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# Adverse childhood experiences, internalizing/externalizing symptoms, and associated prescription opioid misuse: A mediation analysis

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## Abstract

Adverse childhood experiences (ACEs) are associated with mental health and substance use problems, but lesser known is how they interconnect. The objective of this study was to examine how internalizing and externalizing symptoms mediate the association of ACEs with prescription opioid misuse in order to understand how ACEs interconnect with mental health and substance use problems. Adults aged 18 or older from the National Epidemiological Survey on Alcohol and Related Conditions Wave 3 (NESARC-III) conducted in 2012–2013 were included (N = 36,309). The prescription opioid misuse outcomes examined include prescription opioid misuse status, early-onset status of prescription opioid misuse, frequency of past-year prescription opioid misuse, and opioid use disorder. A natural effect model and regression analyses were used to conduct the mediation analyses. We found that respondents with higher ACE scores had greater odds of reporting past-year and lifetime prescription opioid misuse and DSM-V-diagnosed opioid use disorder as well as early onset of prescription opioid misuse (AORs range from 1.06 to 1.12). These associations are partially mediated by internalizing and externalizing symptoms. The findings suggest that internalizing and externalizing symptoms may be potential pathways through which ACEs are associated with prescription opioid misuse. Our results underscore the importance of preventing ACEs and reducing risk for internalizing and externalizing symptoms after exposure, which may reduce later prescription opioid misuse.

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Credit author statement

Lin designed and conceptualized the study. Tang conducted the statistical analysis and literature searches. Ports and Zhang helped with conceptualization of the study and interpretation of findings. Tang drafted the manuscript. Lin, Ports, and Zhang critically revised the manuscript. All authors contributed to and have approved the final manuscript.

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Declaration of competing interest

The authors have no competing interests or conflicts to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2020.106034.

**Keywords**

Prescription opioid misuse; Adverse childhood experiences; Internalizing symptoms; Externalizing symptoms; Mediation

## 1. Introduction

Since 1999, the number of overdose deaths involving opioids has increased dramatically. In 2017, 47,600 people died from drug overdose involving an opioid (Seth et al., 2018b), and the rate of deaths involving prescription opioids was five times higher than that in 1999 (Seth et al., 2018a). According to a nationally representative survey conducted in 2017, about 10.3 million adults aged 18 years or older misused prescription opioids, and 1.6 million had an opioid use disorder (OUD) (Center for Behavioral Health Statistics and Quality, 2018). The associated economic costs of prescription opioid misuse and overdose are substantial. The total estimated economic burden was $78.5 billion in 2013, which is attributed to healthcare and substance abuse treatment costs, lost productivity, and criminal justice costs (Florence et al., 2016). Collectively, these findings underscore the urgent need to address factors that contribute to prescription opioid misuse and overdose.

An area with promise to prevent prescription opioid misuse is the body of work focused on preventing and addressing Adverse Childhood Experiences (ACEs)-a collection of potentially, traumatic experiences that occur during the first 18 years of life. ACEs often include exposure to abuse (emotional, physical, sexual), neglect (emotional and physical) and household challenges (domestic violence, substance abuse, mental illness, parental separation or divorce and incarcerated family member) (Felitti et al., 1998; Merrick et al., 2018). While some degree of childhood adversity is a normal and essential part of human development, chronic or repeated exposure to ACEs can result in a toxic stress response that derails optimal development by producing changes in gene expression, brain function, immune function, and coping strategies adopted (Shonkoff and Garner, 2012), which may contribute to an individual's risk for substance misuse, including prescription opioid misuse (Norman et al., 2011).

Previous studies demonstrate robust associations between ACEs and substance misuse (Dube et al., 2003; Orsi et al., 2018). Specifically, childhood emotional abuse, physical abuse, and sexual abuse are associated with high risk of using/misusing substances in later adolescence and adulthood. In studies that focused specifically on opioid misuse, the prevalence of childhood trauma was high among people with OUD (Conroy et al., 2009). ACEs were also associated with early onset for opioid misuse among patients with OUD (Stein et al., 2017). However, the number of studies focused on the association between ACEs and prescription opioid misuse and the pathways between these experiences is limited. One previous study documented the associations between ACEs and prescription opioid misuse (Austin and Shanahan, 2018), identifying ACEs as a risk factor that predict prescription opioid misuse. However, the pathways through which ACEs are associated with prescription opioid misuse remain unclear. Mediation analyses are needed to understand

these pathways to uncover the underlying mechanisms which can inform more specific public health interventions based on different mechanisms.

Previous studies have shown the association of internalizing (depression, anxiety, and traumatic distress) and externalizing (aggression, delinquency, and hyperactivity) symptoms with both ACEs and prescription opioid misuse (Hunt et al., 2017; Martins et al., 2012; Young et al., 2012). However, few studies have explicitly tested whether internalizing and externalizing symptoms mediate the relationship between ACEs and opioid misuse. In addition, understanding this mediated association is important for designing or identifying existing interventions that address internalizing and externalizing symptoms for those exposed to ACEs to prevent them from misusing prescription opioids later.

Given these connections, this study focuses on internalizing and externalizing symptoms as potential mediators of the association between ACEs and prescription opioid misuse. Internalizing and externalizing symptoms may mediate the association between ACEs and prescription opioid misuse in different ways and may uncover important implications for interventions. For example, the potential pathway through which internalizing symptoms mediate the association between ACEs and prescription opioid misuse is based on the self-medication hypothesis that prescription opioids are used to alleviate distress and anxiety disorders (Garland et al., 2015; Martins et al., 2012). Only one study has examined this potential pathway using the National Longitudinal Study of Adolescent to Adult Health data, which found that distress and anxiety disorders did not mediate the association between ACEs and prescription opioid misuse (Austin and Shanahan, 2018). The authors thought one explanation for this finding was the inadequate measures for anxiety disorders that only captured symptoms in a short time frame (the past week). Externalizing symptoms may also mediate the association between ACEs and prescription opioid misuse based on the sensation seeking hypothesis that prescription opioids are used to meet the need for excitement (Boyd et al., 2006; Horvath et al., 2004; Young et al., 2012). Sensation seeking was defined as a trait of seeking varied, novel, complex and intense sensations and experiences (Zuckerman and Kuhlman, 2000) and was linked to externalizing symptoms (Joireman et al., 2003; Wilson and Scarpa, 2011). We therefore hypothesized that some individuals exposed to ACEs were likely to develop externalizing symptoms and misused prescription opioids for sensation seeking. Past studies demonstrate that externalizing symptoms, such as aggression, are associated with substance use/misuse (Colder et al., 2013). However, to our knowledge, no research has examined how externalizing symptoms mediate the association between ACEs and prescription opioid misuse.

Although previous studies have concluded that ACEs are risk factors for prescription opioid misuse, the pathways through which ACEs are associated with prescription opioid misuse are not clearly identified. This study aimed to address the following research gaps: 1) studying the associations between ACEs and prescription opioid misuse; 2) examining how internalizing symptoms and externalizing symptoms mediate this association by examining multiple prescription opioid misuse outcomes. In the present study, we hypothesize that 1) having a history of ACEs is associated with prescription opioid misuse in adulthood; 2) both internalizing and externalizing symptoms are positively associated with ACEs and

prescription opioid misuse; 3) internalizing symptoms and externalizing symptoms mediate the association.

## 2. Methods

### 2.1. Data and study sample

We used data from Wave 3 of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC-III) conducted in 2012–2013 by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The NESARC-III is a nationally representative sample of the non-institutionalized adult population 18 years and older in the United States (N = 36,309). Multistage probability sampling is used to randomly select respondents from the U.S. adult population (Grant et al., 2015). This study was deemed exempt for review from the Institutional Review Board of Indiana University.

### 2.2. Measures

**2.2.1. Outcome variables—**The six prescription opioid misuse outcomes examined include prescription opioid misuse status (past-year and lifetime), early-onset status of prescription opioid misuse, opioid use disorder (past-year and lifetime), and frequency of past-year prescription opioid misuse. These measures have been used in previous literature (Arterberry et al., 2016).

**2.2.1.1. Prescription opioid misuse status.:** NESARC respondents were asked about their misuse of prescription opioids. We used two variables to measure prescription opioid misuse status: lifetime (ever before) and past-year (in the past 12 months) misuse. Both variables are binary. In the survey, for instance, respondents were asked “Have you ever used any of these painkillers, for example… methadone, codeine, Demerol, Vicodin, Oxycontin, opium, oxy, Percocet, Dilaudid, Percodan, morphine that you may have used on your own - that is, either without a doctor’s prescription; in greater amounts, more often, or longer than prescribed; or for a reason other than a doctor said you should use them?”

**2.2.1.2. Early-onset status of prescription opioid misuse.:** Previous studies using NESARC utilized 25th percentile of the onset age to define the cutoff for early-onset status for substance use (equal or younger than age 17). Based on this, we created a binary early onset variable based on this cutoff coded “1” for early onset and “0” otherwise (Arterberry et al., 2016; Lin et al., 2016).

**2.2.1.3. Opioid use disorder.:** Past-year OUD and lifetime OUD status variables were created by NESARC-III based on validated DSM-V criteria. OUD was assessed based on the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5), which was designed to assess the diagnostic definitions in the DSM-V. The disorder diagnosis has been validated (Grant et al., 2015; Grant et al., 2016). Both variables are binary.

**2.2.1.4. Frequency of past-year prescription opioid misuse.:** The frequency of prescription opioid misuse in the past 12 months is coded with a 0–10 scale: 0 = never, 1 =

once a year, 2 = 2 times a year, 3 = 3–6 times a year, 4 = 7–11 times a year, 5 = once a month, 6 = 2–3 times a month, 7 = 1–2 times a week, 8 = 3–4 times a week, 9 = nearly every day, and 10 = every day. This variable was treated as continuous.

**2.2.2. Primary independent variable—**The ACEs variable serves as the primary independent variable. The ACE score variable was created based on twenty-nine questions regarding ten ACEs categories (see Appendix A): emotional abuse, physical abuse, sexual abuse, physical neglect, emotional neglect, household physical violence, household substance abuse, incarcerated household member, household mental illness, and parental separation or divorce. Following the same method that a previous study used for ACEs coding, questions were collapsed for each ACE category, and exposure was determined. Respondents were coded as a "1" if they were exposed to that category of ACE, as specified in the previous study (Dong et al., 2004). We then summed the number of ACEs categories each respondent was exposed to (score ranged from 0 to 10).

**2.2.3. Mediator variable—**In the present study, the mediator variables are internalizing symptoms and externalizing symptoms. Global Appraisal of Individual Needs - Shorter Screener (GAIN-SS) provides a list of items that can be used to identify individuals who have lifetime internalizing or externalizing symptoms. The reliability of GAIN-SS has been validated (Dennis et al., 2006). We chose items from NESARC-III based on the GAIN-SS manual and further conducted factor analysis using the NESAR-III data to ensure the validity of the selected items. Fourteen items measuring internalizing symptoms and fourteen items measuring externalizing symptoms (see Appendix B) were included. Cronbach's alpha coefficients suggest that our scales for internalizing ($\alpha = 0.80$) and externalizing ($\alpha = 0.76$) symptoms are reliable. Reports of yes are coded as 1, or 0 otherwise and summed. Each respondent received a total score for lifetime internalizing symptoms (score ranged from 0 to 14) and externalizing symptoms respectively (score ranged from 0 to 14). Both of the variables are continuous.

**2.2.4. Sociodemographic and other substances misuse/use variables—**The sociodemographic control variables include self-reported sex (male/female) at the time of the survey, age, race/ethnicity (non-Hispanic white, non-Hispanic black, Non-Hispanic American Indian, Non-Hispanic Asian, Hispanic), education (less than high school, high school, some college, college, or graduate school), marital status (married or not), region (Northeast, Midwest, South, or West), and employment status (employed or not). Because studies have shown that cigarette and cannabis use are associated with prescription opioid misuse (Fiellin et al., 2013; Griesler et al., 2019; Romberg et al., 2019), we also controlled for lifetime cannabis use (yes/no) and lifetime use of at least 100 cigarettes (yes/no).

## 2.3. Statistical analyses

To understand the mechanism through which ACEs are associated with prescription opioid misuse, mediation analyses were conducted. There are two mediators in the present study: internalizing symptoms and externalizing symptoms. Fig. 1 provides a depiction of the mediation models. Path *c* represents direct effects of ACEs on prescription opioid misuse outcomes. Path *a* and path *b* together represent indirect effects of ACEs on prescription

opioid misuse. We used the natural effect model (NEM) (Valeri and VanderWeele, 2013) to examine the association between ACEs and prescription opioid misuse outcomes, the mediating influences of internalizing and externalizing symptoms, while controlling for socioeconomic variables. The NEM can estimate the indirect effect of ACEs on prescription opioid misuse through internalizing symptoms and through externalizing symptoms. Because there are two mediators, one mediator was controlled for while the mediation effect of the other was estimated. All statistical analyses were conducted using Stata SE 15. The Stata package "paramed" was used to conduct all mediation analyses because it provides correct estimates of standard errors of indirect effect in the logistic regression model; it also allows hypothesis testing for the mediation. One limitation of this package is that it does not allow analysis with complex survey weighting, which prevented this study from conducting weighted analysis.

## 3. Results

### 3.1. Descriptive statistics and direct effect

The descriptive statistics of the sample are reported in Table 1. Table 2 contains the estimates of the direct association between ACEs and prescription opioid misuse, while controlling for internalizing symptoms, externalizing symptoms and sociodemographic and other substance use variables. Adjusted odds ratios (AOR) and beta coefficients (β) are reported for binary outcomes and continuous outcomes, respectively, in this study. Each unit increase in ACE score is directly associated with greater odds of past-year prescription opioid misuse (direct AOR = 1.03, 95% CI = 1.00–1.06), lifetime prescription opioid misuse (direct AOR = 1.04, 95% CI = 1.02–1.06), early onset of prescription opioid misuse (direct AOR = 1.07, 95% CI = 1.03–1.11), having lifetime prescription OUD (direct AOR = 1.06, 95% CI = 1.02–1.10), and higher frequency of prescription opioid misuse (β = 0.01, 95% CI = 0.002–0.02). ACE score was not associated with past-year prescription OUD.

### 3.2. Mediation analysis

Table 3 presents mediation analyses results. The second column of Table 3 demonstrates the estimates of the total effect. The total effect is equal to the summation of the indirect effect and the direct effect. As we have two mediators, total effects were calculated for internalizing symptoms and externalizing symptoms, respectively.

The forth column of Table 3 presents the estimates of the indirect effect. Both lifetime internalizing and externalizing symptoms partially mediate the association between ACEs and all prescription opioid misuse outcomes. In particular, internalizing symptoms partially mediate the association between ACEs and past-year prescription opioid misuse (indirect AOR = 1.03, 95% CI = 1.02–1.03, proportion mediated = 47%), lifetime prescription opioid misuse (indirect AOR = 1.02, 95% CI = 1.02–1.03, proportion mediated = 34%), early onset of prescription opioid misuse (indirect AOR = 1.02, 95% CI = 1.01–1.03, proportion mediated = 22%), past-year OUD (indirect AOR = 1.06, 95% CI = 1.05–1.08, proportion mediated = 58%), lifetime OUD (indirect AOR = 1.06, 95% CI = 1.05–1.07, proportion mediated = 50%), and frequency of prescription opioid misuse (indirect β = 0.01, 95% CI = 0.008–0.012, proportion mediated = 49%).

Externalizing symptoms partially mediate the association between ACEs and past-year prescription opioid misuse (indirect AOR = 1.03, 95% CI = 1.02–1.04, proportion mediated = 50%), lifetime prescription opioid misuse (indirect AOR = 1.04, 95% CI = 1.03–1.04, proportion mediated = 48%), early onset of prescription opioid misuse (indirect AOR = 1.05, 95% CI = 1.04–1.05, proportion mediated = 43%), past-year OUD (indirect AOR = 1.04, 95% CI = 1.03–1.05, proportion mediated = 46%), lifetime OUD (indirect AOR = 1.04, 95% CI = 1.04–1.05, proportion mediated = 43%), and frequency of prescription opioid misuse (indirect β = 0.02, 95% CI = 0.01–0.02, proportion mediated = 61%).

## 4. Discussion

The present study examined the association between ACEs and prescription opioid misuse and whether internalizing symptoms and externalizing symptoms mediate this relationship. To our knowledge, this is the first study to examine the mediation effect of internalizing and externalizing symptoms on the association between ACEs and prescription opioid misuse.

The first hypothesis, that history of ACEs is associated with prescription opioid misuse in adulthood, was supported. Furthermore, among our prescription opioid misuse outcomes, ACEs had the strongest direct effect on early onset of prescription opioid misuse, which is consistent with previous studies on the association of ACEs with substance use/misuse initiation (Dube et al., 2003; Ompad et al., 2005; Stein et al., 2017). This suggests that ACEs play an important role in the early initiation of prescription opioid misuse. Although the odds ratios are not large, preventing ACEs may reduce the risk of early initiation of prescription opioid misuse and thus reduce the risk of future illicit opioid use, prescription opioid injection misuse (Jones et al., 2017), and adverse health outcomes, such as OUD and overdose. Policies, practices, and programs that change conditions for children and families can prevent ACEs from occurring in the first place and may simultaneously mitigate the impact of ACE exposure on later outcomes (e.g., prescription opioid misuse) (Fortson et al., 2016).

In line with the second and third hypotheses, the mediation analysis supports that lifetime internalizing and externalizing symptoms partially mediate the association between ACEs and prescription opioid misuse. Both internalizing and externalizing symptoms were positively associated with ACEs and were positively associated with each of the prescription opioid misuse outcomes. Our finding regarding the mediating role of internalizing symptoms supports the self-medication hypothesis (Colder et al., 2013; Garland et al., 2015; Martins et al., 2012). This hypothesis states that individuals who have experienced ACEs may misuse opioids to cope with internalizing symptoms, such as depression symptoms. Our findings regarding externalizing symptoms reveal another potential pathway between ACEs and prescription opioid misuse and supports the Behavioral Disinhibition Model, which suggests that individuals with behavioral disinhibition, an inability to self-regulate and to inhibit socially undesirable actions (i.e., aggression, delinquency), are often comorbid with substance use/misuse (Iacono et al., 2008; Young et al., 2012).

In general, the mediation effect of externalizing symptoms was larger than that of the internalizing symptoms. This finding suggests that among those individuals exposed to

ACEs, externalizing symptoms may play a greater role in predicting prescription opioid misuse. This is consistent with previous findings that the association between externalizing symptoms and substance misuse is stronger than that for internalizing symptoms (Colder et al., 2013; King et al., 2004). Moreover, intervening with children who are exposed to ACEs to prevent externalizing symptoms, such as bullying or aggressive behaviors, may reduce their risk of misusing prescription opioids (David-Ferdon et al., 2016; Pophillat et al., 2016). For instance, a classroom-based program, Life Skills Training (LST), is effective at improving social skills and reducing risk behaviors including drug use and might also be effective at mitigating opioid misuse (David-Ferdon et al., 2016). A combination of LST and Strengthening Families Program (SFP), another evidence based prevention program that aims to improve children's social skills, was implemented and demonstrated protective effects for prescription opioid misuse into early adulthood (Spoth et al., 2013).

This study also found that the mediation effects of internalizing symptoms and externalizing symptoms on opioids outcomes were heterogeneous. For example, internalizing symptoms played a relatively smaller role in mediating the early onset of prescription opioids, and a larger role in mediating both past-year and lifetime OUD. This suggests that interventions to prevent internalizing symptoms may have differential effects on different prescription opioid misuse outcomes. In contrast, externalizing symptoms had a much larger effect on early onset of prescription opioids than internalizing symptoms, which implies that efforts to prevent externalizing symptoms may be more effective in reducing the chance of early onset of prescription opioid misuse than internalizing symptoms. The heterogeneity implies that different approaches to preventing internalizing and externalizing symptoms may lead to different effects on prescription opioid misuse outcomes. Nevertheless, it remains important to prevent ACEs given the direct relationship between ACEs and opioid misuse.

There were limitations of the present study. First, we were not able to determine the temporal sequence of internalizing and externalizing symptoms, because respondents were asked whether those symptoms ever happened during their lifetime. It is possible that individuals may experience ACEs, misuse prescription opioids and internalizing and externalizing symptoms simultaneously. It is also possible that internalizing or externalizing symptoms developed after the onset of prescription opioid misuse for some individuals as a result of their misuse or life factors. Future longitudinal research to disentangle the temporal relationships among the ACEs, internalizing and externalizing symptoms and prescription opioid misuse are warranted. Second, given the complex statistical analyses, survey weights were not used in this study, and as such, our results may not yield national estimates, which limit generalizability. Third, NESARC-III was conducted in 2012–2013 and therefore our findings may not fully reflect the more recent opioid epidemic (e.g., rapid increase in overdose deaths involving synthetic opioids such as illicitly manufactured fentanyl since 2013). In addition, we used a conservative criterion (Dong et al., 2004; Roos et al., 2013) to establish ACE exposure. While this resulted in a lower ACE score, it may provide a truer sense of exposure to trauma. Despite these limitations, this study still provides important findings to inform the development of public health interventions.

## 5. Conclusions

Efforts to support safe, stable, and nurturing relationships and environments that can prevent ACEs may also provide an upstream approach to reducing risk for internalizing and externalizing symptoms and prescription opioid misuse (Centers for Disease Control and Prevention, 2014). In addition, interventions that prevent or treat mental health symptoms (e.g., trauma-focused cognitive behavioral therapy, multisystemic therapy) (Cary and McMillen, 2012; van der Stouwe et al., 2014) may reduce the risk of misusing prescription opioids for those already exposed to ACEs. Taken together, these findings highlight the importance of preventing and mitigating the impact of ACEs as a component of the public health strategy for addressing the opioid overdose epidemic.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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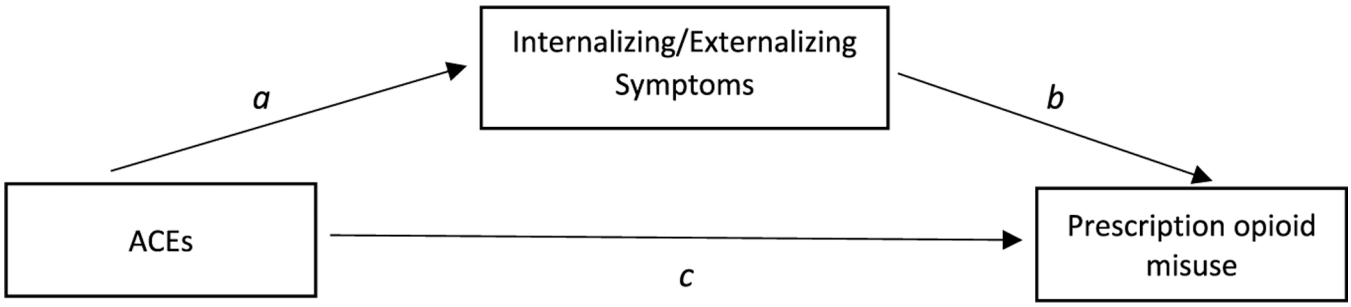


**Fig. 1.**
The concept model of the mediation relationship.

## Table 1

Descriptive Statistics: National Epidemiological Survey on Alcohol and Related Conditions, 2012–2013 (n = 36,309)

| Variable | n (%) |
|---|---|
| **Past-year opioid misuse** | |
| Misused | 1,579 (4.38%) |
| Not misused | 34,509 (95.62%) |
| **Lifetime opioid misuse** | |
| Misused | 4,090 (11.28%) |
| Not misused | 32,167 (88.72%) |
| **Early-onset opioid misuse** | |
| Yes | 1,003 (2.78%) |
| No | 35,118 (97.22%) |
| **Past-year OUD** | |
| Yes | 330 (0.91%) |
| No | 35,979 (99.09%) |
| **Lifetime OUD** | |
| Yes | 688 (1.89%) |
| No | 35,621 (98.11%) |
| **Opioid misuse frequency** | 0.25 (1.35)[a] |
| **ACE score** | 1.26 (1.75)[a] |
| **Internalizing symptoms** | 2.24 (3.44)[a] |
| **Externalizing symptoms** | 1.09 (1.75)[a] |
| **Sex** | |
| Female | 20,447 (56.31%) |
| Male | 15,862 (43.69%) |
| **Age** | 45.63 (17.53)[a] |
| **Race/ethnicity** | |
| Non-Hispanic white | 19,194 (52.86%) |
| Non-Hispanic black | 7,766 (21.39%) |
| American Indian | 511 (1.41%) |
| Non-Hispanic Asian | 1,801 (4.96%) |
| Hispanic | 7,037 (19.38%) |
| **Education** | |
| Less than high school | 5,490 (15.12%) |
| High school | 9,799 (26.99%) |
| Some college | 12,105 (33.34%) |
| College | 5,889 (16.22%) |
| Graduate school | 3,026 (8.33%) |
| **Marital status** | |
| Married | 14,482 (39.89%) |

| Variable | n (%) |
|---|---|
| Not married | 21,827 (60.11%) |
| **Region** | |
| Northeast | 5,180 (14.27%) |
| Midwest | 7,566 (20.84%) |
| South | 14,532 (40.02%) |
| West | 9,031 (24.87%) |
| **Employment** | |
| Unemployed | 2,557 (7.04%) |
| Employed | 33,752 (92.96%) |
| **Cannabis use** | |
| Used | 11,272 (31.10%) |
| Not used | 24, 971 (68.90%) |
| **Tobacco use** | |
| Used | 14, 778 (40.75%) |
| Not used | 21,491 (59.25%) |

[a]Mean (standard deviation) are calculated for continuous variables.

**Table 2**

Direct Effect of ACEs on Prescription Opioid Misuse: National Epidemiological Survey on Alcohol and Related Conditions, 2012–2013

| Variable | Prescription opioid misuse outcomes | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Past-year opioid misuse | | Lifetime opioid misuse | | Early onset of opioid misuse | | Past-year OUD | | Lifetime OUD | | Opioid misuse frequency | |
| | AOR | (95% CI) | AOR | (95% CI) | AOR | (95% CI) | AOR | (95% CI) | AOR | (95% CI) | β | (95% CI) |
| ACE score | 1.03 | (1.00, 1.06) | 1.04 | (1.02, 1.06) | 1.07 | (1.03, 1.10) | 1.05 | (0.99, 1.10) | 1.06 | (1.02, 1.10) | 0.01 | (0.002, 0.02) |
| Internalizing symptoms | 1.06 | (1.04, 1.07) | 1.05 | (1.04, 1.06) | 1.04 | (1.02, 1.06) | 1.14 | (1.11, 1.17) | 1.13 | (1.11, 1.15) | 0.02 | (0.02, 0.03) |
| Externalizing symptoms | 1.13 | (1.10, 1.16) | 1.16 | (1.14, 1.18) | 1.20 | (1.17, 1.24) | 1.16 | (1.11, 1.22) | 1.19 | (1.15, 1.23) | 0.07 | (0.06, 0.08) |
| Sex: female | 1.04 | (0.93, 1.16) | 0.91 | (0.85, 0.98) | 0.86 | (0.75, 0.99) | 0.97 | (0.77, 1.23) | 0.98 | (0.82, 1.15) | 0.02 | (−0.01, 0.05) |
| Age | 0.99 | (0.99, 1.00) | 0.99 | (0.99, 1.00) | 0.96 | (0.95, 0.96) | 1.00 | (0.99, 1.01) | 0.99 | (0.99, 1.00) | 0.001 | (0.001, 0.002) |
| Race/ethnicity | | | | | | | | | | | | |
| Non-Hispanic white | (Ref) | | (Ref) | | (Ref) | | (Ref) | | (Ref) | | (Ref) | |
| Non-Hispanic black | 1.06 | (0.92, 1.21) | 0.66 | (0.60, 0.73) | 0.52 | (0.43, 0.63) | 0.96 | (0.72, 1.28) | 0.51 | (0.40, 0.64) | 0.04 | (−0.002, 0.07) |
| American Indian | 0.90 | (0.61, 1.31) | 0.69 | (0.53, 0.91) | 0.45 | (0.26, 0.78) | 0.83 | (0.40, 1.75) | 0.72 | (0.43, 1.21) | −0.04 | (−0.16, 0.08) |
| Non-Hispanic Asian | 0.62 | (0.43, 0.90) | 0.60 | (0.48, 0.75) | 0.51 | (0.32, 0.82) | 0.38 | (0.12, 1.21) | 0.39 | (0.19, 0.80) | −0.04 | (−0.11, 0.02) |
| Hispanic | 0.88 | (0.75, 1.03) | 0.67 | (0.60, 0.74) | 0.60 | (0.49, 0.73) | 0.85 | (0.61, 1.20) | 0.51 | (0.39, 0.66) | −0.03 | (−0.07, 0.01) |
| Education | | | | | | | | | | | | |
| Less than high school | (Ret) | | (Ref) | | (Ref) | | (Ref) | | (Ref) | | (Ref) | |
| High school | 0.98 | (0.83, 1.15) | 1.03 | (0.92, 1.16) | 1.09 | (0.88, 1.35) | 0.83 | (0.61, 1.12) | 0.88 | (0.69, 1.12) | −0.05 | (−0.10, −0.01) |
| Some college | 0.90 | (0.77, 1.05) | 1.15 | (1.03. 1.29) | 1.11 | (0.90, 1.37) | 0.67 | (0.49, 0.91) | 0.80 | (0.63, 1.01) | −0.08 | (−0.12, −0.04) |
| College | 0.78 | (0.63, 0.95) | 1.09 | (0.95, 1.26) | 0.94 | (0.71, 1.23) | 0.40 | (0.25, 0.66) | 0.59 | (0.43, 0.82) | −0.13 | (−0.18, −0.08) |
| Graduate school | 0.76 | (0.59, 1.00) | 0.96 | (0.81, 1.14) | 0.90 | (0.62, 1.32) | 0.33 | (0.16, 0.68) | 0.45 | (0.28, 0.72) | −0.12 | (−0.18, −0.06) |
| Married: yes | 0.75 | (0.66, 0.84) | 0.81 | (0.75, 0.87) | 0.86 | (0.74, 1.01) | 0.81 | (0.62, 1.05) | 0.92 | (0.77, 1.10) | −0.06 | (−0.09, −0.03) |
| Region | | | | | | | | | | | | |
| Northeast | (Ref) | | (Ref) | | (Ref) | | (Ref) | | (Ref) | | (Ref) | |
| Midwest | 1.31 | (1.10, 1.57) | 1.23 | (1.09, 1.39) | 1.52 | (1.20, 1.93) | 0.96 | (0.67, 1.37) | 0.80 | (0.61, 1.04) | 0.07 | (0.02, 0.12) |
| South | 1.14 | (0.97, 1.36) | 1.17 | (1.04, 1.31) | 1.33 | (1.06, 1.67) | 0.85 | (0.61, 1.18) | 0.90 | (0.71, 1.14) | 0.05 | (0.01, 0.09) |
| West | 1.28 | (1.07, 1.53) | 1.27 | (1.13, 1.44) | 1.49 | (1.17, 1.88) | 0.83 | (0.58, 1.19) | 0.87 | (0.68, 1.12) | 0.06 | (0.01, 0.10) |
| Unemployed: yes | 1.06 | (0.89, 1.27) | 1.11 | (0.98, 1.26) | 1.00 | (0.81, 1.23) | 0.95 | (0.66, 1.36) | 1.13 | (0.88, 1.45) | −0.01 | (−0.07, 0.04) |
| Cannabis use: yes | 2.90 | (2.57, 3.28) | 4.35 | (4.01, 4.71) | 4.20 | (3.54, 5.00) | 2.56 | (1.95, 3.37) | 4.08 | (3.30, 5.04) | 0.23 | (0.20, 0.26) |
| Tobacco use: yes | 1.56 | (1.39, 1.76) | 1.48 | (1.36, 1.60) | 1.76 | (1.51, 2.06) | 1.73 | (1.31, 2.27) | 1.81 | (1.48, 2.21) | 0.11 | (0.08, 0.14) |

| Variable | Prescription opioid misuse outcomes | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Past-year opioid misuse | | Lifetime opioid misuse | | Early onset of opioid misuse | | Past-year OUD | | Lifetime OUD | | Opioid misuse frequency | |
| | AOR | (95% CI) | AOR | (95% CI) | AOR | (95% CI) | AOR | (95% CI) | AOR | (95% CI) | β | (95% CI) |
| n | 36,034 | | 36,201 | | 36,066 | | 36,211 | | 36,211 | | 36,022 | |

AOR = adjusted odds ratio; CI = confidence interval

All models were adjusted for internalizing and externalizing symptoms, sex, race/ethnicity, education, marital status, region, employment status, cannabis use, and tobacco use.

**Table 3**

Mediation Effect of Lifetime Externalizing and Internalizing Symptoms on the Association between ACEs and Prescription Opioid Misuse: National Epidemiological Survey on Alcohol and Related Conditions, 2012–2013

| Outcome Variable | Total Effect | | Natural Indirect Effect | | Proportion Mediated |
|---|---|---|---|---|---|
| | AOR or β | (95% CI) | AOR or β | (95% CI) | |
| Mediator: internalizing symptoms | | | | | |
| Past-year opioid misuse | 1.06 | (1.03, 1.09) | 1.03 | (1.02, 1.03) | 47% |
| Lifetime opioid misuse | 1.07 | (1.05, 1.09) | 1.02 | (1.02, 1.03) | 34% |
| Early onset of opioid misuse | 1.09 | (1.05, 1.12) | 1.02 | (1.01, 1.03) | 22% |
| Past-year OUD | 1.11 | (1.06, 1.17) | 1.06 | (1.05, 1.08) | 58% |
| Lifetime OUD | 1.12 | (1.08, 1.17) | 1.06 | (1.05, 1.07) | 50% |
| Frequency of opioid misuse[a] | 0.02 | (0.01, 0.03) | 0.01 | (0.008, 0.012) | 49% |
| Mediator: externalizing symptoms | | | | | |
| Past-year opioid misuse | 1.06 | (1.04, 1.09) | 1.03 | (1.02, 1.04) | 50% |
| Lifetime opioid misuse | 1.08 | (1.06, 1.10) | 1.04 | (1.03, 1.04) | 48% |
| Early onset of opioid misuse | 1.12 | (1.08, 1.15) | 1.05 | (1.04, 1.05) | 43% |
| Past-year OUD | 1.09 | (1.03, 1.14) | 1.04 | (1.03, 1.05) | 46% |
| Lifetime OUD | 1.11 | (1.07, 1.15) | 1.04 | (1.04, 1.05) | 43% |
| Frequency of opioid misuse[a] | 0.03 | (0.02, 0.04) | 0.02 | (0.01, 0.02) | 61% |

AOR = adjusted odds ratio; CI = confidence interval.

All models were adjusted for internalizing and externalizing symptoms, sex, race/ethnicity, education, marital status, region, employment status, cannabis use, and tobacco use.

[a] β coefficient was reported.