

An Umbrella Review of the Links Between Adverse Childhood Experiences and Substance Misuse: What, Why, and Where Do We Go from Here?

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Background and Objectives: A wealth of research has identified adverse childhood experiences (ACEs; abuse, neglect, violence or disorder in the home) as a strong risk factor for substance misuse. Synthesis of the existing evidence is critical to shape policy and inform directions for future research. Existing reviews have focused on specific substances or substance use outcomes (eg, disorder), and do not include discussion of the mechanisms that operate between ACEs and substance misuse. The current umbrella review aims to synthesize reviews on the relationship between ACEs and substance misuse, review the evidence on the mechanisms linking these, identify existing gaps in our knowledge, and discuss critical directions for future research, practice, and public policy.

Methods: Two electronic databases (PsycINFO and Medline) were searched for reviews published between 1998 and 2022 on the link between ACEs and substance misuse. Twenty articles met eligibility criteria and were qualitatively synthesized.

Results: Results overwhelmingly demonstrated an elevated risk of substance misuse or disorder, among adolescents and adults exposed to ACEs. Research on the mechanisms that explain this link highlights a multitude of potential intervention targets, with childhood stress propelling a cascade of effects across neurobiological, endocrine, immune, metabolic, and nervous systems, impacting psychosocial and cognitive functioning. Nonetheless, the literature is subject to limitations surrounding potential unmeasured cofounders and causality, as well as decontextualizing childhood adversity from broader structural issues that influence the link between ACEs and substance misuse. Research, policy, and practice that seek to holistically understand and address the relationship between ACEs and substance misuse within the broader social determinants of health is crucial.

Keywords: adverse childhood experiences, substance misuse, umbrella review, social determinants of health

Introduction

Substance misuse refers to the use of alcohol and other drugs in ways that confer harm to the user or those around them.¹ Accordingly, substance misuse accounts for a substantial burden of disease globally, through substance use disorders as well as associated unintentional injuries, chronic diseases, and suicide.² Reducing this disease burden necessitates prevention approaches at both the universal level (ie, delivered to all), and critically, targeted to those most at risk of substance misuse. Moreover, treatment and rehabilitative approaches that recognize drivers of substance misuse and disorder are critical. In this respect, a life course approach that considers the upstream, social determinants of health is vital,³ and has identified exposure to adverse childhood experiences (ACEs) as an important determinant to reduce the burden of substance misuse.⁴

While the relationship between early-life stressors and subsequent risk for substance misuse has been recognized for decades, in 1998 the CDC-ACE study examined associations of a set of seven types of ACEs (emotional, physical, sexual abuse, domestic violence, living with a household member with a mental illness, substance use problems, or ever

incarcerated) with health risk behaviors and disease in over 9500 adult members of the Kaiser Permanente Health Maintenance Organisation.⁵ A graded association was found between the number of ACEs experienced and all studied health risk behaviors and diseases, including substance misuse, mental illness, sexually transmitted disease, obesity, heart disease and cancer.⁵ This study spurred a wealth of research demonstrating associations between a specific set of childhood adversity types (which was expanded to include emotional and physical neglect, and parental divorce^{6,7}) and physical and mental health outcomes, including substance misuse. This research has drawn attention to ACEs as a public health issue, highlighting the critical role of public policy, population health, and clinical practice in preventing ACE exposure and intervening on the pathways linking exposure to elevated risk for substance misuse and other poor health outcomes.⁸ Encouragingly, policy and practice changes arising out of the ACEs literature indicate some success in reducing the prevalence of certain types of ACEs⁹ and a growing recognition of the importance of applying a trauma-informed lens to research and clinical practice addressing substance misuse.^{10,11}

Given the substantial and accumulating research available, synthesis of the existing evidence is critical to continue to shape policy and inform directions for future research. While some reviews of the literature have examined the association between ACEs and the misuse of specific substances or other substance use outcomes (eg, disorder), to our knowledge there exists no synthesis of the relationship between ACEs and substance misuse that synthesizes the evidence more broadly. Moreover, reviews considering the potential mechanisms that operate between ACEs and substance misuse, as well as critiquing existing limitations, are rarely conducted alongside the evidence synthesis. The current umbrella review aims to synthesize the last quarter century of reviews on the relationship between ACEs and substance misuse, the mechanisms linking these, identify existing gaps in our knowledge and critical directions for future research.

Defining Adverse Childhood Experiences (ACEs)

In this umbrella review, ACEs are conceptualized as experiences of severe threat or deprivation occurring in childhood, approximately aligned with the CDC definition of ACEs that includes physical, sexual, or emotional abuse, physical or emotional neglect, exposure to domestic violence, household mental illness or substance misuse, household incarceration, and parental separation.^{5,6} In recent years, researchers have called attention to some of the limitations of the ACEs framework: that it excludes other exposures that constitute childhood adverse experiences, such as bullying or community violence;¹² and that it removes childhood adversity from its broader structural context and thus oversimplifies the issue as rooted in individuals and families.^{13,14} Nonetheless, the current synthesis conceptualizes ACEs according to this framework given its predominance throughout the last quarter-century of research and its influence on public policy.¹⁵ We acknowledge its limitations and do not exclude studies that include a broader conceptualization of ACEs, as long as they also include some of the traditional set of 10 ACEs. We employ an aggregative approach to ACEs, rather than reviewing evidence from specific types of ACEs (eg, solely sexual abuse), as this enables a synthesis of the complex and abundant existing evidence. This approach is supported by prevalence studies demonstrating the majority of children exposed to adversity will experience multiple types,^{16,17} rendering examination of the unique effects of one type of ACE on substance misuse as limiting ecologically validity. Further, there is robust evidence of a dose–response effect linking an increasing number of different types of ACEs with an elevated risk of substance use problems,⁴ highlighting that the number of ACEs itself is an important risk factor. Finally, much of the evidence on the biological embedding of adversity stems from the concept of allostatic load, which incorporates all-cause stress in examining associations with pathology.¹⁸ However, we also acknowledge that considering ACEs in the aggregate compared to distinct types of exposures may obscure nuances in the developmental mechanisms linking ACEs to substance misuse.¹⁹ Our approach to review the available evidence on the conceptualization of ACEs arising from the landmark ACE study and ACEs in the aggregate is to reduce heterogeneity where possible and facilitate an overarching review on the existing evidence.

Methods

An umbrella review of the link between ACEs and substance misuse was conducted. An umbrella review is a review of existing reviews, to give a high-level overview of a given topic. Two electronic databases (PsycINFO and Medline) were searched on March 4, 2022, and review articles known to the authors were also assessed for eligibility. Eligible study designs were systematic reviews (both qualitative and quantitative) and meta-analyses that examined associations between ACEs and

substance misuse. Studies were eligible if a peer-reviewed full text was available between January 1, 1998 to March 4, 2022 (1998 being the year of publication of the original ACE study), included human participants, and included associations between aggregative ACEs (at least two types of ACEs) measured between age 0 and 18 years and a substance misuse outcome. For the purposes of this review, substance misuse was the use of alcohol and/or other drugs in such a way that confers social, occupational, justice- or health-related harm to the individual or others. Alcohol and cannabis outcomes were included if studies indicated some form of harmful use (eg, heavy use, increased use, problem use, dependence, disorder) or any use under the age of 18 in line with guidelines for the safe consumption of alcohol.²⁰ For prescription drugs harm was defined as any use contrary to prescribed instructions; for illicit drugs and tobacco smoking this was defined as any use given the potential for social, occupational, justice- or health-related harm arising from any use. Studies assessing scale formation only, or dissertations were excluded. Search terms are presented in [Supplementary Table 1](#). References were exported to systematic review software (Covidence) and duplicates removed automatically by the software. Titles and abstracts were screened to ascertain eligibility in a first step. For articles that were deemed potentially eligible after this first step, full-text articles were then reviewed against eligibility criteria. Data extracted from the eligible studies included first author, publication date, the ACEs included, the substance misuse outcome(s) measured, the sample characteristics, sample size, and main findings. Results from quantitative syntheses (eg, meta-analyses) are presented in the first section of the results; results from qualitative systematic reviews are summarized in the second section of the results. Given the substantial heterogeneity between samples of individual studies, most systematic reviews employed qualitative synthesis, and thus, the current umbrella review includes predominately qualitative synthesis. The current review synthesizes the overall findings of the included reviews, rather than the findings of individual primary studies included in these reviews.

Results

What is the Relationship Between ACEs and Substance Misuse?

[Figure 1](#) presents the PRISMA flow chart²¹ of the study screening process. After duplicates were removed, 846 titles and abstracts were screened, and 97 full-text articles were assessed. Twenty articles met all eligibility criteria and were included in the evidence synthesis.^{4,22–40}

The evidence on associations between ACEs and substance misuse is robust and alarming. All reviews concluded that the majority of studies show an elevated risk of substance misuse or disorder, among adolescents and adults exposed to ACEs. Specific results are summarized below.

Umbrella Review of Systematic Reviews Employing Quantitative Synthesis

[Table 1](#) presents the study characteristics and estimates of the magnitude of the association between different levels of ACE exposure and alcohol, tobacco, and other drug use respectively, based on the six quantitative syntheses included in the current review.^{4,22,25,26,34,40} As shown, meta-analytic estimates demonstrate an increased pooled risk associated with just one ACE for harmful alcohol use, illicit drug use, and smoking.^{22,25,26,34} The strength of this association increases for those experiencing more than one ACE,^{22,25,26,34} which sadly represents the majority of children who experience any adversity.¹⁷ For those experiencing four or more ACEs compared to no ACEs, the odds are markedly high for problematic alcohol use (OR=5.84), for illicit drug use (OR=5.62), and problematic drug use (OR=10.22).²⁵ Population attributable fractions (PAFs), that is, estimates of the proportion of an outcome that can be attributed to an exposure, indicate that in the US, approximately 13–29% of cases of drug use, 10–15% of harmful alcohol use, and 5–14% of cases of smoking can be attributed to ACEs.⁴ At a population level, this corresponds to over 21 million people using illicit drugs, 10.5 million engaging in tobacco smoking, and 6.5 million engaging in harmful alcohol use.⁴ In Europe, 15–45% of cases of drug use and 16–45% of harmful alcohol use were attributable to ACEs.²⁶

Umbrella Review of Systematic Reviews Employing Qualitative Synthesis

Associations Between ACEs and Measures of Substance Misuse

[Table 2](#) presents the characteristics of included studies that examined the relationship between ACEs and substance misuse through qualitative synthesis. This relationship appears to hold across the spectrum of substance use behaviors, from age of initiation, consumption, and extending to harmful use, disorder, and dependence.^{27,29,30} A recent review

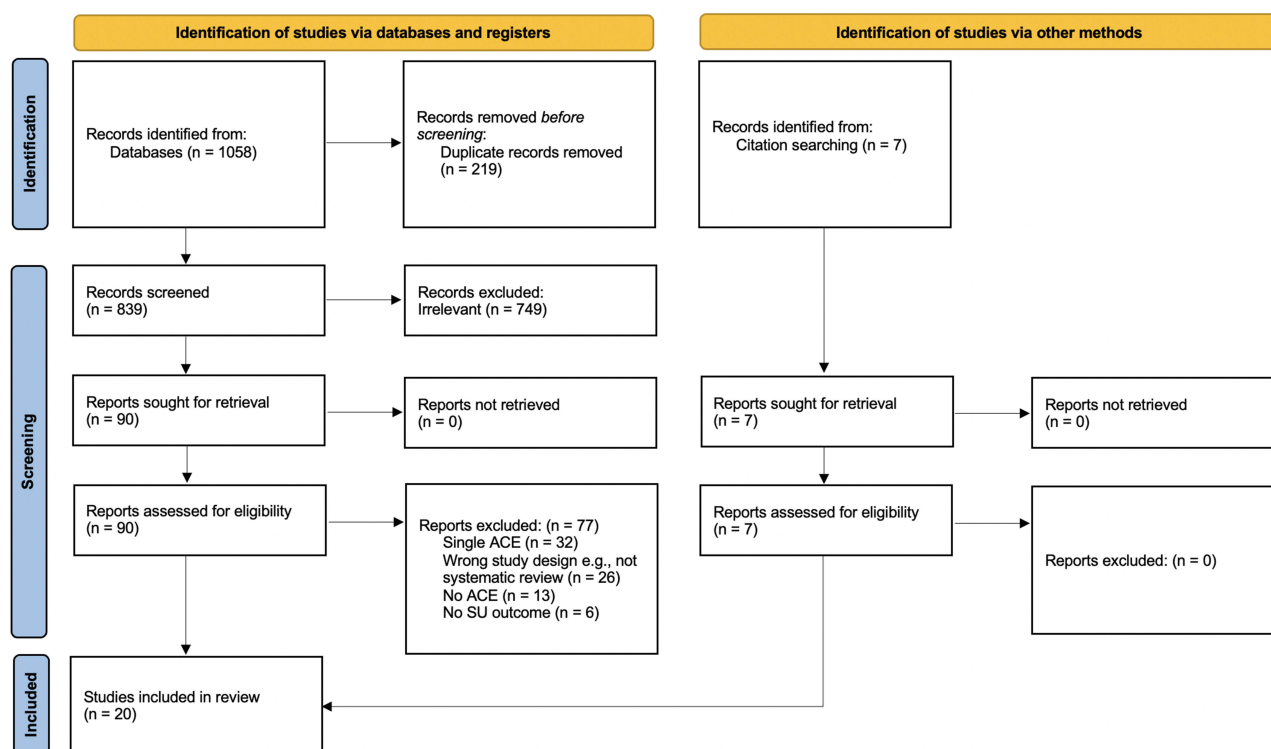


Figure 1 PRISMA 2020 flow diagram. Study screening flow chart for studies identified in the umbrella review. Titles and abstracts were screened for 846 studies, resulting in 97 studies for full-text review. Of these, 20 studies were included in the current synthesis.

reported that all included studies found the development and severity of substance use disorder (SUD) to be positively associated with the number of ACEs,²⁹ and another review reported an average of those exposed to ACEs being 1.8 times more likely to have a SUD in adulthood.³³ Indeed, reviews report markedly higher prevalence rates of ACE exposure among those with a SUD compared to community estimates,²⁹ with between 85% and 100% of patients in treatment for SUD reporting at least one ACE compared to population estimates of between 46% and 62%.²⁹ Among adolescents in addiction treatment, a greater number of ACEs was associated with an earlier age of drug initiation.²⁹ ACEs were found to be associated with earlier onset of use and hazardous use of alcohol, and a shorter transition between the two.³⁰ Evidence is also consistent across substance types, although the bulk of research has been conducted on alcohol, tobacco, and cannabis. ACEs are associated with lifetime smoking, current smoking, heavy smoking, younger age of initiation, difficulty in smoking cessation.^{27,30} They show graded associations with alcohol and other drug outcomes, including early onset, heavy use, and disorder.^{29,30}

Associations Among Different Age Groups and Sex

While most studies have been conducted in adult samples, the existing evidence suggests a similar pattern among adolescent and young adult samples. Indeed, adolescence appears to be a critical developmental period during which the harmful effects of ACEs may manifest, due to biological and social changes as well as greater opportunity to use substances.^{41–43} This burden appears to persist into adulthood, as evidenced by the large PAFs for childhood adversity and substance misuse among adults, highlighting the need for early intervention.^{4,26} Recent reviews have found that the positive associations between ACEs and substance misuse are evident by adolescence. Specifically, Hoffmann and Jones reviewed the literature on cumulative adversities and adolescent substance use, and found evidence of a positive association for initiation, frequency of use, disorder, and dependence.²⁴ Moreover, among young adults, Rogers et al found that greater ACEs predicted increased quantity and frequency of alcohol consumption, harmful alcohol use, and alcohol use disorder.³¹ This was also confirmed for other drugs, with studies finding a positive association between ACEs and tobacco and e-cigarette use, cannabis dependence, other illicit drugs and non-medical prescription opioid use.³¹

Table I Characteristics and Main Findings of Included Studies That Used Quantitative Synthesis to Examine the Relationship Between ACEs and Substance Misuse

Reference	ACEs Included	SU Outcome	Sample Characteristics	Sample Size	Main Findings. Social/Structural Factors Assessed
Agnew-Blais and Danese 2016 ⁴⁰	PA, SA, EA, N	SUD AUD	Bipolar disorder patients. Mean age: 22.4–50.9 years	SUD: 5469 AUD: 5040	Bipolar disorder patients with a history of childhood maltreatment had SUD: OR 1.84 (1.41–2.39) AUD: OR 1.44 (1.13–1.83) compared to bipolar disorder patients without childhood maltreatment history. Proportion of white or female participants in sample did not change effect sizes of meta-analysis.
Bellis et al 2019 ²²	PA, SA, EA, N, DV, household SU, household MI, PS, household incarceration	Harmful alcohol use, illicit drug use, smoking	Age range: 18–92 years. General pop (17/23 studies) Students (1/23) HMO (3/23) Primary care (2/23). Included studies that were done in Europe or North America only.	Harmful alcohol: 106,172 Illicit drug use: 38,702 Smoking: 134,741	<u>Alcohol use</u> 1 ACE RR: 1.47 (1.29–1.69) 2+ ACEs RR: 1.94 (1.43–2.63) <u>Tobacco</u> 1 ACE RR: 1.24 (1.11–1.39) 2+ ACEs RR: 1.78 (1.60–1.98) <u>Drug use</u> 1 ACE RR: 1.64 (1.48–1.83) 2+ ACEs RR: 2.79 (2.63–2.97)
Grummitt et al 2021b ⁴	PA, SA, EA, EN, PN, DV, household SU, household MI, household incarceration, PS	Proportion of harmful alcohol use, smoking, and drug use attributable to ACE exposure	Adults >18 years. US general population.	Not provided for substance-related outcomes. Overall sample size: 20,654,832	<u>Harmful alcohol use</u> 1 ACE: 9.6% 2 ACEs: 11.6% 3 ACEs: 15.3% 4+ ACEs: 9% <u>Smoking</u> 1 ACE: 5.2% 2 ACEs: 6% 3 ACEs: 5.3% 4+ ACEs: 14% <u>Drug use</u> 1 ACE: 13.3% 2 ACEs: 17.6% 3 ACEs: 15.1% 4+ ACEs: 29.2%
Hughes et al 2017 ²⁵	At least 4 ACEs including both maltreatment and household dysfunction. PA, SA, EA, N, DV, household SU, household MI, household incarceration, PS	Heavy alcohol use Smoking Illicit drug use Problematic alcohol use Problematic drug use	Age range: 15–79. General population 21/37 HMO: 6/37 Students: 3/37 Primary care: 2/37 Military: 1/37 Tribal communities: 1/37 Civil servants: 1/37 Urban minority: 1/37 Head start parents: 1/37	Heavy alcohol use: 84,904 Smoking: 152,830 Illicit drug use: 42,816 Problematic alcohol use: 33,992 Problematic drug use: 30,101	<u>Heavy alcohol use</u> 4+ ACEs OR: 2.20 (1.74–2.78) <u>Smoking</u> 4+ ACEs OR: 2.82 (2.38–3.34) <u>Illicit drug use</u> 4+ ACEs OR: 5.62 (4.46–7.07) <u>Problematic alcohol use</u> 4+ ACEs OR: 5.84 (3.99–8.56) <u>Problematic drug use</u> 4+ ACEs OR: 10.22 (7.62–13.71)

(Continued)

Table 1 (Continued).

Reference	ACEs Included	SU Outcome	Sample Characteristics	Sample Size	Main Findings. Social/Structural Factors Assessed
Hughes et al 2021 ²⁶	PA, SA, EA, N, DV, household SU, household MI, household incarceration, PS	Harmful alcohol use Smoking Illicit drug use	Age 14+. Europe and the UK only, general population, students, or older adults.	Harmful alcohol use: 29,013 Smoking: 32,173 Illicit drug use: 32,513	<u>Alcohol use</u> 1 ACE RR: 1.64 (1.43–1.88) 2+ ACEs RR: 2.60 (2.07–3.27) <u>Tobacco</u> 1 ACE RR: 1.27 (1.18–1.35) 2+ ACEs RR: 1.74 (1.55–1.95) <u>Drug use</u> 1 ACE RR: 1.59 (1.44–1.76) 2+ ACEs RR: 2.63 (2.27–3.05)
Petrucelli et al 2019 ³⁴	ACEs from the CDC-Kaiser ACE scale: PA, SA, EA, EN, PN, DV, household SU, household MI, household incarceration, PS	Alcohol problem, tobacco use, illicit drug use	12/96 studies on ≤ 18-year-olds 84/96 studies on > 18-year-olds General population sample only.	Not provided	<u>Alcohol problem</u> 1 ACE OR: 1.46 (1.40–1.53) 2 ACEs OR: 1.89 (1.82–1.98) 3 ACEs OR: 2.99 (2.80–3.20) 4+ ACEs OR: 4.31 (3.90–4.76) <u>Tobacco use</u> 1 ACE OR: 1.24 (1.20–1.26) 2 ACEs OR: 1.43 (1.39–1.47) 3 ACEs OR: 1.62 (1.56–1.68) 4+ ACEs OR: 1.90 (1.81–2.00) <u>Drug use</u> 1 ACE OR: 1.61 (1.52–1.71) 2 ACEs OR: 2.44 (2.28–2.62) 3 ACEs OR: 2.95 (2.71–3.21) 4+ ACEs OR: 3.66 (3.27–4.09) Females reported more ACEs than males. Non-White, lower education, and lower SES were more likely to report any ACE compared to no ACE.

Abbreviations: ACE, adverse childhood experience; AoD, alcohol and other drugs; AUD, alcohol use disorder; DV, domestic violence; EA, emotional abuse; EN, emotional neglect; HMO, health maintenance organisation; MI, mental illness; N, neglect; OR, odds ratio; PA, physical abuse; PN, physical neglect; PS, parental separation; RR, risk ratio; SA, sexual abuse; SU, substance use; SUD, substance use disorder.

Sex differences are typically found in the prevalence of ACEs, with a higher prevalence and greater number of ACEs among females.^{16,34,44} Evidence for sex-related differences in the link between ACEs and substance misuse is somewhat mixed, though tentatively suggests a stronger association between ACEs and substance misuse for females, compared to males. A review of longitudinal studies found that six out of 10 articles reported that the relationship between ACEs (specifically maltreatment) and substance misuse differed depending on sex.²⁸ Five of these found the relationship was stronger for women, compared to men; the remaining study found that sex moderated the relationship between sexual abuse only and drug use, with the association stronger for men compared to women.²⁸ A further study reported the test of sex differences was not significant, yet when models were run separately by sex only the relationship between maltreatment to drug use was significant for women, but not men.²⁸ Another included review found that several studies concluded stronger associations between cumulative adversity and substance use in adolescent females, compared to males.²⁴ Yet among young adults in a recent review, three of the five studies examining sex as a moderator of the ACE-substance misuse relationship found significant moderation, specifically, that the relationships between ACEs and alcohol use problems, illicit drug use, and e-cigarette use, were found to be stronger for males, compared to females.³¹ Moreover, in a meta-analysis of the association between childhood maltreatment and SUD among bipolar

Table 2 Characteristics and Main Findings of Included Studies That Used Qualitative Synthesis to Examine the Relationship Between ACEs and Substance Misuse

Reference	ACEs Included	SU Outcome	Sample Characteristics	Sample Size	Main Findings. Social/Structural Factors Assessed
Bowen et al 2018 ³⁵	PA, SA, household SU, household MI, EN, PN	Alcohol dependence Drug dependence SUD Illicit drug use Increased alcohol use	Adult prisoners. Mean age: 19.1–41.9	19,446	A history of ACE was consistently associated with substance misuse in male and female prisoners. All studies found substantially higher prevalence of ACEs in prisoners compared to community samples.
deVenter et al 2013 ³³	PA, SA, EA, EN, PN, PS, household SU, household MI, DV, household incarceration	SUD	General population, Adults.	Not provided	Those with a history of ACEs have 1.8 (1.5–2.5) times the odds of developing a SUD in adulthood, compared to those without an ACE history.
Folk et al 2021 ³⁶	PA, SA, EA, EN, PN, DV, household SU, household MI, household incarceration, PS	AoD use Substance use problems	Justice-involved youth. US population only. Aged 10–18 at study enrolment. Over-representation of males, Black and Latinx youth (consistent with justice-involved population)	67,305	Greater number of ACEs associated with AoD use and substance use problems. Two studies found that females and White youth were reported a greater number of ACEs, though Black youth were most likely to report any ACE, compared to no ACEs.
Goddard and Pooley 2019 ³⁷	PA, SA, EA, N, household dysfunction	Problem substance use Age of onset of AoD use	Adult male prisoners. Mean age: 34–42	579	ACEs were positively associated with problem substance use and earlier age of initiation.
Grummitt et al 2021a ²³	PA, SA, EA, EN, PN, DV, household SU, household MI, household incarceration, PS	Substance misuse, SUD, SU dependence, age of SU initiation	Youth with SU outcome measured ≤ age 24 Longitudinal studies only	59,798	Found the relationship between ACEs and substance misuse was mediated by anger, coping motives, posttraumatic stress symptoms, externalizing behavior, peer relationships, mother-child relationship, school mobility, and educational achievement. The link between ACEs and substance misuse was moderated by depressive symptoms, religiosity, future orientation, family cohesion and quality of relationships.
Hoffman and Jones 2020 ²⁴	PA, SA, EA, N, DV, household SU, household MI, household incarceration, PS	SUD, misuse, dependence.	General population of adolescents or adolescents from secondary schools.	Not provided	6/7 studies that examined associations between ACEs and substance use problems found a significant, positive association. Association between ACEs and adolescent SU was more robust among females.
Kalmakis and Chandler 2015 ²⁷	Multiple ACEs, unspecified.	Substance misuse Smoking Illicit drug use Binge drinking	Age: ≥ 18 years. US population, inc. general population, military, prison, HMO	140,093	Consistent positive associations between ACEs and substance outcomes.
Kristman-Valente and Wells 2013 ²⁸	PA, SA, EA, N	Initiation Disorder or dependence	US population, longitudinal studies only.	~2,283	Focused on sex as a moderator in the relationship between CM and substance misuse. 6/10 studies found the relationship differed by sex, with 5/6 finding a stronger relationship for women, compared to men.

(Continued)

Table 2 (Continued).

Reference	ACEs Included	SU Outcome	Sample Characteristics	Sample Size	Main Findings. Social/Structural Factors Assessed
Leza et al 2021 ²⁹	PA, SA, EA, N, DV, household SU, household MI, household incarceration, PS. Only studies that made reference to the “ACE concept” were included	Diagnosed SUD	Age ≥ 18 years for 11/12 studies Mix of general population, treatment-seeking population	61,486	Greater prevalence of ACEs among those with SUD. ACEs are positively associated with SUD development and severity.
Liu et al 2021 ³⁸	PA, SA, EA, N, DV, household MI, household incarceration, household SU, PS	Substance misuse	Homeless adults, mean age range: 21–41 years 29–34% female	1790	ACE exposure associated with greater odds of substance misuse. Overall prevalence of any ACE among homeless population 89.8%.
McGeough and Sterzing 2018 ³⁹	PA, SA	Alcohol dependence Tobacco use Illicit drug use	US samples only. Sexual minority youth (gay, lesbian, bisexual). Age range = 18–83	14,409	Greater exposure to PA and SA associated with greater alcohol dependence, smoking, and other drug use among sexual minority youth. ACE prevalence was consistently higher among sexual minorities compared to heterosexual youth. Sexual minority youth exposed to ACEs had higher rates of substance misuse compared to heterosexual or non-abused sexual minority youth.
Ports et al 2019 ³⁰	PA, SA, EA, PN, EN, DV, household SU, household MI, household incarceration, PS	Problematic alcohol-related behaviours Tobacco smoking	Alcohol mean age range: 19–57 Tobacco mean age range: 20–57	Alcohol: 491,350 Tobacco: 345,447	Evidence of positive association between cumulative ACE scores and problematic alcohol behaviors (35/59 studies), mixed effects (13/59 studies), and null effects (11/59 studies). Evidence of positive association between cumulative ACE scores and tobacco smoking (31/41 studies), mixed associations (5/41), and null effects (5/41). Positive associations similarly existed among White, Black, and Hispanic ethnicities.
Rogers et al 2022 ³¹	PA, SA, EA, N, household SU, DV, household MI, household incarceration, PS	Binge drinking Alcohol use problems AUD Smoking Cannabis problems Illicit drug use Prescription drug misuse	Young adults (aged 18–29 years). 50% majority white samples, 22% majority Hispanic samples, 16% majority Asian samples, 6% majority Black samples, 6% majority multi-ethnic. 50% college samples, 38% community samples, 12% other eg, military	158,621	ACEs were positively associated with alcohol outcomes in 24/28 studies; 4 studies found no association. 19/22 studies found positive association between ACEs and smoking; 3 found no association. All studies (n=3) that assessed cannabis use problems found a positive association with ACEs. 13/14 studies found ACEs were positively associated with illicit and/or prescription drug misuse.
Teixeira et al 2017 ³²	EN, PN, PA, SA	Problem alcohol use Problem drug use	Adults	437	Substance misuse was a way of coping with early-life stress.

Abbreviations: ACE, adverse childhood experience; AoD, alcohol and other drugs; AUD, alcohol use disorder; DV, domestic violence; EA, emotional abuse; EN, emotional neglect; HMO, health maintenance organisation; MI, mental illness; N, neglect; OR, odds ratio; PA, physical abuse; PN, physical neglect; PS, parental separation; RR, risk ratio; SA, sexual abuse; SU, substance use; SUD, substance use disorder.

disorder patients, meta-regression revealed the proportion of female participants in the sample did not change the effect size.⁴⁰

Associations Among Specific Populations and Social / Structural Factors Assessed

Six studies in the umbrella review examined the relationship between ACEs and substance misuse in specific populations: justice-involved youth; incarcerated adults; those with bipolar disorder; adults experiencing homelessness; and sexual minority populations. These reinforced the overall findings of this review. Among incarcerated adults, exposure to ACEs were associated with an increased likelihood of substance misuse, and earlier initiation of substance use.^{35,37} Similarly, among justice-involved youth a greater number of ACEs were associated with more substance use problems.³⁶ Childhood physical and sexual abuse were positively associated with alcohol dependence and other drug use among sexual minority youth.³⁹ Among patients with bipolar disorder, those with a history of childhood maltreatment had 1.84 times the odds of also experiencing a SUD and 1.44 times the odds of also experiencing an alcohol use disorder compared to bipolar disorder patients who did not experience childhood maltreatment.⁴⁰ Among adults experiencing homelessness, ACE exposure was associated with substance misuse.³⁸

While most of these studies acknowledged a greater prevalence of ACEs among socially disadvantaged or minority groups,^{35,36,38,39} there was little assessment of whether this affected the strength or manner of the association between ACEs and substance misuse. One systematic review examined social factors as mediating or moderating the relationship between ACEs and substance misuse.²³ ACE exposure was found to be associated with increased substance misuse through lower educational opportunity and achievement and involvement with the justice system.²³ Moreover, living in a neighborhood characterized by greater trust and social cohesion reduced the association between ACEs and alcohol misuse.²³

Systematic Reviews Examining Mechanisms in the Link Between ACEs and Substance Misuse

All studies included in a meta-synthesis of qualitative reviews examining the link between ACEs and addiction found that substance use served as a coping mechanism in an attempt to avoid feelings of low self-worth, depression, shame, and inadequacy arising from childhood adversity.³² Another review focused on evidence from longitudinal studies identified a multitude of psychosocial mediators of the relationship between ACEs and substance misuse in adolescence and early adulthood.²³ This review reinforced the importance of coping motives, finding individuals exposed to ACEs more likely to endorse coping motives for substance use compared to non-exposed peers, in turn increasing substance misuse.²³ Internalizing symptoms (ie, of major depression, anxiety, post-traumatic stress) were commonly found to mediate the relationship between ACEs and substance misuse, including age of initiation and problem use,²³ and were also found to predict increased coping motives for drinking, further exacerbating substance misuse.²³ Externalizing symptoms (eg, behavioral disinhibition) were also found to mediate the relationship between ACEs and substance misuse, with ACEs predicting increased externalizing symptoms, which in turn predicted worse substance use outcomes, including age of initiation and disorder.²³ Moreover, interpersonal factors, such as parent and peer relationships, were commonly found to mediate the relationship between ACEs and substance misuse, highlighting that links between ACEs and substance misuse are dependent on social factors.²³

Limitations of Existing Research

Some important caveats arise when reviewing the existing literature. Firstly, while there is consistent evidence reporting positive associations between ACEs and substance misuse, there remain a number of studies reporting null or mixed findings on this relationship. Moreover, due to biases such as the file drawer problem, it is likely that some null associations have gone unpublished and are thus not reflected in the existing literature. While differences in methodology may go some way to accounting for null findings, it is also evident that certain factors confound the relationship between ACEs and substance misuse. These could both inflate and reduce the magnitude of associations between ACEs and substance misuse, with protective factors such as degree of social support reducing this association, and other factors associated with greater disadvantage, or social contributors to substance misuse such as peers or parental factors, strengthening the relationship between ACEs and substance misuse. Despite the inconsistency with some studies

reporting null findings, there is an extraordinary number of rigorous studies that report positive associations between ACEs and substance misuse, highlighting the improbability that the association is an artefact of publication bias or unmeasured confounders. However, this issue highlights the importance of including the context in which ACEs occur to better understand the nuance in this relationship.

A second caveat is that of causality. The relationship between ACEs and substance misuse reviewed above is based on associations, yet it is often implied as causal. In addition, many of these associations are based on cross-sectional data, which cannot provide evidence on the hypothesized direction of association between ACEs and substance misuse, and which often finds a stronger association between ACEs and substance misuse compared to longitudinal studies.²⁴ Importantly, ACEs often co-occur in environments where the presence of other confounding factors can limit the ability to infer causality in the absence of rigorous study design. For example, parental alcohol use disorder can confer risk for offspring alcohol use problems through both genetic and environmental pathways, but living with a parent suffering an alcohol use disorder may also increase the risk of accumulating ACEs through reduced capacity of the parent to provide physical and emotional needs, as well as supervision.⁴⁵ However, it is also evident that many of the current methods used in quantitative causal inference, advanced from fields such as biomedical research, do not adequately assess the upstream causal effects pertinent to the social determinants of health.⁴⁶ Rigid adherence to these methods typically engenders moving downstream toward proximal causes of disorder without appropriately taking into account the upstream social determinants causes that lead to the downstream factors.⁴⁶ Incorporating methodology advanced in the field of social epidemiology is an important future direction to strengthen causal claims in the relationship between ACEs and substance misuse. Meanwhile, diverging lines of evidence tentatively support the causal effects of ACEs on substance misuse. Firstly, prospective studies confirm the hypothesized temporal pathway with ACEs preceding substance misuse and mental illness.^{47–50} Secondly, many studies adjusting for known and strongly associated covariates (parental mental illness, substance use, family conflict, divorce, sociodemographic factors, parental discipline) find that these relationships hold^{45,51} (although some do not, see⁵² for review). Third, studies on twins discordant for sexual abuse exposure demonstrate that the risk of alcohol use problems following sexual abuse holds above family background confounders, with a ratio of 2.8 for the exposed twin developing AUD to the non-exposed twin.⁴⁵ Finally, animal models support causal associations between early-life adversity and addiction.^{51,53}

Discussion

The literature reviewed above suggests a robust link between ACEs and substance misuse, based on almost a quarter century of research. All articles identified by this umbrella review concluded that the majority of studies show an elevated risk of substance misuse, dependence or disorder, among adolescents and adults exposed to ACEs. Reviews confirmed a graded response between the number of ACEs experienced and the risk of substance misuse. A link between ACEs and substance misuse was supported for a range of outcomes, from age of initiation, harmful use, disorder, and dependence; as well as across adolescent, adult, male, and female populations. These findings highlight that clinical practice addressing substance use disorder must reflect trauma-informed care; that is, recognize the impact, signs, and symptoms of trauma, resist re-traumatizing those seeking treatment, and integrate understanding of trauma into practice and policies.⁵⁴

Why are ACEs Associated with Substance Misuse?

Only two studies included in the current review investigated the mechanisms that might explain the link between ACEs and substance misuse, finding support for the self-medication hypothesis and other psychological factors. There is also a vast literature examining neurobiological mechanisms linking experiences of early-life stress to substance misuse. In addition, genetic factors, including genes related to glucocorticoid functioning, serotonin transporting, and risk of alcohol dependence have been found to moderate the association between ACEs and substance misuse,^{24,52} and interact with environmental factors in the pathway from ACEs to substance misuse and disorder.^{43,51} Mechanisms linking ACEs and substance misuse appear to unfold on a continuum whereby severe and chronic stress caused by ACEs propels a cascade of effects across neurobiological, endocrine, immune, metabolic, and nervous systems, which impact psychosocial and cognitive functioning throughout childhood and adolescence, that in turn increase vulnerability to substance misuse and disorder. Such latent vulnerability to substance misuse may be triggered by subsequent stressors along the life course,

with theoretical and empirical support for stress sensitization among those experiencing early life stress.^{55–57} Importantly, the resilience demonstrated by many individuals exposed to ACEs highlights that the pathway from ACEs to substance misuse is undoubtedly complex and influenced by individual, social, and environmental factors.⁴³ This is critically important, as it highlights the multitude of potential intervention targets to prevent substance use problems following ACEs. Commonly proposed mechanisms linking ACEs and substance misuse are briefly reviewed below.

The Stress Response

One of the most commonly reviewed mechanisms as to how ACEs become biologically embedded centers on the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis coordinates release of the stress-response hormone, cortisol. In typical functioning of the HPA axis, cortisol is released in response to stress, and exerts a range of effects across immune, metabolic, and cardiovascular systems, which helps humans enact a fight or flight response.⁵³ After the threat has passed, cortisol levels return to normal, maintaining homeostasis in the HPA axis.⁵³ However, in cases of ongoing stress, such as adverse experiences in childhood, the downregulation of the HPA axis may be prevented, leading to hypersecretion of cortisol. This can result in what has been termed “allostatic load”, which, over the long-term may wear out this and other biological systems.⁵⁸

Dysregulation of the HPA axis may lead to either hypo- (ie, reduced) or hyper-secretion of cortisol. It is currently unclear why different studies find either hypo- or hyper-secretion of cortisol, though hypotheses and empirical investigations have pursued differences in the type, severity, timing, or recency of ACE exposure, the age of measurement of cortisol, the cortisol indicator measured, sex effects, and the presence of psychopathology such as depression.^{59,60} One prevailing view aligns with the Protection Hypothesis, which posits that HPA axis hyperactivity is observed in children but may subsequently transform into hypoactivity during later adolescence and adulthood in an attempt to protect brain regions from the damage from chronically elevated cortisol levels.^{61–63} However, findings remain inconsistent across studies. The functioning of the HPA axis is undoubtedly complex, and rigorous attention to procedural and sample details will be required if we are to understand with greater precision how ACEs impact HPA axis functioning.

Despite these uncertainties, dysregulation of the HPA axis (both hypo- and hyper-activity) is implicated in substance misuse and disorder.^{63,64} It is possible these reflect multiple pathways to substance misuse, with researchers hypothesizing that those with a hyper-reactive HPA axis may be more likely to engage in substance use to dampen the resulting negative affect.^{65,66} The HPA axis interacts with brain regions and systems, such as the hippocampus, amygdala, pre-frontal cortex, and mesocorticolimbic dopaminergic pathway, involved in cognition, memory, impulse control, emotional regulation, threat, and reward processing. These structures and systems have a high density of cortisol receptors and even brief periods of exposure to stress appear sufficient to cause significant structural and functional alterations, including decreased neurogenesis in adulthood and atrophy caused by repeated stress.^{58,67} It is these structural and functional alterations that appear to confer vulnerability to substance misuse via a blunted response to natural reward coupled with a sensitized reward response to substances, as well as attention biases to threat processing at the expense of successful emotion regulation and cognitive functioning (explored in the following paragraphs). Heavy use of psychoactive substances can further alter the HPA axis, and these changes are associated with increased motivations to use substances and do so at higher levels.⁶⁴

The Reward System

It is recognized that differences in both behavioral and biological sensitivity to reward is a hallmark feature of substance-related problems. Both animal and human studies have demonstrated disruption to the reward system following early stress, typically finding reduced neural and behavioral sensitivity to natural (eg food) and monetary reward.⁶⁸ This is consistent with the blunted response to natural reward observed in humans with substance use disorder.⁶⁸ In humans, maltreated children showed greater impulsivity in reward tasks, insensitive to changing values of reward.⁶⁸ In humans, those exposed to ACEs show a stronger dopamine response to drugs, report greater pleasurable effects (eg euphoria), greater desire for more, and fewer negative effects of opioids compared to those non-exposed to ACEs, as well as a positive association between the number of adverse events in adulthood and dopamine response.^{68,69} These alterations may potentially enhance the rewarding effects of substances, increasing the risk of transitioning from controlled to

compulsive use of substances, and help to explain severity of those presenting with substance use disorder with a history of ACEs.^{63,68} Indeed, differences in function and structure of these brain regions have been shown to mediate the relationship between ACEs and subsequent alcohol dependence.^{63,68} Animal models support a causal role of early-life stress on reward sensitivity, demonstrating enduring changes in the dopamine response to drugs following maternal separation or handling in rats.⁴³

Neurocognitive Pathways

Imaging evidence shows reduced grey matter volume in the pre-frontal cortex of children and adults who experienced ACEs, with corresponding deficits in emotion regulation, executive control, and memory.⁶⁸ These difficulties are strongly implicated in the development and maintenance of substance misuse and disorder.^{70–72} Moreover, accumulating evidence suggests that altered threat processing may link ACEs and substance misuse. Children exposed to violence appear to be particularly wired to identify and respond to threat. They show an over-generalization of threat to non-threatening stimuli, biases in information processing toward prioritizing threat, greater amygdala reactivity to aversive stimuli, heightened emotional reactivity to potentially threatening cues, and altered emotion regulation in responding to threat.^{73,74} Adolescents exposed to ACEs displayed greater recruitment of effortful control from pre-frontal regions in response to negative stimuli compared to non-maltreated adolescents, yet it is postulated that the aforementioned deficits in pre-frontal control over amygdala reactivity may limit successful emotion regulation.⁶⁸ Together, these findings suggest ACEs result in neurological changes that facilitate rapid identification of threat at the expense of effective emotion regulation and adaptive emotional reactivity. Increasingly, studies are showing similar responses to threat and emotion processing among humans with substance use disorders.⁶⁸ Moreover, alcohol use acutely reduces amygdala reactivity to emotional cues and dampens connectivity between the amygdala and pre-frontal cortex, possibly contributing to motivations to use alcohol.^{63,68} Several studies have demonstrated an association between elevated amygdala reactivity and drug craving among those with substance use disorder, suggesting this may play an important role in conditioned stimulus associations and stress-related relapse.⁶⁸

Psychological Pathways

The self-medication hypothesis views substance use as an attempt to cope with or reduce negative affect.⁷⁵ However, the use of substances to cope may only temporarily alleviate negative emotions, and in fact can lead to greater negative affect and a cycle of comorbid mental health and substance use disorder.⁷⁶ ACEs are undoubtedly a significant source of distress and negative affect; therefore, self-medication is a pertinent theoretical mechanism linking ACEs to substance misuse and disorder. This was empirically supported by two systematic reviews in the current umbrella review.^{23,32} Relatedly, overarching coping styles, that is, the tendency toward certain cognitive and behavioral coping strategies when faced with stressors, may increase susceptibility to substance misuse. Coping styles develop early in life, through modelling and communication from interpersonal relationships, and are built and refined through a dynamic interplay between the person's beliefs, values, genes, personality, and their social environment.^{77,78} This interplay between factors unique to an individual explain why the same event may be perceived and reacted to differently by two individuals.⁷⁷ Coping strategies characterized by avoidance (eg, denial, distraction) have been hypothesized as linking ACE exposure to substance misuse. Children exposed to ACEs may lack effective models of coping, or may employ avoidant styles of coping to facilitate survival and reduce the potential for harm in a traumatic environment that is beyond their ability to control.^{78,79} Evidence has found a greater tendency for maltreated adolescents to use avoidant coping strategies compared to non-exposed peers.^{78,80–82} Yet in the long-term, the use of avoidance to cope with stressors appears to confer risk for psychiatric symptoms, including substance misuse.⁸³ For example, children exposed to abuse are more likely to attempt to flee from stressors.⁸⁴ However, if the stressor is unavoidable, faced with threat these individuals display greater stress reactivity, as measured by amygdala response, and struggle to recruit the pre-frontal cortex to successfully regulate emotional response.⁸⁴ This stress reactivity is itself aversive, and coupled with the anxiolytic effects of some substances, may reinforce drug-related cravings and substance misuse. Indeed, avoidant coping has been found to mediate the association between ACEs and substance use in varying samples.^{33,85} Importantly, stress-process models postulate that ACEs lead to substance misuse to reduce negative affect when other coping resources are absent. Indeed, evidence

suggests that the degree to which individuals use substances to cope depends on the availability of other resources that can be recruited to help individuals cope (eg, social support, self-control, emotion regulation).²⁴ Importantly, this advances the concept of resiliency as dependent on both individual and social-environmental resources and highlights a substantial opportunity for early intervention.¹³

Within the current umbrella review, one systematic review was found that points to a multitude of intervention targets that can be addressed early in the life course. These include coping motives, internalizing symptoms, externalizing symptoms, and parent and peer relationships. Early intervention will be critical in reducing the burden of substance use problems, with evidence that childhood stress may increase vulnerability to early use of substances, which in itself shapes the susceptibility of the brain to substances, thereby further increasing the risk for addiction and disorder.^{43,51} This is supported by many studies finding that ACEs increase risk for early onset substance use, even after controlling for parental and peer confounding factors.⁵¹ In turn, literature supports early initiation of substance use as a risk factor for disorder.⁵¹

It is also important to note the potential for differential associations between ACEs and substance misuse depending on the specific ACE or type of ACE studied. While the current review focuses on cumulative trauma, there is growing theoretical and empirical support for a dimensional model of adversity, that separates experiences of threat (eg, abuse) and deprivation (eg, neglect) to understand more nuanced pathways linking ACEs to psychiatric outcomes.¹⁹ For example, empirical evidence suggests that altered threat processing may arise from abuse, rather than neglect, and that pathways from neglect to psychopathology are more consistently characterized by alterations in executive function, cognition, and processing of social information.⁷³ There is also empirical support for different patterns of activation in reward learning for children exposed to threat, versus deprivation.⁷³ These findings suggest that despite similar presentations, effective interventions to prevent or treat substance misuse might be different depending on the type of adversity experienced. Accumulating research is examining these nuances to improve our understanding of how best to intervene. Other research has examined the synergistic effects of certain pairs of ACEs, finding the strongest increases in the probability of internalizing and externalizing disorders for women when sexual abuse was experienced in tandem with domestic violence or household mental illness, or household substance misuse was experienced with physical abuse.⁸⁶ For men, experiencing household mental illness and household substance misuse or sexual abuse increased the probability of disorder, as did the combination of physical abuse and domestic violence.⁸⁶ Further research has examined associations between each specific ACE and substance misuse, finding the strongest predictors for adult substance misuse to be emotional abuse, household substance misuse, and household mental illness,⁸⁷ and deprivation less robustly associated with substance misuse among young adults.⁸⁸ However, here it is important to consider ACEs cumulatively and independently, rather than relying on one method, given the inter-relationship and co-occurrence of multiple adversity types.⁸⁷ Findings of the current umbrella review should be interpreted with the context that the ACEs assessed are skewed towards experiences of threat, particularly physical and sexual abuse. This reflects a long-term bias in the existing literature, which may mean that our understanding of the link between ACEs and substance misuse is predominantly reflective of the link between abuse and substance misuse. Conclusions arising from the current review may be less generalizable to experiences of deprivation or other ACEs. Future research must examine the mechanisms linking ACEs and substance misuse with more attention to the type of exposure, with the hope to harness these more nuanced findings in order to develop tailored interventions to prevent and treat ACE-related substance misuse.

Where Do We Go from Here?

The ACEs literature has been critiqued as oversimplistic and reductionist in decontextualizing childhood adversity from broader structural issues and focusing solely on individuals or families.¹³ Given the wealth of evidence reporting associations between ACEs and substance misuse as summarized by the current umbrella review, future research must seriously address the limitations of the current evidence base or examine the mechanisms that explain this link to advance the field, rather than continuing to identify associations between ACEs and substance use outcomes. In this way, research can inform the development of effective interventions to prevent substance use problems among those exposed to ACEs, at both policy and practice levels.

Addressing limitations in the ACEs literature will most notably require thorough recognition that the link between ACEs and substance misuse is influenced by the socio-cultural context in which this relationship occurs. There was

virtually no assessment of this in the included reviews, highlighting that this issue has been severely neglected compared to the wealth of literature demonstrating overall associations between ACEs and substance misuse. Critiques of the ACEs and health outcomes literature have identified that ACE exposure is commonly decontextualized from broader social, economic, and structural conditions,¹³ and that ACEs may be better conceptualized as manifestations of poverty, deprivation, and social and gender inequality which have long been shown to affect health and opportunity across the life course.⁸⁹ Critics argue that the narrative that ACEs lead to poor health and disadvantage, rather than being manifestations of it, has contributed to focusing on individuals and families as the required target for intervention.⁸⁹ Broader social and structural determinants of health influence both the occurrence of ACEs and the risk of substance misuse arising from exposure, and must be addressed to improve the outcomes of those who have experienced ACEs. This growing recognition is an important shift toward attributing responsibility to structures and systems rather than on individuals and families, which has implicitly dominated the intervention landscape over the last 25 years. For example, evidence indicates that children of Indigenous parents with alcohol use problems show 2–3 times greater odds of alcohol use and problem drinking compared to children of non-Indigenous parents with alcohol use problems.⁹⁰

Structural barriers that account for these disparities in the health impacts of ACEs should form targets for intervention. This will critically require policy-driven approaches fueled by recognition that both the social distribution of ACEs and means to mitigate their impacts are products of social inequality. Ensuring health care is accessible to all, reducing barriers to accessing care associated with stigma, language, and cultural sensitivity, and incorporating cultural assets into prevention and treatment approaches may be critical in addressing the link between ACEs and substance misuse.³¹ However, even when receiving equal access to care, recent research has found poorer treatment outcomes for depression among more disadvantaged groups.⁹¹ The differential exposure hypothesis posits that these observed social inequalities in health arise from variation in levels of exposure to stressors, and highlights that the efficacy of treating an individual in clinical practice may be limited until broader structural changes are meaningfully addressed through policy and public health. While ACEs are experienced by all creeds, they are not randomly distributed across the population. The prevalence of ACEs is concentrated among marginalized groups, such as low-income earners, those with no or limited access to health insurance, minority sexual orientation, racial/ethnic minority groups,^{92,93} and in counties of greater deprivation.⁹⁴ This greater prevalence of ACEs reflects structural inequalities, such as disproportionate rates of incarceration among Black and Indigenous populations or greater financial strain among low-income earners and marginalized groups.^{95,96} The disproportionate contact of the justice system with minority race/ethnicities may compound the deleterious effect of ACEs on a range of health, legal, and economic outcomes, including substance misuse. Moreover, ACEs occur in addition to stressors related to discrimination, poverty, and racism. Thus, addressing the compounding syndemics of ACEs and other social determinants of health, and the systems that underlie the inequities in these exposures will undoubtedly be critical in the prevention and treatment of substance misuse and disorder as well as public health more broadly.

Future research should interrogate how the mechanisms linking ACEs and substance misuse differ depending on the socio-economic context, or demographic factors, such as sex differences. Mechanisms operating between ACEs and substance misuse are the key to developing interventions to prevent and treat substance misuse among those exposed to ACEs, as such, understanding moderating factors would help to maximize the efficacy of these approaches. For example, safe and supportive interpersonal relationships in both childhood and adulthood can buffer the impact of ACEs on mental health and substance misuse.^{97–99} There is evidence that these positive relationships may model effective coping strategies and help to undo dysregulation in the stress system.⁶³ There may also be sex differences in the mechanisms linking ACEs to substance misuse. Research has found that externalizing symptoms and enhancement motives for substance use are mechanisms for males, whereas internalizing symptoms and coping motivates, as well as externalizing symptoms, may be mechanisms for females.⁶³ Moreover, female internalizing symptoms in response to a stressor predicted subsequent drug use, whereas for males it was a blunted autonomic nervous system measure that predicted drug use in response to the same stressor.⁶⁴ Better understanding of these nuances will be critical in the development of prevention and treatment approaches to address the link between ACEs and substance misuse. Effective substance misuse prevention programs exist,^{100,101} but it is critical these adopt a trauma-informed approach and establish efficacy among those exposed to ACEs. Encouragingly, previously independent approaches to treating substance use disorder and

traumatic stress are just beginning to be integrated,^{102–104} reflecting increased awareness of the critical importance of trauma-informed prevention and treatment of substance use disorders.¹¹ More rigorous research in developing, evaluating, and implementing effective interventions for young people that take into account the findings from this umbrella review is needed.

Conclusions

Evidence from almost 25 years of ACEs research converges on ACEs as strong and consistent risk factors for subsequent substance misuse and disorder. ACEs account for 13–29% of cases of drug use, 10–15% of harmful alcohol use, and 5–14% of cases of smoking in the US, and 15–45% of cases of drug use and 16–45% of harmful alcohol use in Europe.^{4,26} However, this link is undoubtedly complex, and shaped by a multitude of individual, social, and structural factors, that interact with each other in the risk for substance use problems. Importantly, many children exposed to ACEs show remarkable resilience in the face of adversity, highlighting the multifaceted nature of risk and the multitude of potential intermediary factors that can be harnessed to prevent substance misuse and disorder. Research that seeks to holistically understand and address the relationship between ACEs and substance misuse within the broader social determinants of health, incorporating a broad range of risk and protective factors, is a crucial future direction.

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