5) facilitating access to providers outside of school for health services; 6) facilitating access to providers outside of school for social and psychological services; and 7) providing curriculum relevant to LGBTQ youth (Centers for Disease Control and Prevention, 2019). Consistent with previous studies using SHP data these measures were aggregated to the state-level, and then averaged, and the mean was centered at 0 (Adams et al., 2020; Coulter et al., 2016; Hatzenbuehler et al., 2014). Scores above 0 indicate characteristics that were higher than the average, while scores below 0 indicate characteristics less than the average (Adams et al., 2020; Coulter et al., 2016; Hatzenbuehler et al., 2014). This measure also had good internal consistency in the sample (Cronbach's  $\alpha=0.91$ ).

#### Outcome (Individual-level)

##### *Lifetime Nonmedical Use of Prescription Opioids (NMUPO)*

The outcome, lifetime NMUPO was assessed using the YRBS question "During your life, how many times have you taken prescription pain medicine without a doctor's prescription or differently than how a doctor told you to use it?" Those indicating 0 times were dichotomized as No and those indicating 1 to 40 or more times were dichotomized as Yes. This dichotomization was done due to sample size among SMY and to ensure comparability to previous studies (Jones et al., 2020; Kaczowski et al., 2022; Watson et al., 2020).

#### Individual-Level Covariates

Similar to previous research and in line with CDC analytical documentation, sexual identity was categorized into lesbian, gay or bisexual, heterosexual (straight), and not sure based on student self-report of sexual orientation (Adams et al., 2020; Centers for Disease Control and Prevention, 2020a). Sexual identity was then recategorized into SMY due to sample size (lesbian, gay or bisexual, and not sure) and non-SMY (heterosexual). Students reporting not sure were included in the SMY group since a previous CDC report showed that the prevalence of NMUPO among not sure students was more in line with SMY than heterosexual youth (Centers for Disease Control and Prevention, 2020b). Since the majority of states do not include a question on gender identity, we were unable to identify transgender students in the sample. Age was categorized as 14 years of age or younger, 15 years old, 16 years old, 17 years old, and 18 years of age or older. Sex was made up of male and female. Race/ethnicity was recategorized into White (non-Hispanic), Black (non-Hispanic), Hispanic, and Other (non-Hispanic), which includes Asian, American Indian/Alaskan Native, Multi-racial, and Other. These race/ethnicity categories were adopted from previous studies using similar categories (Adams et al., 2020; Coulter et al., 2016; Hatzenbuehler et al., 2014).

#### State-Level Covariates

At the state-level, we used publicly available data from the Census Bureau and the National Center for Education Statistics (NCES, n.d.; U.S. Census Bureau, 2021). To account for state-level income inequality, we included the Gini index from the Census Bureau's 2019

American Community Survey as a continuous variable, which is a measure of income dispersion across household incomes, since it has been found that higher income inequality is associated with higher rates of substance misuse (Galea et al., 2007; Lynch et al., 2001; U.S. Census Bureau, 2021). To account for differences in urban and rural settings between states, we also included percentage of urban inhabitants in each state as a continuous variable based on 2010 decennial census data from the Census Bureau, which collects population data every 10 years, since literature suggests that there are school resource disparities between urban and rural areas, especially when it pertains to sexual and gender minority services and behavioral health outcomes (Rand & Pacey, 2021; U.S. Census Bureau, 2022). To account for socio-economic status, we included the 2019 percentage of students eligible for free/reduced lunch at the state-level as a continuous variable from the National Center for Education Statistics, which collects data from educational institutions across the U.S. (NCES, n.d.).

## Analyses

Analyses were conducted in SAS Version 9.4 and STATA Version 16, using procedures recommended by the CDC (Brener et al., 2013). Since data represented 24 different states and across multiple years, data were pooled using procedures that are described elsewhere, which involved incorporating the design effect into the analytic weights, followed by simple random sampling estimation of standard errors to compute standard errors that are adjusted for sample design (Brener et al., 2013; Mustanski et al., 2014).

Weighted descriptive statistics were computed for the overall sample. The prevalence of lifetime NMUPO by individual indicators was also calculated and Chi-squared tests were calculated to show differences in indicators by outcome status. We ran generalized linear mixed models and accounted for clustering at the school- and state-levels. We computed unadjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) for all individual- and state-level indicators stratified by sexual minority status. We then computed adjusted odds ratios (aOR) and corresponding 95% CI between state-level 1) SEI and 2) supportive school environment indicators for LGBTQ youth (summed and individually) with lifetime NMUPO stratified by sexual minority status, adjusting for individual- (age, sex, race/ethnicity), and state-level socio-demographic indicators (Gini index, urbanization percentage, and free/reduced lunch eligibility) characteristics.

## **Results**

Table 1 shows the characteristics of the sample. Briefly, nearly 85% of students reported being heterosexual, followed by bisexual (8%). The sample was mostly White, non-Hispanic (46.2%), followed by Hispanic (25.7%) and about half of the sample was 15-16 years of age (50.7%). Overall, 13.5% of youth reported NMUPO (Table 1).

Table 2 shows the prevalence of NMUPO by individual characteristics. SMY had a higher prevalence of lifetime NMUPO compared to non-SMY (23.2% vs. 11.8%,  $p$ -value $>0.001$ ). Female students had a higher prevalence of lifetime NMUPO compared to males (14.3% vs. 12.5%,  $p$ -

value<0.0001) and Black, non-Hispanic students had the highest prevalence of lifetime NMUPO (14.9%).

As shown in Table 3, SMY in states with high SEI were less likely to report NMUPO compared to SMY in states with low SEI (OR=0.82, 95% CI=0.70-0.96). Among both SMY (OR=0.82, 95% CI=0.70-0.96) and non-SMY (OR=0.95, 95% CI=0.88-0.99) the odds of reporting lifetime NMUPO were lower among students in states with more supportive school environments for LGBTQ youth.

After adjusting for individual- and state-level socio-demographic factors, the relationship between SEI and lifetime NMUPO was no longer statistically significant (aOR=0.92, 95% CI=0.79-1.07). The relationship between supportive school environment and NMUPO persisted after adjustment; SMY in states with more supportive school environments for LGBTQ youth were less likely to report NMUPO (aOR=0.79, 95% CI=0.71-0.89). Among SMY, individual supportive school environments for LGBTQ youth indicators were shown to all be associated with a reduced odds of lifetime NMUPO, most notably LGBTQ-inclusive curricula (aOR=0.37, 95% CI=0.18-0.73). However, the association between supportive school environments for LGBTQ youth and NMUPO was no longer significant for non-SMY (aOR=1.09, 95% CI=0.99-1.19). For non-SMY, only prohibiting harassment was associated with a reduced odds of NMUPO (aOR=0.95, 95% CI=0.91-0.98) (Table 4).

## **Discussion**

The primary objective was to determine whether state equality and LGBTQ supportive school environments are associated with NMUPO among SMY. Before adjustment for individual- and state-level sociodemographic factors, we found that SMY living in states with a high SEI were less likely to report NMUPO compared to those who lived in states with a low SEI. However, after adjustment, this relationship remained protective, but was no longer statistically significant. Previous research that found that individual state policies that provided protections for LGBTQ persons such as anti-bullying and anti-discriminatory practices can reduce substance use among SMY compared to SMY living in states without these practices (Chien et al., 2022; Watson et al., 2021). We expanded upon this by focusing on a more comprehensive measure of a state's climate by incorporating several different laws related to non-discrimination, anti-bullying, hate crimes, and anti-conversion therapy, concurrently. Although key facets of state policies that provide protections for LGBTQ persons, such as anti-bullying or anti-discrimination laws are an important foundation to equity laws to put protections in place for SMY, they have been mentioned by some scholars as merely a first step (Russell et al., 2010). Just because policies have been put in place at the state-level does not necessarily mean that all areas within a state may enforce it to the same standard (Meyer et al., 2019). Although there is promise with these findings, state-level policies alone may not be sufficient to remove disparities based on sexual identity, and additional approaches at the school-level and individual-level may be needed to reduce negative health behaviors among youth (Meyer et al., 2019).

When looking at the supportive school environment, SMY in states with more supportive school environments for LGBTQ youth were less likely to engage in NMUPO. These findings are in line with previous research that found that supportive school environments were associated with reductions in alcohol and illicit substance use among SMY (Coulter et al., 2016; Kaczkowski et al., 2022). When looking more closely at the individual indicators of the supportive school environment, prohibiting harassment on the basis of sexual identity reduced the odds of NMUPO among SMY and non-SMY. While SMY face disparities in regard to bullying and victimization (Goodenow et al., 2016), anti-bullying practices, prohibiting harassment, and fostering more supportive environments that obstruct victimization may benefit all youth regardless of sexual identity (Radliff et al., 2012). Although most schools have anti-bullying policies, some are quite vague, and may not explicitly mention no bullying or harassment on the basis of sexual identity. Expanding anti-bullying and harassment policies to be more inclusive may provide further health benefits to not just SMY, but non-SMY (Meyer et al., 2019).

These findings have implications for substance use prevention within schools. SMY may not be aware of state-level policies that affect them, but do spend much of their time within the school environment. While evidence-based substance use prevention programs that discourage substance use are present in some form in schools across the U.S., the same is not true for LGBTQ inclusive curricula (Kumar et al., 2013; Warbelow et al., 2020). LGBTQ inclusive curricula instructional materials include content on sexual orientation and gender identity, family structure, history, and includes representation by LGBTQ persons (Snapp et al., 2015). In

this study, it was found that LGBTQ inclusive curricula were associated with a reduced odds of NMUPO among SMY. Schools should focus on supporting SMY by incorporating LGBTQ inclusive curricula within substance use prevention programming, since making the content more relevant and impactful to them may reduce some of the disparities SMY may face in regard to substance use (Russell et al., 2021). There is still work that needs to be done in this area, since some states still restrict the inclusion of relevant topics for LGBTQ youth in schools (Warbelow et al., 2020). However, focusing on school-level factors is important during a time when many states are moving toward less supportive policies for LGBTQ persons at the state-level that may negatively affect SMY (Warbelow et al., 2020).

### Limitations

The findings of this study are subject to a few limitations. This was a cross-sectional study, and it is difficult to ascertain if the main exposures of SEI and supportive school environment preceded the outcome of lifetime NMUPO question, so we cannot infer causality. Additionally, this study included states that had representative data for the YRBS and SHP, and asked the sexual identity and nonmedical use of prescription opioids YRBS questions, so findings are only generalizable to these particular states used in the study.

Students indicating not sure of their sexual identity were included in the SMY group. While students may have been unsure of their sexual identity, some students may not have

known what the question asked. Additionally, we were only able to assess sexual identity since very few states in the sample ask the YRBS question on gender identity.

The SEI measure was created by the HRC based on their review of the policies within a state. Although the SEI took into account many policies that impact LGBTQ persons, there may have been other policies that were missed, which may have also influenced NMUPO. Also, we dichotomized the measure due to small sample size and to be consistent with previous studies, but this may have led to misclassification of state equality and may partially explain the null findings in the fully adjusted model.

Finally, it is important to note that SHP data is reported by principals and lead health teachers. Students may not have known services or policies were in place at their school, especially if they are younger. Additionally, YRBS and SHP data were not necessarily drawn from the same schools and the LGBTQ supportive school environment measures were aggregated to the state-level, and may not be indicative of what is going on at the school-level. The results reflect state-level averages of school environments and do not capture school-level heterogeneity.

## Conclusion

This study highlights the role state-level and school-level environmental factors play in nonmedical use of prescription opioids. In particular, we found that supportive school environments for LGBTQ youth are associated with a reduced odds of nonmedical use of

prescription opioids among sexual minority youth. Prevention efforts should focus on working to strengthen upstream protective factors to improve health outcomes among sexual minority youth.

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**Table 1. Individual- and state-level indicators, YRBSS 2017-2019 and SHP 2016-2018**

	<b>N=156149</b>	<b>Weighted %</b>
<b>Sociodemographic Indicators</b>		
<b>Individual-level</b>		
<b>Sexual Identity</b>		
Heterosexual	129947	84.9%
Gay or lesbian	4547	2.9%
Bisexual	13307	8.0%
Not Sure	7158	4.2%
<b>Sex</b>		
Male	75748	50.7%
Female	77986	49.3%
<b>Race/Ethnicity</b>		
White, non-Hispanic	84796	46.2%
Black, non-Hispanic	12253	13.4%
Hispanic	30683	25.7%
Other <sup>a</sup> , non-Hispanic	23518	14.7%
<b>Age</b>		
14 years or younger	21187	12.5%
15 years old	41306	24.7%
16 years old	40713	26.0%
17 years old	34667	23.4%
18 years or older	16715	13.4%
<b>Lifetime Nonmedical Use of Prescription Opioids</b>		
Yes	18585	13.5%
No	136084	86.5%
<b>State-level</b>		
	<b>Mean (SD)</b>	<b>Median</b>
Gini Index	46.56 (10.90)	46.90
Urbanization Percentage	73.01 (113.65)	73.85
Percent Eligible for Free/Reduced Lunch	50.32 (67.16)	48.90

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**Protective Environmental Indicators**


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	N	%
<b>State Equality Index<sup>b</sup> (SEI)</b>		
High SEI <sup>c</sup>	61286	38.75%
Low SEI <sup>d</sup>	93673	61.25%
	<b>Mean (SD)</b>	<b>Median</b>
<b>LGBTQ Supportive School Environment<sup>e</sup></b>	5.10 (4.14)	5.08
Gay Straight Alliance	0.61 (1.20)	0.56
Safe Spaces	0.84 (0.58)	0.85
Prohibits harassment	0.97 (0.24)	0.98
Professional Development	0.78 (0.64)	0.78
Health Services	0.64 (0.66)	0.64
Social/Psychological Services	0.69 (0.64)	0.67
LGBTQ-Inclusive Curricula	0.56 (0.99)	0.54

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**SD=Standard Deviation.**

<sup>a</sup>Other Race/Ethnicity includes Asian, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native.

<sup>b</sup>State Equality Index (SEI) was created and based on the type of advocacy that occurs and the presence of statewide laws and policies that impact LGBTQ people.

<sup>c</sup>Low SEI consists of states that were designated as being a high priority to achieve basic equality or building equality.

<sup>d</sup>High SEI consists of states given the designation of solidifying equality and working toward innovative equality.

<sup>e</sup>LGBTQ supportive school environment was summed using 7 continuous measures from the School Health Profiles Principal and Teacher Surveys.

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**Table 2. Individual characteristics associated with lifetime nonmedical use of prescription opioids, YRBSS 2017-2019 and SHP 2016-2018**

	N=18585	Use Weighted %	95% CI	N=136084	No Use Weighted %	95% CI	p-value <sup>a</sup>
<b>Sociodemographic Indicators</b>							
<b>Individual-level</b>							
<b>Sex</b>							
Male	8811	12.51%	11.96, 13.06	66937	87.49%	86.94, 88.03	<.0001
Female	9729	14.29%	13.47, 15.11	68257	85.71%	84.88, 86.53	
<b>Race/Ethnicity</b>							
White, non-Hispanic	8545	12.81%	12.21, 13.42	76251	87.19%	86.58, 87.79	<.0001
Black, non-Hispanic	1855	14.89%	13.87, 15.92	10398	85.11%	84.08, 86.12	
Hispanic	4765	14.62%	13.30, 15.95	25918	85.38%	84.05, 86.70	
Other <sup>b</sup> , non-Hispanic	3046	11.09%	9.89, 12.29	20472	88.91%	87.71, 90.11	
<b>Age</b>							
14 years or younger	2377	12.31%	11.25, 13.38	18810	87.69%	86.62, 88.75	<.0001
15 years old	4714	12.29%	11.39, 13.19	36592	87.71%	86.81, 88.61	
16 years old	5018	13.05%	12.14, 13.96	35695	86.95%	86.03, 87.86	
17 years old	4431	14.98%	14.02, 15.94	30236	85.02%	84.06, 85.98	
18 years or older	2273	14.97%	13.77, 16.18	14442	85.03%	83.82, 86.23	
<b>Sexual Identity</b>							
Sexual minority youth <sup>c</sup>	5375	23.15%	21.59, 24.72	19637	76.85%	75.28, 78.41	<.0001
Non-sexual minority youth <sup>d</sup>	13500	11.78%	11.27, 12.30	116447	88.22%	87.70, 88.73	

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**CI=Confidence Interval**

<sup>a</sup>P-value calculated using Chi-square tests to assess differences in characteristics by lifetime nonmedical use of prescription opioids.

<sup>b</sup>Other Race/Ethnicity includes Asian, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native.

<sup>c</sup>Sexual minority youth includes students reporting a sexual identity of gay, lesbian, bisexual, and not sure.

<sup>d</sup>Non-Sexual minority youth include students reporting a sexual identity of heterosexual.

**Table 3. Unadjusted associations between characteristics and lifetime nonmedical use of prescription opioids by sexual minority status, YRBSS 2017-2019 and SHP 2016-2018**

Sociodemographic Indicators	All Students (N=156149)		Sexual Minority Youth <sup>a</sup> (N=25195)		Non-Sexual Minority Youth <sup>b</sup> (N=130954)	
	OR	95% CI	OR	95% CI	OR	95% CI
<b>Individual-level</b>						
<b>Sex</b>						
Male (ref)	1.00	-	1.00	-	1.00	-
Female	<b>1.16</b>	<b>1.09, 1.25</b>	0.97	0.84, 1.12	<b>1.08</b>	<b>1.01, 1.17</b>
<b>Race/Ethnicity</b>						
White, non-Hispanic (ref)	1.00	-	1.00	-	1.00	-
Black, non-Hispanic	<b>1.19</b>	<b>1.09, 1.30</b>	1.16	0.97, 1.39	<b>1.15</b>	<b>1.03, 1.27</b>
Hispanic	<b>1.17</b>	<b>1.07, 1.28</b>	0.98	0.82, 1.18	<b>1.21</b>	<b>1.09, 1.34</b>
Other <sup>c</sup> , non-Hispanic	<b>0.85</b>	<b>0.76, 0.96</b>	<b>0.70</b>	<b>0.56, 0.88</b>	0.88	0.77, 1.02
<b>Age</b>						
14 years or younger (ref)	1.00	-	1.00	-	1.00	-
15 years old	1.01	0.88, 1.14	0.95	0.74, 1.21	1.03	0.89, 1.20
16 years old	1.07	0.94, 1.21	0.98	0.77, 1.25	1.11	0.96, 1.29
17 years old	<b>1.25</b>	<b>1.11, 1.42</b>	1.16	0.91, 1.47	<b>1.31</b>	<b>1.13, 1.52</b>
18 years or older	<b>1.26</b>	<b>1.09, 1.44</b>	1.29	0.99, 1.68	<b>1.26</b>	<b>1.07, 1.49</b>
<b>State-level<sup>d</sup></b>						
Gini Index	1.04	0.99, 1.09	1.02	0.94, 1.10	1.05	0.98, 1.12
Urbanization Percentage	<b>0.94</b>	<b>0.91, 0.98</b>	<b>0.87</b>	<b>0.80, 0.94</b>	0.97	0.93, 1.02
Percent Eligible for Free/Reduced Lunch	<b>1.12</b>	<b>1.07, 1.17</b>	<b>1.09</b>	<b>1.01, 1.19</b>	<b>1.11</b>	<b>1.06, 1.17</b>
<b>Environmental Indicators</b>						
<b>State Equality Index<sup>e</sup> (SEI)</b>						
High SEI <sup>f</sup>	0.97	0.89, 1.05	<b>0.82</b>	<b>0.70, 0.96</b>	1.01	0.92, 1.11
Low SEI <sup>g</sup> (ref)	<b>1.00</b>	-	<b>1.00</b>	-	<b>1.00</b>	-

<b>LGBTQ Supportive School Environment<sup>d,h</sup></b>	<b>0.90</b>	<b>0.86, 0.95</b>	<b>0.79</b>	<b>0.72, 0.87</b>	<b>0.95</b>	<b>0.88, 0.99</b>
Gay Straight Alliance	<b>0.93</b>	<b>0.89, 0.97</b>	<b>0.82</b>	<b>0.76, 0.90</b>	0.96	0.91, 1.01
Safe Spaces	<b>0.91</b>	<b>0.87, 0.95</b>	<b>0.81</b>	<b>0.74, 0.87</b>	<b>0.94</b>	<b>0.89, 0.99</b>
Prohibits harassment	<b>0.91</b>	<b>0.89, 0.94</b>	<b>0.89</b>	<b>0.85, 0.94</b>	<b>0.92</b>	<b>0.89, 0.95</b>
Professional Development	<b>0.91</b>	<b>0.87, 0.94</b>	<b>0.83</b>	<b>0.76, 0.90</b>	<b>0.93</b>	<b>0.88, 0.97</b>
Health Services	<b>0.91</b>	<b>0.87, 0.96</b>	<b>0.80</b>	<b>0.73, 0.88</b>	0.95	0.90, 1.01
Social/Psychological Services	<b>0.92</b>	<b>0.88, 0.97</b>	<b>0.81</b>	<b>0.73, 0.88</b>	<b>0.96</b>	<b>0.91, 1.02</b>
LGBTQ-Inclusive Curricula	<b>0.53</b>	<b>0.40, 0.70</b>	<b>0.24</b>	<b>0.14, 0.43</b>	<b>0.64</b>	<b>0.46, 0.89</b>

**OR=odds ratio. CI=confidence interval.**

<sup>a</sup>Sexual minority youth includes students reporting a sexual identity of gay, lesbian, bisexual, and not sure.

<sup>b</sup>Non-Sexual minority youth include students reporting a sexual identity of heterosexual.

<sup>c</sup>Other Race/Ethnicity includes Asian, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native.

<sup>d</sup>For continuous measures, odds ratio (OR) represents a 1-unit increase.

<sup>e</sup>State Equality Index (SEI) was created and based on the type of advocacy that occurs and the presence of statewide laws and policies that impact LGBTQ people.

<sup>f</sup>High SEI consists of states given the designation of solidifying equality and working toward innovative equality.

<sup>g</sup>Low SEI consists of states that were designated as being a high priority to achieve basic equality or building equality.

<sup>h</sup>LGBTQ Supportive environment was summed using 7 measures from the School Health Profiles Principal and Teacher Surveys and the average centered at 0.

**Table 4. Adjusted associations between environmental indicators and lifetime nonmedical use of prescription opioids by sexual minority status, YRBSS 2017-2019 and SHP 2016-2018**

Environmental Indicators	All Students (N=156149)		Sexual Minority Youth <sup>a</sup> (N=25195)		Non-Sexual Minority Youth <sup>b</sup> (N=130954)	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
<b>State Equality Index<sup>c</sup></b>						
High SEI <sup>d</sup>	1.05	0.98, 1.13	0.92	0.79, 1.07	1.09	0.99, 1.19
Low SEI <sup>e</sup>	<b>1.00</b>	-	<b>1.00</b>	-	<b>1.00</b>	-
<b>LGBTQ Supportive School Environment<sup>f,g</sup></b>	0.94	0.89, 1.00	<b>0.79</b>	<b>0.71, 0.89</b>	0.98	0.92, 1.05
Gay Straight Alliance	0.96	0.92, 1.01	<b>0.84</b>	<b>0.76, 0.93</b>	0.99	0.95, 1.06
Safe Spaces	0.96	0.90, 1.02	<b>0.80</b>	<b>0.71, 0.90</b>	0.99	0.94, 1.07
Prohibits harassment	<b>0.94</b>	<b>0.91, 0.97</b>	<b>0.93</b>	<b>0.87, 0.99</b>	<b>0.95</b>	<b>0.91, 0.98</b>
Professional Development	<b>0.94</b>	<b>0.91, 0.99</b>	<b>0.86</b>	<b>0.78, 0.95</b>	0.96	0.91, 1.02
Health Services	<b>0.92</b>	<b>0.88, 0.97</b>	<b>0.79</b>	<b>0.72, 0.88</b>	0.96	0.91, 1.02
Social/Psychological Services	0.96	0.92, 1.01	<b>0.84</b>	<b>0.76, 0.92</b>	1.00	0.95, 1.06
LGBTQ-Inclusive Curricula	0.87	0.63, 1.21	<b>0.37</b>	<b>0.18, 0.73</b>	1.04	0.72, 1.52

aOR=adjusted odds ratio. CI=confidence interval.

<sup>a</sup>Sexual minority youth includes students reporting a sexual identity of gay, lesbian, bisexual, and not sure.

<sup>b</sup>Non-Sexual minority youth include students reporting a sexual identity of heterosexual.

<sup>c</sup>State Equality Index (SEI) was created and based on the type of advocacy that occurs and the presence of statewide laws and policies that impact LGBTQ people.

<sup>d</sup>High SEI consists of states given the designation of solidifying equality and working toward innovative equality.

<sup>e</sup>Low SEI consists of states that were designated as being a high priority to achieve basic equality or building equality.

<sup>f</sup>For continuous measures, odds ratio (OR) represents a 1-unit increase.

<sup>g</sup>LGBTQ Supportive environment was summed using 7 measures from the School Health Profiles Principal and Teacher Surveys and the average centered at 0.

## Chapter 3

### **Adverse childhood experiences, stressful life events, and marijuana use during pregnancy: A population-based study**

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**Abstract:**

**Introduction:** Cumulative exposure to adverse childhood experiences (ACEs) and stressful life events (SLEs) are independently associated with marijuana use during pregnancy. However, research has not explored how both exposures may influence marijuana use concurrently. Assessing the joint effects of ACEs and recent SLEs on marijuana use can identify people who may benefit from early interventions addressing these exposures.

**Methods:** Data come from the Nevada Pregnancy Risk Assessment Monitoring System, 2017-2020 (N=2483). We assessed eight measures of ACEs before age 18 and fourteen measures of SLEs twelve months before birth. Generalized estimating equations estimated the direct and joint effects (additive and multiplicative scales) of ACEs and SLEs on marijuana use during pregnancy.

**Results:** 9.8% used marijuana during most recent pregnancy. Compared to people who reported no ACEs, those reporting 1 ACE (adjusted prevalence ratio[aPR]= 1.96, 95% confidence interval[CI]=1.30-2.94), 2 ACEs (aPR=1.53, 95%CI=0.80-2.96), 3 ACEs (aPR=3.58, 95%CI=2.69-4.77), and 4+ ACEs (aPR=3.67, 95%CI=2.36-5.72) were more likely to use marijuana. Compared to people reporting no SLEs, those reporting 1 SLE (aPR=0.68, 95%CI=0.30-1.50), 2 SLEs (aPR=1.93, 95%CI=0.80-4.70), 3 SLEs (aPR=1.65, 95%CI=0.42-6.53), and 4+ SLEs (aPR=3.12, 95%CI=1.64-5.92) were more likely to use marijuana. There was evidence of interaction for high ACE and SLE exposure on an additive scale.

**Conclusions:** ACEs and SLEs were associated with marijuana use during pregnancy, and there was evidence of additive interaction. Screening of ACEs and SLEs during pregnancy, referrals to behavioral health services if needed, and healthcare providers taking a trauma-informed approach are important to address marijuana use during pregnancy.

**Keywords:** childhood adversity, stress, marijuana, pregnancy

## **Introduction**

Research indicates that marijuana use during pregnancy is associated with several potential negative health outcomes, such as more admissions to neonatal intensive care, premature birth, and low birth weight of the infant (Grzeskowiak et al., 2020; Mark et al., 2016; Nashed et al., 2020; Sarrafpour et al., 2020). Current evidence demonstrating harm on the fetus is not as strong as other substances such as alcohol and opioid use, but emerging research shows that prenatal marijuana use adversely affects infant development and contributes to visual problem solving, hand-eye coordination, and other developmental problems (De Moraes Barros et al., 2008; Goldschmidt et al., 2000; National Academics of Sciences, 2017; Richardson et al., 2002; Sarmah et al., 2020). Although the American Academy of Pediatrics recommends people who are pregnant or breastfeeding to avoid marijuana use, the prevalence of marijuana use has been increasing in the U.S., from 4.7% in 2018 to 8% in 2020 among pregnant people aged 15 to 44 (Ryan et al., 2018; SAMHSA, 2022).

Several recent changes in the policy environment and norms around marijuana use may explain increasing prevalence of use during pregnancy. Marijuana has been legalized for recreational use in 18 states as of 2021, and a recent study found that legalization was associated with increases in maternal use before and shortly after pregnancy (Hanson, 2021; Skelton et al., 2021). It has been suggested that recreational legalization of marijuana may lead to greater social acceptance of marijuana due to increasing availability and ease of access, which may promote its use (Budney & Borodovsky, 2017). Researchers have found that pregnant people who reported using marijuana perceived less risk, less knowledge of potential adverse consequences, and an increase in perceived therapeutic benefits, compared to those who did not use marijuana during pregnancy (Weisbeck et al., 2020). Studies have also shown that pregnant people may use marijuana to reduce the effects of morning sickness, as well as a coping mechanism to address stressors, both pregnancy-related and from other aspects of their life, which may also partially explain the recent increase in marijuana use (Vanstone et al., 2022).

One such stressor is adverse childhood experiences (ACEs), which are potentially traumatic events occurring before the age of 18, and include such things as childhood abuse and household dysfunction (Felitti et al., 2019). Recent research suggests that ACEs are associated with marijuana use during pregnancy, with studies finding that pregnant people reporting higher ACE scores are more likely to use marijuana compared to those reporting no ACEs (Jasthi et al., 2021; Klasner et al., 2022; Osofsky et al., 2021; Testa et al., 2022a). However,

most of these studies focused on smaller, specific populations of pregnant people, such as those receiving prenatal care, receiving care at one hospital, or low-income populations (Jasthi et al., 2021; Klasner et al., 2022; Osofsky et al., 2021). One recent population-based study also reported that pregnant people reporting higher ACE scores are more likely to use marijuana compared to those reporting no ACEs, but did not adequately control for confounding variables such as pregnancy intention, health insurance during pregnancy, and prenatal cigarette use (Testa et al., 2022a).

Antenatal stressful life events (SLEs) are major life events that commonly occur among pregnant people prior to birth that may cause harm or stress to an individual such as having financial issues, divorce or difficulties with a partner, and death of a spouse (Allen et al., 2020). Recent attention has been placed on studying the relationship between SLEs and substance use during pregnancy, with studies finding associations between SLEs and substance use during pregnancy in the form of alcohol, cigarettes, e-cigarettes, opioids, and marijuana (Allen et al., 2019; Allen et al., 2020; Esper et al., 2019; Testa et al., 2021; Testa et al., 2022b). One recent study found that pregnant people reporting high cumulative SLE scores were more likely to use marijuana during pregnancy compared to those who reported no SLEs (Allen et al., 2020). However, this study did not adjust for pregnancy intention, and adjusted for marital status, which is an SLE (Allen et al., 2020).

Although research has found that ACEs and SLEs are associated with marijuana use among pregnant people, limited research has assessed the effect of these factors jointly in

analyses for substance use behaviors (Buehler et al., 2022). ACEs occur during childhood and have the ability to have a negative influence on health, which can further exacerbate SLEs that occur later in life (Buehler et al., 2022). In line with a life course approach, childhood is a sensitive developmental period in a person's life that plays a critical role in shaping a person's future life trajectory (McLaughlin et al., 2010). During childhood, exposure to child abuse and neglect may negatively affect child development and weaken their response to chronic stressors (Felitti et al., 1998). Prolonged exposure and response to stressors may lead to self-medicating substance use behaviors in later life (Felitti et al., 1998). During pregnancy, which can be considered a sensitive life period, stressful events may affect a pregnant person differently than when it occurs outside this sensitive period, potentially leading to substance use behaviors such as marijuana use to cope with these stressors (Kuh et al., 2003; Mishra et al., 2010). This effect may be further exacerbated due to previous exposure to childhood adversity (McLaughlin et al., 2010). Stress sensitization theory suggests that childhood adversity reduces an individual's ability to cope in adulthood, causing a worse reaction toward subsequent stressful events (Stroud, 2018). Individuals who experience childhood adversity may be more sensitive to future stressors during sensitive periods, increasing their risk for substance use-related outcomes (Harkness & Hayden, 2018). Consideration of recent SLEs within the context of childhood adversity is important to prevent substance use during pregnancy since prior traumas play a pivotal role in shaping how individuals cope with current stress (Osofsky et al., 2021). Since pregnancy is a sensitive life period, assessing the joint effects

of ACEs and recent SLEs on marijuana use can identify people who may benefit from early interventions that address these exposures. Using Nevada Pregnancy Risk Assessment Monitoring System (PRAMS) population-based data from 2017-2020, we propose to 1) explore the direct effects of ACEs and SLEs on marijuana use during pregnancy and 2) examine the joint effects of ACEs and SLEs on marijuana use during pregnancy.

## **Methods**

### **Study Design**

The Nevada Pregnancy Risk Assessment Monitoring System (PRAMS) is a state and CDC co-sponsored population-based surveillance system that collects information on maternal attitudes and behaviors before, during, and shortly after pregnancy (Centers for Disease Control and Prevention, 2019). Nevada's first data collection beginning in 2017 utilizing both paper and telephone surveys, and additional information about the survey is described elsewhere (Centers for Disease Control and Prevention, 2019). To account for the complex survey design, PRAMS data undergoes a weighting process that takes into consideration the state's sampling frame, nonresponse, and noncoverage components to create an analysis weight. This analysis weight takes into account the stratified sample, the tendency for people with certain characteristics to respond at lower rates, and to adjust for what a typical number of births each year would be in the state (Centers for Disease Control and Prevention, 2019). In Nevada, marijuana was legalized for recreational use beginning January 2017, with the first dispensaries

opening in July 2017. This cross-sectional study combined Nevada PRAMS data from 2017-2020, with 2017 being a partial year with birth certificates from August 2017 (N=2635). Similar to previous studies, we dropped those having multiple infants born (N=42), missing the outcome variable (N=58), and missing ACEs and/or SLEs (N=52) (Testa et al., 2022a). The final analytical sample contained 2483 people. The average response rate across years was 40%. This study received IRB approval from the University of Nevada, Reno.

## Measures

### Outcome

Marijuana use during pregnancy, was operationalized using the question, “During your most recent pregnancy, did you take or use any of the following drugs for any reason?” People were asked to check a box denoting whether or not they used “Marijuana or hash.” Responses were dichotomized as yes or no. This question is one of the standard core questions created by CDC for all states, first asked beginning in June 2016, and has been demonstrated to be both reliable and valid (Ko et al., 2020). People were informed before answering substance use questions that all their answers would remain strictly confidential.

### Exposures

#### Adverse Childhood Experiences (ACEs)

Adverse childhood experiences (ACEs) were measured using state-added questions adapted from the Behavioral Risk Factor Surveillance System (BRFSS) ACEs module (Centers for Disease Control and Prevention, 2020). Eleven questions generated eight ACE measures: 1) emotional abuse, 2) physical abuse, 3) sexual abuse, 4) intimate partner violence, 5) substance abuse in the household, 6) mental illness in the household, 7) parental separation or divorce, and 8) incarcerated household member (Appendix I). Responses were all dichotomized into yes or no, with exception of witnessing intimate partner violence, emotional abuse, physical abuse, and sexual abuse which were categorized “yes” if it occurred sometimes or most of the time. Individual ACEs were summed up to create a total ACE score. For analyses assessing direct effects, ACEs were categorized into 0, 1, 2, 3, and 4+ ACEs as done previously in other studies (Felitti et al., 1998; Racine et al., 2018). For interaction analyses, ACEs were dichotomized into high ACE exposure (3 or more ACEs) and low ACE exposure (0-2 ACEs) (Julian et al., 2017).

#### Stressful Life Events (SLEs)

Fourteen stressful life events (SLEs) during the 12 months before birth were assessed using a subset of the Modified Life Events Inventory (Newton et al., 1979). This question was preceded with “This question is about things that may have happened during the 12 months before your new baby was born. For each item, check no if it did not happen to you or yes if it did. (It may help to look at the calendar when you answer these questions)” (Allen et al., 2020). A list of these fourteen events can be found in Appendix II. SLEs were assessed individually and

similarly to other studies, categorized into 0, 1, 2, 3, and 4+ (Allen et al., 2020). For interaction analyses, SLEs were dichotomized into high SLE exposure (4 or more SLEs) and low SLE exposure (0-3 SLEs) based on their distribution.

### Covariates

Demographic characteristics used in analyses include age (<20, 20-29, 30+), race/ethnicity (non-Hispanic White, Hispanic, non-Hispanic Other: includes non-Hispanic Alaskan native, American Indian, Asian, Black or African American, Hawaiian/Other Pacific Islander, other non-White race, or mixed race), and highest level of education attained (less than high school, high school/some college, college graduate or higher). Additionally, we also controlled for health insurance (Medicaid, Private/Other Insurance, and None), previous pregnancy (yes/no), pregnancy intention (intended vs. unintended/mistimed), cigarette use 3 months prior to pregnancy (yes/no), and rurality using the U.S. Census Bureau definition (urban/rural) (US Census Bureau, 2023).

### Analyses

Weighted Chi-square and 95% confidence intervals (CI) were calculated to assess differences in characteristics between those who used marijuana and those who did not use marijuana during pregnancy. Weighted generalized estimating equations with unstructured correlation and robust variance estimators were used to calculate adjusted prevalence ratios

(aPR) and corresponding 95% CI, accounting for the complex sampling frame, nonresponse, and noncoverage of the survey (Centers for Disease Control and Prevention, 2019). All models were adjusted for age, race/ethnicity, highest level of education, smoked cigarettes 3 months before pregnancy, health insurance, previous pregnancy, pregnancy intention, and rurality. To assess aim 1, we first explored the direct effect of ACE score on marijuana use during pregnancy. We then explored the direct effect of SLE score on marijuana use during pregnancy.

To assess aim 2, interaction analyses were conducted to measure the interactive influence of ACEs and current SLEs on marijuana use during pregnancy on both the multiplicative and additive scales (VanderWeele & Knoll, 2014). The fully adjusted model for the multiplicative interaction included high ACE exposure, high SLEs, and an interaction term for the two (i.e. high ACE exposure + high SLEs + high ACE exposure\*high SLEs). Relative excess risk due to interaction (RERI) was used to translate multiplicative interaction measures to the additive scale, and corresponding 95% confidence intervals were calculated using the delta method (Hosmer & Lemeshow, 1992; VanderWeele & Knoll, 2014). The delta method estimates the risk ratio based off of the prevalence ratio, and is used to estimate interaction on the additive scale when risks cannot be directly calculated (Hosmer & Lemeshow, 1992).

Overall, the amount of missing data for individual measures was well below 5%, with highest level of education (2.5%) having the greatest amount of missing data. We used Little's test to assess whether data were missing completely at random (Li, 2013). The test was significant, therefore we conducted multiple imputation using chained equations using the fully

conditional method; twenty imputations were performed (White et al., 2011). All analyses were conducted utilizing SAS Version 9.4 and a p-value < 0.05 was used as a cutoff for significance.

## Results

The characteristics of the sample can be found in Table 1. Briefly, over half the sample was above the age of 30 (52.1%), White, non-Hispanic (38.3%), and had a high school degree or some post high school education (60.8%). The prevalence of marijuana use during most recent pregnancy was 9.8%. In our sample, 64.4% reported at least one ACE, with 30% reporting 3 or more ACEs. For SLEs, 71.4% reported at least one past year SLE, with 30% reporting 3 or more SLEs. There was a graded relationship observed, where the prevalence of marijuana use increased with an increase in ACE score (0 ACEs=4.0%, 1 ACE=7.5%, 2 ACEs=6.0%, 3 ACEs=15.6%, and 4+ ACEs=21.5%, p-value<0.001). There was also an increasing prevalence of marijuana use with an increase in SLE score (0 SLEs=4.2%, 1 SLE=3.6%, 2 SLEs=16.0%, 3 SLEs=9.9% and 4+ SLEs=25.1%, p<0.001).

The prevalence of marijuana use for all characteristics is shown in Table 2. The prevalence of marijuana use was higher among people <24 years old (16.2%) compared to those who were 25-29 years old (10.4%) and 30+ years old (7.2%) (p<0.001). Prevalence of marijuana use was higher among those who had Medicaid insurance during their most recent pregnancy compared to private/other insurance (18.5% vs. 5.3%, p<0.0001), and those who had an unintended/mistimed pregnancy compared to those who intended to become pregnant

(12.1% vs. 6.0%,  $p < 0.001$ ). Prevalence of marijuana use was higher among those reported smoking cigarettes 3 months before pregnancy compared to those who did not (35.8% vs. 8.2%,  $p < 0.0001$ ).

*Aim 1: Explore the direct effects of ACEs and SLEs on marijuana use during pregnancy*

Table 3 shows the adjusted prevalence ratios (aPR) for ACEs, SLEs, and marijuana use during pregnancy. People who reported 3 ACEs (aPR=3.58, 95% CI=2.69-4.77) and 4 or more ACEs (aPR=3.67, 95% CI=2.36-5.72) were more likely to use marijuana during their most recent pregnancy compared to those who reported 0 ACEs. As for SLEs, people reporting 4+ SLEs (aPR=3.12, 95% CI=1.64-5.92) were more likely to use marijuana during their most recent pregnancy compared to those who reported 0 SLEs.

*Aim 2: Examine the joint effects of ACEs and SLEs on marijuana use during pregnancy.*

Table 4 shows the results of the interaction analyses. After adjusting for age, race/ethnicity, highest level of education, smoked cigarettes 3 months before pregnancy, health insurance, previous pregnancy, pregnancy intention, and rurality, there was evidence of interaction on the additive scale (RERI=2.06, 95% CI=1.09-3.04,  $p$ -value=0.0003). There was no evidence of interaction for ACEs and SLEs observed on the multiplicative scale. However, there was a high prevalence of marijuana use among pregnant people who reported high ACE and

high SLE scores compared to pregnant people who reported low ACE and low SLEs (aPR=5.39, 95% CI=4.30, 6.75).

## **Discussion**

The purpose of this study was to assess the direct association of ACEs and SLEs with marijuana use during pregnancy and to determine if ACEs and SLEs interact to increase risk for marijuana use during pregnancy. We found that people who reported higher exposure to ACEs or SLEs were more likely to use marijuana during their most recent pregnancy compared to those who reported no ACEs or SLEs. Our findings are consistent with previous studies that also found that these exposures were associated with marijuana use during pregnancy (Allen et al., 2020; Testa et al., 2022a).

To our knowledge, this was the first study to assess the joint effects of ACEs and SLEs on marijuana use during pregnancy. We found evidence of additive interaction for ACEs and SLEs and their relationship with marijuana use consistent with the stress sensitization theory, which posits that childhood adversity may reduce their ability to manage stressors occurring in the future (Stroud, 2018). This reduced ability to cope with stress may lead to the use of marijuana during pregnancy to self-medicate during this sensitive life period (Kuh et al., 2003). Additive interaction has important public health implications, since it can show which subgroups can benefit the most from interventions for a particular health outcome (VanderWeele & Knol,

2014). People reporting high ACE and high SLE exposure have a high prevalence of marijuana use compared to those with low ACE and low SLE exposure, so have the most to gain from early interventions to mitigate use. Screening for ACEs and SLEs early in the pregnancy during the prenatal care visit can identify at-risk people, and referrals to resources may help prevent marijuana use during pregnancy.

### Limitations

The limitations of this study need to be acknowledged. First, the survey did not ask a question about marijuana use before pregnancy, so we were unable to determine if pregnant people began use during pregnancy or used prior to pregnancy and continued use. This may have some influence on the internal validity of the study since we cannot say for certain if all people began use in pregnancy or used prior to pregnancy and just continued use. We believe the findings for the direct of effects and interactions of both exposures on marijuana use may be slightly overestimated. However, we believe this influence to be minimal since previous research has found that most women (>80%) stop using marijuana during pregnancy (Klasner et al., 2022; Mark et al., 2020; Volkow et al., 2017). Third, there is the possibility of dependent error since people who are willing to report ACEs or SLEs may be more willing to report marijuana use during pregnancy. Additionally, substance use questions asked to pregnant people may be sensitive, with some mothers fearing to disclose due to the possibility of the state getting access to their answers and involving Child Protective Services. Participants who

used marijuana may have feared to disclose, and since those who used marijuana were also more likely to report high exposure to ACEs and SLEs, this may have resulted in differential misclassification, which may have underestimated our measure of effect. However, people completing the survey were reminded before each of these sections that their answers will remain private and be strictly confidential. Next, the results of this study are generalizable only to the population of pregnant people who gave birth in Nevada from 2017-2020, during a time period when recreational sales first began. Next, the PRAMS survey did not ask about the severity of the stressful life event, so we were unable to determine if they were positive or negative (i.e. moving addresses to a larger home may be seen as positive). Lastly, the survey did have a low response rate that averaged around 40% for the years of data included in this study, which was under the CDC's required response rate threshold of 55%.

### **Implications for Practice and/or Policy**

We found evidence of additive interaction of ACEs and SLEs on marijuana use during recent pregnancy, which has important implications for prevention at the population-level. Healthcare providers can screen pregnant people for ACEs and SLEs early on and throughout the pregnancy and take the necessary actions to provide trauma-informed care and connect patients to behavioral health services if needed (Racine et al., 2021; Sperlich et al., 2017). Trauma informed care is best described as when providers understand trauma, recognize the signs of trauma, integrate knowledge trauma knowledge in practice and policies, and resist re-

traumatization of patients (SAMHSA, 2020). Healthcare providers play an integral role in the care of pregnant people, and there is a great need to integrate regular screenings of ACEs and SLEs into maternity care to mitigate their associated substance use and mental health outcomes (Sperlich et al., 2017). Screening for ACEs and SLEs during prenatal care presents an opportunity to identify pregnant people who have experienced early adversity or who might be experiencing recent stressful life events (Racine et al., 2021). Although there is evidence that screening for ACEs or SLEs is feasible in a prenatal care setting, there is the potential risk for harm due to re-traumatization, but this can be reduced by training providers in trauma informed care (Finkelhor, 2018; Flanagan et al., 2018; Racine et al., 2018; SAMHSA, 2020).

Approximately 10% of participants in the study used marijuana during their most recent pregnancy, which highlights the importance of universal screening of all pregnant people. The Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommend regular, universal screening of all pregnant people for substance use using an evidence-based approach of screening, brief intervention, and referral to treatment (SBIRT) (Wright et al., 2016). Screening for substance use can be done beginning at the first prenatal care visit, and throughout the term of the pregnancy as needed (Wright et al., 2016). If the pregnant person has no history of substance use and reports substance use during pregnancy, brief advice can be given about the potential harms of these substances on the pregnant person and infant (Wright et al., 2016). A patient-centered brief intervention can be conducted if the pregnant person has a history of substance use before pregnancy to listen and

understand why they are using, provide feedback, and explore options to address reasons for substance use during pregnancy (Wright et al., 2016). If necessary, the pregnant person may be referred to treatment if it is highly likely they have a substance use disorder, which should be done preferably through a warm handoff (Wright et al., 2016).

### **Conclusions**

In our sample, ACEs and SLEs were shown to be associated with marijuana use during pregnancy and there was evidence of interaction on the additive scale. Screening of ACEs and SLEs during pregnancy, referrals to behavioral health services if needed, and healthcare providers taking a trauma-informed care approach are important to address marijuana use during pregnancy.

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**Table 1. Demographic characteristics of sample, Nevada PRAMS 2017-2020 (N=2483)**

	<b>N</b>	<b>Weighted %</b>
<b>Age</b>		
<24	435	18.7
25-29	715	29.2
30+	1333	52.1
<b>Race/Ethnicity</b>		
White	1252	38.3
Hispanic	823	37.8
Other <sup>a</sup>	399	23.9
<b>Education Level</b>		
Less than H.S.	275	15.8
H.S. degree/some post-H.S.	1471	60.8
College graduate	677	23.4
<b>Previous Live Birth</b>		
Yes	1523	60.3
No	960	39.7
<b>Pregnancy Intention</b>		
Intended	998	37.0
Not Intended/Mistimed	1485	63.0
<b>Rurality</b>		
Urban	1816	90.8
Rural	667	9.2
<b>Medical Insurance for recent pregnancy</b>		
Medicaid	817	35.4
Private/Other	1561	59.4
None	105	5.2
<b>Prenatal care visit during first trimester</b>		
Yes	1948	80.9
No	535	19.1

<b>Smoked cigarettes 3 months before pregnancy</b>		
Yes	140	4.7
No	2306	95.3
<b>ACE Score</b>		
0	866	35.6
1	504	19.4
2	322	13.7
3	255	9.8
4+	536	21.4
<b>SLE Score</b>		
0	738	28.6
1	591	23.8
2	432	16.6
3	265	11.1
4+	457	19.9
<b>Marijuana Use During Most Recent Pregnancy</b>		
Yes	214	9.8
No	2269	90.2

<sup>a</sup>Other Race includes Asian, Black, Native Hawaiian and Pacific Islander, and American Indian/Alaskan Native.

**Table 2. Prevalence of marijuana use during pregnancy by characteristics, Nevada PRAMS 2017-2020 (N=2483)**

	Marijuana Use			No Marijuana Use			p-value
	N=214	Weighted %	95% Confidence Interval	N=2269	Weighted %	95% Confidence Interval	
<b>Age</b>							<b>0.0005</b>
<24	61	16.2	11.2, 21.3	374	83.8	78.7, 88.8	
25-29	68	10.4	7.3, 13.6	647	89.6	86.4, 92.7	
30+	85	7.2	5.2, 9.2	1248	92.8	90.8, 94.8	
<b>Race/Ethnicity</b>							<b>&lt;0.0001</b>
White	122	11.6	8.8, 14.4	1130	88.4	85.6, 91.2	
Hispanic	42	4.9	3.1, 6.8	781	95.1	93.2, 96.9	
Other <sup>a</sup>	47	14.0	9.5, 18.4	352	86.0	81.6, 90.5	
<b>Education Level</b>							<b>&lt;0.0001</b>
Less than H.S.	35	11.7	6.9, 16.5	240	88.3	83.5, 93.1	
H.S. degree/some post-H.S.	159	12.2	9.8, 14.6	1312	87.8	85.4, 90.2	
College graduate	15	3.0	1.1, 4.9	662	97.0	95.0, 99.0	
<b>Previous Live Birth</b>							0.5884
Yes	134	9.5	7.3, 11.6	1389	90.5	86.7, 92.4	
No	80	10.4	7.6, 13.3	880	89.6	88.4, 92.7	
<b>Pregnancy Intention</b>							<b>0.0005</b>
Intended	58	6.0	3.9, 8.1	940	94.0	91.9, 96.1	
Not Intended/Mistimed	156	12.1	9.7, 14.5	1329	87.9	85.5, 90.3	
<b>Rurality</b>							0.4321
Urban	154	9.7	7.8, 11.6	1662	90.3	88.4, 92.1	
Rural	60	11.1	8.0, 14.2	607	88.9	85.8, 92.0	
<b>Medical Insurance for recent pregnancy</b>							<b>&lt;0.0001</b>
Medicaid	144	18.5	14.8, 22.2	673	81.5	77.8, 85.2	

Private/Other	67	5.3	3.6, 7.0	1494	94.7	93.0, 96.4	
None	3	2.7	0.1, 7.3	102	97.3	92.7, 99.8	
<b>Prenatal care visit during first trimester</b>							0.8218
Yes	152	9.7	7.8, 11.7	1796	90.3	88.3, 92.2	
No	62	10.2	6.5, 14.0	473	89.8	86.0, 93.5	
<b>Smoked cigarettes 3 months before pregnancy</b>							<b>&lt;0.0001</b>
Yes	40	35.8	23.4, 48.2	100	64.2	51.8, 76.6	
No	161	8.2	6.6, 9.8	2145	91.8	90.2, 93.4	
<b>ACE Score</b>							<b>&lt;0.0001</b>
0	20	4.0	2.0, 5.9	846	96.0	94.1, 98.0	
1	33	7.5	4.2, 10.9	471	92.5	89.1, 95.8	
2	21	6.0	2.5, 9.5	301	94.0	90.5, 97.5	
3	33	15.6	9.0, 22.1	222	84.4	77.9, 91.0	
4+	107	21.5	16.5, 26.5	429	78.5	73.5, 83.5	
<b>SLE Score</b>							<b>&lt;0.0001</b>
0	28	4.2	2.2, 6.1	710	95.8	93.9, 97.8	
1	26	3.6	1.6, 5.5	565	96.4	94.5, 98.4	
2	35	10.2	5.9, 14.5	397	89.8	85.5, 94.1	
3	27	9.9	4.7, 15.0	238	90.1	85.0, 95.3	
4+	98	25.1	19.5, 30.8	359	74.9	69.2, 80.5	

<sup>a</sup>Other Race includes Asian, Black, Native Hawaiian and Pacific Islander, and American Indian/Alaskan Native.

P-value indicates differences between groups computed by Chi-squared tests or Fisher Exact Test. Bolded p-value<0.05 used to denote statistical significance.

**Table 3. Adjusted prevalence ratios for marijuana use during pregnancy, Nevada PRAMS 2017-2020**

	aPR	95% CI
<b>ACE Score</b>		
0 ACEs	Ref	-
1 ACE	<b>1.96</b>	<b>1.30, 2.94</b>
2 ACEs	1.53	0.80, 2.96
3 ACEs	<b>3.58</b>	<b>2.69, 4.77</b>
4+ ACEs	<b>3.67</b>	<b>2.36, 5.72</b>
<b>SLE Score</b>		
0 SLEs	Ref	-
1 SLEs	0.68	0.30, 1.50
2 SLEs	1.93	0.80, 4.70
3 SLEs	1.65	0.42, 6.53
4+ SLEs	<b>3.12</b>	<b>1.64, 5.92</b>
<b>All models were adjusted for age, race/ethnicity, highest level of education, smoked cigarettes 3 months before pregnancy, health insurance type during pregnancy, previous pregnancy, pregnancy intention, and rurality.</b>		

**Table 4. Multiplicative and additive interaction between ACEs and SLEs on marijuana use during pregnancy, Nevada PRAMS, 2017-2020**

	Marijuana use during pregnancy	
	aPR (95% CI)	aPR (95% CI)
<b>SLEs</b>		
<b>1. Multiplicative Interaction</b>	<b>Low ACEs<sup>a</sup></b>	<b>High ACEs<sup>b</sup></b>
Low SLEs <sup>c</sup>	Reference	2.22 (1.43, 3.44)
High SLEs <sup>d</sup>	2.10 (1.18, 3.74)	5.39 (4.30, 6.75)
<b>Multiplicative Interaction Estimate</b>	1.15 (0.56, 2.39)	
p-value	0.7005	
<b>2. Additive Interaction</b>		
<b>RERI (95% CI)</b>	2.06 (1.09, 3.04)	
p-value	0.0003	

ACEs: adverse childhood experiences; SLEs: stressful life events; aPR: adjusted prevalence ratio; CI: confidence interval.

All models were adjusted for age, race/ethnicity, highest level of education, smoked cigarettes 3 months before pregnancy, health insurance type during pregnancy, previous pregnancy, pregnancy intention, and rurality.

<sup>a</sup>Low ACEs=0-2. <sup>b</sup>High ACEs=3+. <sup>c</sup>Low SLEs=0-3. <sup>d</sup>High SLEs=4+.

## Chapter 4

### **Associations between circumstances surrounding overdose and underlying classes of polysubstance overdose deaths**

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of Public and Behavioral Health, Office of Public Health Investigations and Epidemiology (OPHIE), and Nevada Department of Health and Human Services, Office of Analytics.

### **Abstract**

**Background:** The overdose crisis is worsening, with polysubstance overdose deaths involving psychostimulants increasing in the U.S. Substance-specific prevention and intervention activities may not be as effective for polysubstance use, so we sought to classify substances used among overdose decedents to identify unique factors related to these classes.

**Methods:** We used data from the Nevada State Unintentional Drug Overdose Reporting System, Jan 2019-Jun 2021, from death certificates, coroner/medical examiner reports, and post-mortem toxicology. Latent class analysis, multinomial logistic regression, and Chi-squared tests determined underlying drug classes, differences in characteristics and circumstances surrounding overdose, and assessed relationships between circumstances and classes.

**Results:** We identified four latent classes: 1) prescription drugs (19.1%), 2) predominately methamphetamine (31.4%), 3) multi-drug (28.9%), and 4) opioid and stimulant (20.6%). Compared to other classes, the prescription drug class had a higher percentage of female decedents, from rural counties, with mental health diagnoses, who died at home. The predominately methamphetamine class had a higher percentage of decedents experiencing homelessness. The multi-drug use class had higher percentage of younger and Hispanic decedents. Those in the opioid and stimulant class had higher odds of being recently released from an institutional setting, compared to the multi drug class.

**Conclusions:** These underlying classes were associated with several characteristics and circumstances that can prove useful for prevention, treatment, and harm reduction agencies when designing programs and interventions to target specific groups of people at-risk for drug overdose.

## **Introduction**

Provisional estimates from the National Center for Health Statistics show that 108,642 drug overdose deaths occurred in the U.S. from February 2021-2022, which represents a 12% increase from the year before (NCHS, 2022). The first wave of the overdose epidemic began in the early 2000s with an increase in deaths due to the explosion in prescription opioid use, which was followed by a second wave with an increase in deaths due to heroin use in 2010, and a subsequent third wave beginning in 2013 with increases in overdose deaths involving synthetic opioids such as fentanyl (CDC, 2021). Emerging research suggests a fourth wave of the epidemic involving multiple substances, referred to as polysubstance use, fueled by an increase in stimulant use (Ciccarone, 2021; Han et al., 2021; Hoots et al., 2020).

Although there may be limitations, mortality data is one source of information about factors associated with overdose, and can supplement traditional overdose morbidity surveillance systems (i.e. hospital, emergency medical services) to identify emerging trends and inform best practices to reduce overdose death (Hargrove et al., 2017). Historically, overdose mortality research at the state- and national-level has relied on ICD-10 codes procured from

death certificates, typically only focusing on opioid-involved or stimulant-involved deaths (Barocas et al., 2019; Figgatt et al., 2021; Golladay et al., 2021; Karissa et al., 2021; Konefal et al., 2022; Lim et al., 2021; Shiue et al., 2021). Because not all drugs present at time of death are listed, death certificate data alone may underestimate the involvement of other substances consumed prior to death (Peppin et al., 2020). Post-mortem toxicology data from coroner/medical examiner (CME) offices can be leveraged to identify substances involved in polysubstance overdose deaths at the state-level (Chichester et al., 2020; Korona-Bailey et al., 2021; Park et al., 2021; Rhee et al., 2019; Schneider et al., 2021). It can be complex to interpret the contribution of multiple substances, so previous research has generally restricted to describing the top substances detected (i.e. opioids), or combining common substances (i.e. opioids+stimulants) (Chichester et al., 2020; Korona-Bailey et al., 2021; Rhee et al., 2019).

One recent study attempted to classify multiple substances present in the post-mortem toxicology of overdose decedents using latent class analysis, which classifies subgroups of indicators within a population, and found three classes, which include fentanyl/heroin/cocaine, fentanyl/alcohol, and prescription drugs (Park et al., 2021). However, they focused on data from 2015-2017 during the third wave of the epidemic fueled by fentanyl in an eastern US state (Park et al., 2021). Because drug availability and trends differ over time and geographically, these patterns may not generalize to western states that have higher prevalence of methamphetamine-type stimulant use (Congdon 2020; Park et al., 2021). Recent research has found that the number of substances involved in polysubstance overdose deaths range from 2

to 9 substances (Park et al., 2021; Shiue et al., 2021). There is also evidence of enhanced risk of overdose due to co-ingestion of multiple substances (i.e. alcohol, opioids, stimulants, and other prescription drugs) that produces synergistic and/or antagonistic effects (Dai et al., 2020). The presence of multiple substances and the totality of their effects further complicates polysubstance deaths, which have historically been difficult to measure using mortality data (Dai et al., 2020; Park et al., 2021; Shiue et al., 2021).

State-specific research has found that people who die from polysubstance overdose are more likely to be: younger, socioeconomically disadvantaged, engaged in riskier behaviors such as injection drug use, and were less likely to initiate substance use treatment while alive, than persons who died from opioids alone (Barocas et al., 2019; Chichester et al., 2020; Figgatt et al., 2021). Previous research looking at underlying classes of decedents who died by polysubstance overdose also identified correlates with a fentanyl/heroin/cocaine class, in that they were younger, male, and non-White, compared to the prescription drug class (Park et al., 2021).

Park and colleagues stopped short of identifying the circumstances surrounding the overdose (Park et al., 2021). These factors include events that were related to the decedent's overdose and may have contributed to it, are typically documented as part of the death investigation, but are typically not leveraged by researchers due to the time commitment involved in abstracting them from lengthy investigation reports (Roper-Miller et al., 2020). These factors have strong parallels to the social determinants of health (i.e. social and

community context) and may shed more light on areas where interventions can be placed to prevent overdose death (Barocas et al., 2019; Holland et al., 2021).

Research has looked at a few circumstances such as naloxone administration, previous overdose, recent release from treatment or incarceration, mental health diagnosis, and location of overdose, but have focused on opioid-involved and/or stimulant-involved overdose deaths only (Mattson et al., 2018; O'Donnell et al., 2020). They did not assess relationships between circumstances and substances, which would have provided more depth to their findings by identifying which circumstances would be most beneficial for intervention (Mattson et al., 2018; O'Donnell et al., 2020). To account for polysubstance use, prevention should focus on targeting factors or circumstances that differ amongst multiple substances to prevent polysubstance overdose death (Compton et al., 2020).

Since surveillance systems have detected increases in polysubstance use over time and overdose deaths continue to increase, there is a need to shift focus from singular substances to specific classes of polysubstance use and identify the factors (i.e. circumstances surrounding overdose) that could be leveraged to prevent future polysubstance overdose death (Ciccarone, 2021; Cicero et al., 2020). Using recent overdose mortality surveillance data that includes comprehensive toxicology and medical examiner/coroner reports from a western state that has a high prevalence of stimulant use, we will answer the following research questions:

- 1) What are the underlying drug use classes present in recent overdose deaths in a western state?

- 2) What are the differences in demographics and circumstances between drug use classes?
- 3) What are the circumstances surrounding the overdose associated with drug use classes?

## **Methods**

### **Data Source**

Data were obtained from the Nevada State Unintentional Drug Overdose Reporting System (SUDORS), and include drug-related overdose deaths of unintentional/undetermined intent in Nevada, January 1, 2019-June 30, 2021. SUDORS uses death certificates and CME reports to capture information on toxicology, death scene investigations, and other risk factors that may be associated with unintentional/undetermined fatal drug overdoses (O'Donnell et al., 2020). This information is compiled by abstractors working within the Washoe County Regional Medical Examiner's Office (WCRMEO) and Clark County Office of the Coroner/Medical Examiner (CCOCME) for overdose deaths of unintentional/undetermined intent across the state. Per Nevada Senate Bill 463, an autopsy and comprehensive toxicology testing are performed if the pathologist suspects death was related to drug use (S.B. 463, Nev. 2019). There were 2,019 overdose deaths of unintentional/undetermined intent during the study period. The analytical sample excludes decedents where a CME report was not available and no circumstances were documented (N=71) resulting in an analytic sample of 1948 decedents.

### **Measures**

## Demographics

SUDORS contains demographic indicators based on death certificate information, CME reports, and interviews with next of kin. Such demographic indicators include age, sex, race/ethnicity, highest education level attained, marital status, experienced homelessness prior to death, residency of the decedent, and urban-rural classification for county of death. Age, in line with previous studies, was categorized as under 30, 30-44, 45-59, 60+ (Park et al., 2021). Sex was categorized into male or female. Highest education level attained was categorized into 1) less than high school education; 2) high school degree/some post high school; 3) college graduate. Race/ethnicity was categorized into Black (non-Hispanic), White (non-Hispanic), Hispanic, and Other (non-Hispanic). Marital status was categorized into married or not married (divorced, separated, or never married). Residency of the decedent was categorized into in-state or out-of-state. The county where death occurred was categorized into urban or rural.

## Toxicology

The CMEs contract toxicology to out-of-state laboratories that test for a variety of substances via comprehensive/expanded panels (i.e., 6-AM, amphetamine, antidepressants, antipsychotics, anti-seizure drugs, barbiturates, benzodiazepines, cannabinoids, cocaine, common opioid medications, fentanyl, fentanyl analogs, gabapentin, methamphetamine, muscle relaxants, over-the-counter medications, other synthetic opioids). The CCOCME uses Redwood Toxicology in California and the WCRMEO uses National Medical Services in

Pennsylvania for their post-mortem toxicology. Similar to previous studies, we combined drugs into broader categories representing the most prevalent substances: alcohol, anticonvulsants, antidepressants, benzodiazepines, cocaine, fentanyl, heroin, marijuana, methamphetamine, and prescription opioids (Park et al., 2021).

### *Circumstances surrounding overdose*

SUDORS contains information regarding circumstances surrounding overdose, which comes from the death scene investigation, law enforcement records and reports, and medical records. We focused on ten with highest prevalence to make the most impact if addressed: 1) Released from any institution <1 month prior to death (hospital, treatment facility, or jail); 2) Previous drug overdose (<1 year prior to death); 3) Bystander present at overdose (close proximity to someone experiencing an overdose); 4) Current pain treatment; 5) Fatal drug use witnessed (in the presence of someone taking drugs that overdoses); 6) Overdose occurred in a home setting; 7) Current/past substance use/misuse history; 8) Ever treated for substance use disorder; 9) Mental health diagnosis; 10) Recent period of abstinence followed by opioid use.

### **Analysis**

Mplus was used for all analyses (Muthén & Muthén, 2013). Latent class analysis (LCA) was conducted to identify patterns of substances involved in unintentional/undetermined polysubstance overdose deaths in Nevada. LCA is used to identify distinct subgroups of

individuals across a series of indicator variables (Weller et al., 2020). We conducted a 3-step approach to account for measurement error in the latent class enumeration to assess relationships between circumstances and latent classes (Asparouhov & Muthén, 2014). We first tested the 1-class solution and increased the number of classes until the best fit model was identified. We used the following model selection criteria: Akaike information criteria (AIC), Bayesian information criterion (BIC), adjusted BIC, and Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (LMRT) (Lo, Mendell, & Rubin, 2001; Arminger, Stein, & Wittenberg, 1999; Schwarz, 1978; Akaike, 1974). This was followed by assignment of cases to latent classes based on posterior class membership probabilities. We then compared demographic and circumstance variables among those in each of the classes using Chi-squared tests with Bonferroni correction to adjust for multiple comparisons (adjusted P-value cutoff of 0.008) (Dunnett, 1955). We then conducted multinomial logistic regression considering misclassification in the previous step to estimate the relationship between circumstances and drug classes (Asparouhov & Muthén, 2014). Characteristics that were statistically significant in univariate analyses ( $p$ -value $<0.05$ ) were included in a final multivariate model for each of the ten circumstances. The reference group for multinomial logistic regression was the multi drug class which featured mostly fentanyl, since fentanyl is a major contributor to drug overdose deaths and because polysubstance use is common (Park et al., 2021).

Overall, the amount of missing data for individual measures was  $<5\%$  except for education (8.5%), homelessness (6.7%) and marital status (6.2%). We used Little's test to assess

whether data were missing completely at random (Li, 2013). The test was significant, therefore we conducted multiple imputation using chained equations using the fully conditional method; twenty imputations were performed (Asparouhov & Muthen, 2022).

## **Results**

### **Sample Description**

From January 2019-June 2021, unintentional/undetermined overdose decedents in Nevada were mostly white, non-Hispanic (63.5%), male (67.7%), aged 30-59 (63.6%), and had a high school education or some post-high school education (68.5%) (Table 1). The top ten substances detected and circumstances are shown in table 2. Half of decedents tested positive for methamphetamine (51.2%), 38.1% tested positive for prescription opioids, and over a quarter tested positive for fentanyl (27.7%). The mean (M) number of substances detected was 2.51, standard deviation (SD)=1.28, with a maximum of 7 substances. Over two-thirds (69.7%) of overdoses occurred in a home setting, 65.3% of decedents had current/past substance use/misuse, and half had a bystander present at time of overdose (53.8%) (Table 2).

### **What are the underlying drug use classes present in recent overdose deaths in a western state?**

Table 3 shows the LCA fit statistics and information criteria. Based on information criteria (lower better), entropy (higher better), LMRT, and meaningful interpretation of classes,

we determined four classes to be ideal in describing this dataset. Table 4 shows the probabilities of indicators in the four-class solution. Since multiple substances were used as indicators, we paid attention to the highest probabilities within each class. Class 1 (prescription drug class, 19.1% of sample) was characterized by high prevalence of prescription opioids, antidepressants, benzodiazepines, and anticonvulsants, ( $M=1.69$ ,  $SD=0.78$ ). Class 2 (predominately methamphetamine class, 31.4%) was characterized by predominantly methamphetamine ( $M=3.12$ ,  $SD=1.33$ ). Class 3 (multi-drug class, 28.9%) was characterized by high prevalence of fentanyl, marijuana, benzodiazepines, and alcohol ( $M=2.44$ ,  $SD=1.23$ ). Class 4 (opioid and stimulant class, 20.6%) was characterized by high prevalence of prescription opioids, heroin, and methamphetamine ( $M=3.39$ ,  $SD=1.10$ ).

***What are the differences in demographics and circumstances between drug use classes?***

Table 5 shows the prevalence of demographics and circumstances, and differences in these indicators, between combinations of drug use classes. Among demographics, the percentages of decedents overdosing in rural counties was significantly higher among those belonging to the prescription drug class (12.1%) compared to multi-drug class (6.6%). The percentage of decedents under the age of 30 was significantly higher among those in the multi-drug class (37.0%) compared to prescription drug class (9.8%), predominately methamphetamine class (8.5%), and opioid and stimulant class (18.6%). The percentage of decedents who were female was significantly higher among those belonging to the prescription

drug class (54.4%) compared to predominately methamphetamine class (27.2%), multi-drug class (26.4%), and opioid and stimulant class (27.4%). The percentage of decedents who were Hispanic was significantly higher among those belonging to the multi-drug class (25.3%) compared to prescription drug class (10.0%), predominately methamphetamine class (14.9%), and opioid and stimulant class (12.9%). The percentage of decedents experiencing homelessness/housing instability was significantly higher among those belonging to the predominately methamphetamine class (26.1%) compared to prescription drug class (1.3%) and multi-drug class (4.2%).

The percentage of decedents who overdosed in a home was significantly higher among those belonging to the prescription drug class (87.4%) compared to predominately methamphetamine class (54.4%), and opioid and stimulant class (64.8%). The percentage of decedents who had known current/past substance use/misuse was significantly higher among those belonging to the opioid and stimulant class (80.4%) compared to prescription drug class (53.0%), predominately methamphetamine class (54.4%), and multi-drug class (66.7%). The percentage of decedents that had a bystander present at the time of overdose was significantly higher among those belonging to the multi-drug class (63.4%) compared to prescription drug class (54.6%), predominately methamphetamine class (45.5%), and opioid and stimulant class (53.5%).

**What are the circumstances surrounding the overdose associated with drug use classes?**

Table 6 shows the univariate analyses for characteristics and class membership, and Table 7 shows the multivariate analyses showing the relationship between circumstances and class membership, while adjusting for demographic variables that were associated with class membership in the univariate analyses (time period, residency, county, age, sex, race/ethnicity, education, marital status, and homelessness), compared to the multi drug class. Decedents in the prescription drug class had higher odds of current pain treatment (aOR=1.59, 95%CI=1.19-2.12), having a mental health diagnosis (aOR=3.45, 95%CI=2.54-4.69), and recent release from an institutional setting (aOR=3.27, 95%CI=1.94, 5.51) prior to death. Those in the predominately methamphetamine class had higher odds of being recently released from an institutional setting (aOR=2.47, 95%CI=1.51-4.04). Those in the opioid and stimulant class had higher odds of recent release from an institutional setting (aOR=3.00, 95%CI=1.80-5.00), current/past substance use/misuse (aOR=2.83, 95%CI=2.02-3.97), having recent opioid use after a period of abstinence (aOR=2.45, 95%CI=1.50-4.01), and ever receiving treatment for SUD (aOR=2.12, 95%CI=1.38-3.27).

## **Discussion**

This study identified differences between polysubstance drug use classes and relationships between circumstances surrounding overdose and these classes. This study identified four classes among unintentional overdose deaths in Nevada from 2019 to 2021; 1)

positive for multiple prescription drugs, 2) positive predominantly for methamphetamine, 3) positive for multiple substances, and 4) positive for opioids and stimulants. Previous research within an eastern U.S. state identified three classes, two involving fentanyl, as well as a prescription drug class (Park et al., 2021). Similar to that study, we also identified a drug class that included fentanyl and other drugs, as well as a prescription drug class, but our study also identified two classes with stimulants (Park et al., 2021). This finding can be explained by geographic differences in the U.S. drug supply. Fentanyl has been present in the eastern parts of the U.S. for a longer period of time and has more recently spread to the west, whereas western states have historically had higher prevalence of methamphetamine use, which has recently spread to the east (Han et al., 2021; Mattson et al., 2021). Synthetic opioids and psychostimulants are no longer specific to a certain region, and public health prevention activities need to adapt to this challenge (Mattson et al., 2021).

We identified differences in demographic and circumstances between classes, and assessed relationships between circumstances and classes. The prescription drug class had a significantly higher percentage of decedents overdosing in rural counties, being female, having a mental health diagnosis, and overdosing in a home compared to other classes. This is in line with national trends in prescription opioid-related deaths, where overdose death rates were higher in rural areas than urban and higher among females than males (CDC, 2021b). Previous research also found that prescription opioid-involved deaths were more likely to occur in the home among those with mental health concerns than those that involved illicit drugs

(Easterling et al., 2016; Mattson et al., 2018). Interventions to reduce overdose due to prescription drugs should focus on improving mental health care and treatment among females living in rural areas. The National Rural Health Association recommends increasing the availability of mental health providers in rural areas, improving accessibility and affordability of services, and acceptability by reducing the stigma associated with receiving care in smaller communities to increase treatment uptake (NRHA, 2015).

The predominately methamphetamine class had a significantly higher percentage of decedents experiencing homelessness/housing instability compared to other classes. This finding is consistent with previous research that found that decedents experiencing homelessness were more likely to overdose using stimulants compared to opioids (Barocas et al., 2019). To address methamphetamine overdose, contingency management is effective, but may not be sustainable, and combining it with other interventions designed to address some of the underlying risk factors related to methamphetamine overdose may be useful in reducing overdose death (Mimiaga et al. 2018; Zastepa et al., 2020). Housing instability could also be targeted, since 26% of this class were experiencing homelessness. Expanding access to affordable housing, as well as other medical, social, and employment assistance programs for people who are unhoused, may increase the likelihood of these individuals entering treatment and staying in recovery, while decreasing misuse and overdose (NHCHC, n.d.).

The multi-drug class had a significantly higher percentage of Hispanic decedents and those under the age of 30, compared to other classes. Previous research suggests that those

who use multiple drugs are typically younger than those who use one type such as opioids (Barocas et al., 2019). Since a large percentage of decedents in this class had someone witness or were present during their overdose, culturally appropriate interventions for this class should focus on the role of the bystander in preventing death among those who are younger and persons of color (Kariisa et al., 2022). Bystanders can play a crucial role in reducing overdose death by taking life-saving measures such as calling 911 and administering naloxone, especially when opioids (or unanticipated fentanyl) are present (Gigliio et al., 2015).

Those in the opioid and stimulant class shared some commonalities with the multi-drug class. In addition to leveraging the role of the bystander, preventing people from returning to use after a period of abstinence (i.e. recent release from incarceration or experiencing homelessness) and ensuring access to harm reduction tools if one does return to use are vital to reduce overdose deaths among people who use opioids and stimulants. For example, interventions that link people to appropriate services upon release or when experiencing financial difficulties (Goldman-Hasbun et al., 2019), and ensuring easy access to naloxone to people who use drugs and those most likely to be present at an overdose can enable them to take life-saving measures if necessary (Gigliio et al., 2015).

These findings have implications for the prevention of overdose deaths. There is a need to bolster mental health care capacity, especially in rural areas, by increasing workforce capacity and reducing stigma. There is also need to increase capacity for emergency overdose response by increasing access to and education about naloxone, especially to potential

bystanders. Additionally, there is a need to increase capacity for harm reduction programs, such as expanding syringe exchange programs and establishing supervised consumption sites, where other social services can be made available so that PWUDs are able to get help if they need it. These findings could be used by policymakers, public health agencies, and clinicians to create and target interventions to improve prevention and treatment outcomes in Nevada.

### **Limitations**

The limitations of this study need to be acknowledged. These underlying classes are only specific to unintentional and undetermined drug overdose deaths in Nevada that occurred from January 2019 to June 2021. Although Nevada began SUDORS data collection in 2017, we only included data from 2019 and afterwards. This was due to a change in case definition, where prior to 2019 SUDORS was limited to flagging opioid-involved overdose deaths. In 2019, the case definition changed to include any drug overdose deaths, and our findings would not be generalizable to prior years. The circumstances data is only as good as the information obtained during the investigation, with some cases having more complete information than others depending on information compiled during the death investigation. Those without bystanders they knew well at the scene or who were from out-of-state may not have circumstances well documented, leading to an underestimation of associations for these circumstances and individual classes. Additionally, the death investigation relied heavily on reports by bystanders or next of kin. Recall and social desirability bias may be present since those interviewed most

likely had varied information about the decedent's life depending on their relationship, which may have underestimated our measure of effect. There is also the possibility for misclassification among the circumstances surrounding overdose. Some questions, especially asking about a previous overdose or previous history of substance use/misuse, may have been prone to bias, especially in the case for those whose medical records may not have been available (out-of-state residents).

The data used in this study also includes data from the beginning and during the COVID pandemic, where drug use trends and data quality may have been impacted. It has been reported that there were changes in drug use behaviors during the COVID-19 pandemic which led to an increase in riskier drug use, including the use of multiple substances, but mortality data trends were already showing evidence of polysubstance use (Otiashvili et al., 2022). Additionally, although autopsy and comprehensive toxicology testing is performed for suspected drug use deaths, the COVID pandemic overwhelmed death investigators and other C/ME staff, which may have led to less time being devoted to case investigations. The impact on data quality on the death investigations is difficult to discern since it varied from investigation to investigation, but we believe the circumstances surrounding overdose that were documented may have been underestimated. Lastly, to reduce instability in our model, we only included the top 10 combinations of substances, so our results may underestimate involvement of other less commonly used substances.

**Conclusion**

The identification of underlying classes of unintentional/undetermined overdose deaths has implications for prevention of these deaths. These underlying classes were associated with several socio-demographic characteristics and circumstances surrounding overdose that can be useful for prevention, treatment, and harm reduction agencies when designing programs and interventions to target specific groups of PWUDs who are at-risk for overdose.

Unintentional/undetermined overdose decedents rarely have just one substance present in toxicology results, and class-specific activities need to be developed to prevent overdose deaths.

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**Table 1. Characteristics of unintentional/undetermined drug overdose deaths in Nevada from SUDORS, Jan 2019-Jun 2021**

<b>Characteristics</b>	<b>N=1948</b>	<b>%<sup>a</sup></b>
<b>Time Period</b>		
Jan-Jun 2019	320	16.4%
Jul-Dec 2019	274	14.1%
Jan-Jun 2020	388	19.9%
Jul-Dec 2020	491	25.2%
Jan-Jun 2021	475	24.4%
<b>Residency of Decedent</b>		
In state	1679	86.2%
Out of state	269	13.8%
<b>County of Death Classification</b>		
Urban	1768	90.8%
Rural	180	9.2%
<b>Age</b>		
Under 30	363	18.6%
30-44	602	30.9%
45-59	636	32.7%
60+	347	17.8%
<b>Sex</b>		
Female	629	32.3%
Male	1319	67.7%
<b>Race/Ethnicity</b>		
White, Non-Hispanic	1237	63.5%
Black, Non-Hispanic	263	13.5%
Hispanic	316	16.2%

Other, Non-Hispanic <sup>b</sup>	93	4.8%
<b>Education</b>		
Less than high school	278	15.6%
High school degree/some post-high school (no degree)	1222	68.5%
College degree or higher	283	15.9%
<b>Marital Status</b>		
Married	337	17.3%
Not Married	1491	76.5%
<b>Homeless<sup>c</sup></b>		
Yes	230	12.7%
No	1587	87.3%

<sup>a</sup>Percentages exclude missing data.

<sup>b</sup>Other race/ethnicity includes American Indian/Alaskan Native, Asian or Other Pacific Islander, and multi-racial.

<sup>c</sup>There was evidence that decedent was experiencing homeless prior to death, which was defined as having no fixed address and living in a shelter, on the street, in a car, or in makeshift quarters in an outdoor setting).

**Table 2. Top 10 substances detected and circumstances surrounding drug overdose deaths in Nevada from SUDORS, Jan 2019- Jun 2021**

<b>Top 10 substances detected<sup>a</sup></b>	<b>N=1948</b>	<b>%</b>
Methamphetamine	997	51.2%
Prescription opioids	742	38.1%
Fentanyl	540	27.7%
Marijuana	523	26.9%
Benzodiazepines	512	26.3%
Alcohol	462	23.7%
Antidepressants	338	17.4%
Heroin	337	17.3%
Cocaine	214	11.0%
Anticonvulsants	212	10.9%
<b>Top 10 circumstances surrounding drug overdose<sup>a,b</sup></b>		
Overdose occurred in a home setting	1357	69.7%
Current/past substance use/misuse	1271	65.3%
Bystander present	1048	53.8%
Mental health diagnosis	606	31.1%
Current pain treatment	376	19.3%
Fatal drug use witnessed	223	11.5%
Recent release from any institution <sup>c</sup>	219	11.2%
Ever treated for substance use disorder	188	9.7%
Recent opioid use relapse <sup>d</sup>	113	5.8%
Prior overdose <sup>e</sup>	112	5.8%

<sup>a</sup>Substances, circumstances preceding death, and characteristics are not mutually exclusive, so totals will not add up to 100%.

<sup>b</sup>Circumstances represent evidence available in source documents (i.e. death investigation reports, medical records), and are likely to underestimate the true occurrence due to limited information during the death investigation.

**<sup>d</sup>Includes release within the past month prior to death from prisons/jails, residential treatment facilities, and psychiatric hospitals.**

**<sup>d</sup>Recent period of abstinence followed by relapse, regardless of timing**

**<sup>e</sup>Previous overdose occurring <1 year prior to death**

**Table 3. Latent class analysis fit statistics**

Number of Classes	Smallest Class Size	Log Likelihood	AIC	BIC	Adjusted BIC	Entropy	LMR
2	875	-9858.157	19758.314	19875.380	19808.662	0.727	<0.0001
3	586	-9506.728	19077.455	19255.841	19154.176	0.761	<0.0001
4 <sup>a</sup>	372	-9334.525	18755.051	18994.757	18858.144	0.766	<0.0001
5	191	-9291.435	18690.870	18991.896	18820.336	0.759	0.1800

<sup>a</sup>Highest number of classes with a statistically significant LMR p-value was chosen as the ideal number of classes.

**Table 4. Probabilities of indicators in each class in the 4-class solution**

	<b>Class 1 (Prescription drugs)</b>	<b>Class 2 (Predominately Methamphetamine)</b>	<b>Class 3 (Multi-drug class)</b>	<b>Class 4 (Opioid and Stimulant)</b>
Anticonvulsants	0.43	0.04	0.01	0.06
Antidepressant	0.57	0.07	0.08	0.10
Cocaine	0.05	0.02	0.28	0.08
Heroin	0.09	0.01	0.02	0.72
Marijuana	0.20	0.22	0.39	0.23
Alcohol	0.26	0.16	0.32	0.22
Benzodiazepines	0.51	0.07	0.33	0.23
Fentanyl	0.20	0.08	0.69	0.06
Methamphetamine	0.11	0.99	0.14	0.67
Prescription Opioids	0.80	0.01	0.17	0.86

**Note: Class 1: Prescription opioids, antidepressants, benzodiazepines, anticonvulsants; Class 2: Methamphetamine; Class 3: Fentanyl, marijuana, benzodiazepines, alcohol; Class 4: Prescription opioids, heroin, Methamphetamine.**

Table 5. Prevalence of characteristics and circumstances surrounding death by latent class in Nevada from SUDORS, Jan 2019- Jun 2021

Characteristics	Class 1 (Prescription drugs)		Class 2 (Predominately Methamphetamine)		Class 3 (Multi- drug)		Class 4 (Opioid and Stimulant)		Sig
	N=379	%	N=651	%	N=54 6	%	N=37 2	%	
<b>Time Period</b>									
Jan-Jun 2019	77	20.3	98	15.1	65	11.9	80	21.5	m
Jul-Dec 2019	56	14.8	100	15.4	60	11.0	58	15.6	
Jan-Jun 2020	89	23.5	112	17.1	117	21.4	70	18.8	
Jul-Dec 2020	73	19.2	181	27.8	148	27.0	89	23.9	h, i
Jan-Jun 2021	84	22.2	160	24.6	156	28.6	75	20.2	m
<b>Residency of Decedent</b>									
In state	349	92.1	530	81.4	484	88.6	316	85	h, j, k
Out of state	30	7.9	121	18.6	62	11.4	56	15.1	h, j, k
<b>County of Death Classification</b>									
Urban	333	87.9	585	89.9	510	93.4	340	91.4	i
Rural	46	12.1	66	10.1	36	6.6	32	8.6	i
<b>Age</b>									
Under 30	37	9.8	55	8.5	202	37.0	69	18.6	i, j, k, l, m
30-44	109	28.8	173	26.6	181	33.2	139	37.4	l
45-59	152	40.1	271	41.6	113	20.7	100	26.9	i, j, k, l,
60+	81	21.4	152	23.4	50	9.2	64	17.2	i, k, m
<b>Sex</b>									
Female	206	54.4	177	27.2	144	26.4	102	27.4	h, i, j
Male	173	45.7	474	72.8	402	73.6	270	72.6	h, i, j
<b>Race/Ethnicity<sup>#</sup></b>									
White, Non-Hispanic	294	77.6	401	61.6	288	52.8	279	75.0	h, i, k, l, m

Black, Non-Hispanic	34	9.0	111	17.1	95	17.4	31	8.3	h, i, l, m
Hispanic	38	10.0	97	14.9	138	25.3	48	12.9	i, k, m
Other, Non-Hispanic <sup>b</sup>	13	3.4	42	6.5	25	4.6	14	3.8	
<b>Education</b>									
Less than high school	49	12.9	118	18.1	85	15.6	59	15.9	
High school degree/some post-high school (no degree)	222	58.6	465	71.4	371	68.0	271	72.9	h, i, j,
College degree or higher	108	28.5	68	10.5	90	16.5	42	11.3	h, i, j, k
<b>Marital Status</b>									
Married	99	26.1	94	14.4	107	19.6	56	15.1	i, j
Not Married	280	73.9	557	85.6	439	80.4	316	84.9	i, j
<b>Homeless<sup>c</sup></b>									
Yes	5	1.3	170	26.1	23	4.2	73	19.6	h, j, k, m
No	374	98.7	481	73.9	523	95.8	299	80.4	h, j, k, m
<b>Top 10 circumstances surrounding drug overdose<sup>d,e</sup></b>									
Overdose occurred in a home setting	331	87.4	354	54.4	431	78.9	241	64.8	h, i, j, k, l, m
Current/past substance use/misuse	201	53.0	407	62.5	364	66.7	299	80.4	h, i, j, l, m
Bystander present	207	54.6	296	45.5	346	63.4	199	53.5	h, i, k, m
Mental health diagnosis	218	57.5	149	22.9	139	25.5	100	26.9	h, i, j
Current pain treatment	217	57.3	35	5.4	73	13.4	51	13.7	h, i, j, k, l
Fatal drug use witnessed	30	7.9	55	8.5	90	16.5	48	12.9	i, k
Recent release from any institution <sup>f</sup>	57	15.0	81	12.4	26	4.8	55	14.8	i, k, m
Ever treated for substance use disorder	48	12.7	28	4.3	50	9.2	62	16.7	h, k, l, m
Recent opioid use relapse <sup>g</sup>	16	4.2	12	1.8	36	6.6	48	12.9	j, k, l, m
Prior overdose <sup>h</sup>	34	9.0	15	2.3	43	7.9	21	5.7	h, k, l

Chi-squared tests were used to assess differences in the prevalence of demographic and circumstance indicators. Bonferroni adjustment P-value cutoff=0.008). <sup>h</sup>Class 1 vs. class 2, <sup>i</sup>Class 1 vs. Class 3, <sup>j</sup>Class 1 vs. Class 4, <sup>k</sup>Class 2 vs. Class3, <sup>l</sup>Class 2 vs. Class 4, <sup>m</sup>Class 3 vs. Class 4.

**Table 6. Unadjusted associations between characteristics with latent classes from Nevada SUDORS Jan 2019- Jun 2021**

Characteristic	Class 1 (Prescription Drugs)		Class 2 (Predominately Methamphetamine)		Class 4 (Opioid and Stimulant)	
	OR <sup>a</sup>	95% CI	OR <sup>a</sup>	95% CI	OR <sup>a</sup>	95% CI
<b>Time Period</b>						
Jan-Jun 2019	1.00	-	1.00	-	1.00	-
Jul-Dec 2019	0.79	0.48, 1.29	1.11	0.71, 1.73	0.79	0.48, 1.28
Jan-Jun 2020	<b>0.64</b>	<b>0.42, 0.99</b>	<b>0.64</b>	<b>0.42, 0.95</b>	<b>0.49</b>	<b>0.31, 0.76</b>
Jul-Dec 2020	<b>0.42</b>	<b>0.27, 0.64</b>	0.81	0.55, 1.19	<b>0.49</b>	<b>0.32, 0.74</b>
Jan-Jun 2021	<b>0.46</b>	<b>0.30, 0.69</b>	0.68	0.46, 1.00	<b>0.39</b>	<b>0.26, 0.60</b>
<b>Residency of Decedent</b>						
In state	1.00	-	1.00	-	1.00	-
Out of state	0.67	0.43, 1.06	<b>1.78</b>	<b>1.28, 2.48</b>	1.38	0.94, 2.04
<b>County of Death Classification</b>						
Urban	<b>0.51</b>	<b>0.32, 0.81</b>	<b>0.63</b>	<b>0.41, 0.96</b>	0.75	0.46, 1.23
Rural	1.00	-	1.00	-	1.00	-
<b>Age</b>						
Under 30	<b>0.11</b>	<b>0.07, 0.19</b>	<b>0.09</b>	<b>0.06, 0.14</b>	<b>0.27</b>	<b>0.17, 0.42</b>
30-44	<b>0.37</b>	<b>0.24, 0.57</b>	<b>0.31</b>	<b>0.22, 0.46</b>	<b>0.60</b>	<b>0.39, 0.92</b>
45-59	0.83	0.54, 1.27	0.79	0.54, 1.16	0.69	0.44, 1.09
60+	1.00	-	1.00	-	1.00	-
<b>Sex</b>						
Female	1.00	-	1.00	-	1.00	-
Male	<b>0.30</b>	<b>0.23, 0.40</b>	0.96	0.74, 1.24	0.95	0.71, 1.28
<b>Race/Ethnicity</b>						
White, Non-Hispanic	1.00	-	1.00	-	1.00	-
Black, Non-Hispanic	<b>0.35</b>	<b>0.23, 0.54</b>	0.84	0.61, 1.15	<b>0.34</b>	<b>0.22, 0.52</b>
Hispanic	<b>0.27</b>	<b>0.18, 0.40</b>	<b>0.51</b>	<b>0.37, 0.68</b>	<b>0.36</b>	<b>0.25, 0.52</b>

Other, Non-Hispanic <sup>b</sup>	0.51	0.26, 1.02	1.21	0.72, 2.03	0.58	0.29, 1.14
<b>Education</b>						
Less than high school	<b>0.48</b>	<b>0.31, 0.75</b>	<b>1.84</b>	<b>1.21, 2.80</b>	1.49	0.91, 2.44
High school degree/some post-high school (no degree)	<b>0.50</b>	<b>0.36, 0.69</b>	<b>1.66</b>	<b>1.18, 2.34</b>	<b>1.57</b>	<b>1.05, 2.33</b>
College degree or higher	1.00	-	1.00	-	1.00	-
<b>Marital Status</b>						
Married	1.00	-	1.00	-	1.00	-
Not Married	<b>0.69</b>	<b>0.51, 0.94</b>	<b>1.44</b>	<b>1.07, 1.96</b>	1.38	0.97, 1.96
<b>Homeless</b>						
Yes	<b>0.32</b>	<b>0.12, 0.85</b>	<b>7.44</b>	<b>4.68, 11.83</b>	<b>5.82</b>	<b>3.54, 9.56</b>
No	1.00	-	1.00	-	1.00	-

<sup>a</sup>Reference is class 3, the multi drug class.

<sup>b</sup>Other race/ethnicity includes American Indian/Alaskan Native, Asian or Other Pacific Islander, and multi-racial.

**Table 7. Adjusted odds ratios for documented circumstances with latent classes from Nevada SUDORS 2019-2021**

Top 10 documented circumstances for drug overdose <sup>a</sup>	Class 1 (Prescription Drugs)		Class 2 (Predominately Methamphetamine)		Class 4 (Opioid and Stimulant)	
	aOR <sup>b</sup>	95% CI	aOR <sup>b</sup>	95% CI	aOR <sup>b</sup>	95% CI
Overdose occurred in a home setting	1.44	0.93, 2.22	<b>0.43</b>	<b>0.31, 0.60</b>	<b>0.67</b>	<b>0.46, 0.96</b>
Current/past substance use/misuse	0.74	0.55, 1.01	1.18	0.90, 1.55	<b>2.83</b>	<b>2.02, 3.97</b>
Bystander present	<b>0.74</b>	<b>0.55, 0.99</b>	<b>0.66</b>	<b>0.51, 0.85</b>	0.89	0.67, 1.18
Mental health diagnosis	<b>3.45</b>	<b>2.54, 4.69</b>	0.99	0.73, 1.32	1.04	0.75, 1.43
Current pain treatment	<b>5.64</b>	<b>3.96, 8.02</b>	<b>0.25</b>	<b>0.16, 0.40</b>	0.87	0.57, 1.31
Recent release from any institution <sup>c</sup>	<b>3.27</b>	<b>1.94, 5.51</b>	<b>2.47</b>	<b>1.51, 4.04</b>	<b>3.00</b>	<b>1.80, 5.00</b>
Fatal drug use witnessed	<b>0.45</b>	<b>0.28, 0.73</b>	<b>0.57</b>	<b>0.39, 0.85</b>	0.88	0.59, 1.32
Ever treated for substance use disorder	<b>1.89</b>	<b>1.19, 3.00</b>	0.63	0.38, 1.05	<b>2.12</b>	<b>1.38, 3.27</b>
Recent opioid use relapse <sup>d</sup>	0.82	0.43, 1.55	<b>0.44</b>	<b>0.22, 0.88</b>	<b>2.45</b>	<b>1.50, 4.01</b>
Prior overdose <sup>e</sup>	1.43	0.85, 2.42	<b>0.29</b>	<b>0.15, 0.56</b>	0.64	0.36, 1.15

<sup>a</sup>Circumstances represent evidence available in source documents (i.e. death investigation reports, medical records), and are likely to underestimate the true occurrence due to limited information during the death investigation.

<sup>b</sup>Reference is class 3, the multi drug class. Adjusted for time period, residency, urban/rural, age, sex, race/ethnicity, education, homelessness, marital status.

<sup>c</sup>Includes release within the past month prior to death from prisons/jails, residential treatment facilities, and psychiatric hospitals.

<sup>d</sup>Recent period of abstinence followed by relapse, regardless of timing

<sup>e</sup>Previous overdose occurring <1 year prior to death

## **Chapter 5: Summary of Findings, Future Directions, Implications**

Studies have explored risk and protective factors for substance use in maternal and adolescent populations (Bond et al., 2007; Cleveland et al., 2008; Harrison et al., 2008; Havens et al., 2009). However, even with this increased understanding of risk and protective factors, trends continue to remain the same or worsen in vulnerable populations such as sexual minority youth, pregnant people, and those who die by drug overdose (CDC, 2020; SAMHSA, 2022). The general aims of this dissertation were to 1) Investigate protective environmental factors among sexual minority youth for nonmedical use of prescription opioids; 2) Explore the direct and interactive effects of stressful life events and adverse childhood experiences among pregnant people on marijuana use; and 3) Identify social and contextual factors associated with substances used among drug overdose decedents.

### **Summary of Findings**

In the first study, I used representative, population-based survey data from Youth Risk Behavior Survey and School Health Profiles from 24 states within the U.S. to investigate protective environmental factors for sexual minority youth (SMY) using the Human Rights Campaign's state equality index (SEI) and supportive school environments for LGBTQ youth and their relationship with nonmedical use of prescription opioids (NMUPO). After adjusting for individual- and state-level indicators, SMY in states with supportive school environments for

LGBTQ youth were less likely to engage in NMUPO. Before adjustment, we found that youth in states with a higher SEI were less likely to engage in NMUPO compared to students in states with lower SEI, but this was no longer statistically significant after adjustment.

In the second study, I used representative, population-based survey data from the Nevada Pregnancy Risk Assessment Monitoring System of people who gave birth in Nevada to determine the direct and joint effects of adverse childhood experiences (ACEs) and stressful life events (SLEs) on marijuana use during pregnancy. In the sample, ACEs and SLEs were shown to be associated with marijuana use during pregnancy. I found that there was evidence of additive interaction when assessing both ACEs and SLEs jointly.

In the third study, I used a data system of all people who died by an accidental or undetermined drug overdose in Nevada to identify the underlying classes of drug overdose decedents. Additionally, I aimed to understand what differences existed between these classes, to better inform prevention of drug overdose death. Compared to other classes, the prescription drug class had a higher percentage of female decedents, from rural counties, with mental health diagnoses, who died at home. The predominately methamphetamine class had a higher percentage of decedents experiencing homelessness. The multi-drug use class had higher percentage of younger and Hispanic decedents. Those in the opioid and stimulant class had higher odds of being recently released from an institutional setting, compared to the multi drug class.

## Strengths and Limitations

Each of these studies had their own strengths and limitations. In the first study, the data we used was representative of the 24 states in the sample and we had a large sample of SMY. We also used a validated measure of the supportive school environment for LGBTQ youth that has been used previously, as well as a comprehensive measure of state equality laws that may affect LGBTQ persons. However, this study is only representative of the states that had representative data for the Youth Risk Behavior Survey and School Health Profiles, and asked the sexual identity and NMUPO questions. We also were unable to assess gender identity since very few states in the sample asked about it. Additionally, since we could not link individual students to the schools they attended given the constraints of the data sources, we aggregated the supportive school environment measures to the state-level. Our results reflect state-level averages of school environments and do not capture school-level heterogeneity.

In the second study, I used a representative sample of people who gave birth in Nevada and used a validated measure of ACEs that comes from the Behavioral Risk Factor Surveillance System ACEs module. However, for the SLE exposure variable, the survey did not ask about severity of life event, so we are not certain if they effected the person positively or negatively. Additionally, we were unable to ask the survey question about marijuana use before pregnancy, so we do not know for certain if people began use during pregnancy or used before pregnancy and just continued use. However, most people (3/4ths) do not continue use of marijuana into pregnancy (Klasner et al., 2022; Mark et al., 2020; Volkow et al., 2017), so we believe this would

slightly overestimate the effects of ACEs and SLEs on marijuana use during pregnancy. Lastly, this was a cross-sectional study, so we were unable to assess causality if the exposures did really lead to the outcome of marijuana use.

In the third study, the data included all people who died by drug overdose in Nevada from January 2019 to June 2021. The circumstances surrounding overdose data is only as good as the information obtained during the death investigation, with some cases having more complete information depending upon the scene evidence. There is also the possibility of misclassification given the types of questions to next of kin or bystanders, who may have varying accounts of the decedent's life. The COVID-19 pandemic also brought forth challenges on staff in this project, and data quality may have been impacted, with the magnitude difficult to discern. However, we believe these to all underestimate the associations between circumstances and individual classes.

### **Implications and Future Directions**

Collectively, the three studies showed evidence that person-based and place-based interventions may be most beneficial in preventing substance use and drug overdose. For SMY, a focus should be on bolstering up anti-bullying policies and LGBTQ inclusive curricula in schools. Although most schools have anti-bullying policies, some are quite vague, and may not explicitly mention no bullying or harassment on the basis of sexual identity. Expanding anti-bullying and harassment policies to be more inclusive may provide further health benefits to

not just SMY, but non-SMY (Meyer et al., 2018). Schools should focus on supporting SMY by incorporating LGBTQ inclusive curricula within substance use prevention programming, since making the content more relevant and impactful to them may reduce some of the disparities SMY may face in regard to substance use (Russell et al., 2021).

There is a great need for interventions in the healthcare setting (i.e. during prenatal care visit) using a trauma-informed care approach (Racine et al., 2021; Sperlich et al., 2017).

Healthcare providers can screen pregnant people for ACEs, SLEs, and substance use, taking the necessary actions to provide trauma-informed care and connect patients to behavioral health services if necessary (Racine et al., 2021; Sperlich et al., 2017). Visits with a healthcare provider would provide an opportunity to identify pregnant people who have a history of childhood trauma or experiencing high levels of life stressors, and provide advice and resources to curb possible substance use as a self-medicating behavior (Racine et al., 2021).

It is clear that addressing the social and contextual factors related to overdose are key in preventing drug overdose. For example, we found that a quarter of those who tested positive for methamphetamine were experiencing homelessness or housing insecurity. Expanding access to affordable housing and medical, social, and employment assistance programs for people who are unhoused, may increase the likelihood of these individuals entering treatment, staying in recovery, and decreasing misuse and overdose (NHCHC, n.d.). Additionally, since younger people of color were more likely to test positive for multiple substances, most notably the powerful synthetic opioid fentanyl, and were likely to have a bystander present at the time

of overdose, leveraging the role of the bystander is critical. Culturally appropriate interventions for potential bystanders to train them to take life-saving measures and administering naloxone, may save lives (Giglio et al., 2015).

There is a need for further study on protective factors among vulnerable populations such as SMY, pregnant persons, as well as the identification of factors that could be leveraged to prevent overdose death. Longitudinal studies across the lifespan with robust and validated social, contextual, and environmental measures, are needed to advance this research. For example, longitudinal research across the lifespan from childhood into adulthood can address the lack of temporality in these studies by being able to observe people over time, compiling a comprehensive list of factors that might reduce substance use and drug overdose. Since most of our studies relied on self-reported measures, more objective measures from medical and administrative records, would be more promising in reducing errors due to self-report.

## **Conclusions**

The first study found that the school environment was associated with a reduced odds of NMUPO, while this finding did not hold up with state equality laws. The second study found that ACEs and SLEs were associated with marijuana use during pregnancy, and there was evidence of additive interaction when assessing both exposures jointly. The third study identified four distinct groups of people who die by drug overdose and several social and contextual factors associated with these groups that may have been able to be leveraged to

prevent overdose death. Collectively, these findings highlight the need for advancing research of protective factors in vulnerable populations, and finding ways to prevent drug overdose.

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## Appendices

### Appendix I. ACE category and corresponding question in the Nevada PRAMS survey.

ACE Category	Survey Question
Emotional Abuse	"How often did a parent or adult in your home ever swear at you, insult you, or put you down?"
Physical Abuse	"Before age 18, how often did a parent or adult in your home ever hit, beat, kick or physically hurt you in any way? Do not include spanking."
Sexual Abuse	"How often did anyone at least 5 years older than you or an adult ever touch you sexually?" "How often did anyone at least 5 years older than you or an adult try to make you touch them sexually?" "How often did anyone at least 5 years older than you or an adult force you to have sex?"
Witness intimate partner violence	"How often did your parents or adults in your home ever slap, hit, kick, punch or beat each other up?"
Substance abuse in the household	"Did you live with anyone who was a problem drinker or alcoholic?" "Did you live with anyone who used illegal street drugs or who abused prescription medications?"
Mental illness in the household	"Did you live with anyone who was depressed, mentally ill, or suicidal?"
Parental separation or divorce	"During the time period before you were 18 years of age did you parents get separated or divorced?"

**Appendix II. SLE description in the Nevada PRAMS survey**

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**SLE Description**

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- 1) A close family member was very sick and had to go into the hospital;
  - 2) I got separated or divorced from my husband or partner;
  - 3) I moved to a new address;
  - 4) I was homeless or had to sleep outside, in a car, or in a shelter;
  - 5) My husband or partner lost their job;
  - 6) I lost my job even though I wanted to go on working;
  - 7) My husband, partner, or I had a cut in work hours or pay;
  - 8) I was apart from my husband or partner due to military deployment or extended work-related travel;
  - 9) I argued with my husband or partner more than usual;
  - 10) My husband or partner said they didn't want me to be pregnant;
  - 11) I had problems paying the rent, mortgage, or other bills;
  - 12) My husband, partner, or I went to jail;
  - 13) Someone very close to me had a problem with drinking or drugs;
  - 14) Someone very close to me died
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