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Timing and type of adverse life events: Impact on substance use among high-risk adolescents

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Abstract

A robust association has been reported between childhood adverse life events (ALEs) and risky substance use in adolescence. It remains unclear, however, what the impact of type and timing of these ALEs is. We investigated the association between ALEs and substance use in adolescents. ALEs were operationalized as broad (e.g., moving, parental divorce, family sickness) or physically threatening (physical and/or sexual abuse). First, we examined lifetime ALEs, followed by an investigation into their timing. The sample consisted of 909 adolescents (aged 12–18 years) from a cohort oversampled on high levels of emotional and behavioral problems. The primary caregiver indicated which ALEs each adolescent experienced across their lifetime. Adolescents self-reported on number and frequency of substances used. Poisson and ordinal regression models were used to model the associations. The associations between lifetime ALEs and a substance used were observed only for physical ALEs (incidence rate ratio 1.18 [1.03, 1.35], $p = 0.02$). When investigating timing, physical ALEs after the age of 12 predicted number of substances used (IRR 1.36 [1.13, 1.63], $p < .001$). Recent ALEs (occurring after age 12) seem to have considerable impact on substance use. Alcohol and drugs as a coping mechanism were considered a plausible explanation for the results.

Introduction

Peak onset of substance use occurs between the ages of 12 and 16 as adolescents start developing risk-taking behaviors among which are alcohol, tobacco, and illicit drug use (ESPAD Group, 2020; Trimbos instituut, 2021). Although most adolescents do not grow up to engage with high-risk substance use (defined here as use of multiple substances with high risk of adverse health outcomes), the burden of substance use ranks amongst the highest contributors to years of life lost among youth (Erskine et al., 2015). Early onset of substance use increases the risk of later abuse and dependance on alcohol and drugs (Dawson et al., 2008; King & Chassin, 2007), up to six times higher among those who first tried illicit drugs before the age of 14 (Substance Abuse and Mental Health Services Administration, 2013). Beyond high-risk drug use in later life, early initiation is further associated with a wide range of psychosocial problems, including repeated criminal offending, mental health problems such as a doubled risk of major depression, and a 15%

increase in school drop-out without any qualification or long-term unemployment (Fergusson & Horwood, 1997; Poudel & Gautam, 2017).

Role of adverse life events

There is therefore a strong evidence base that links early drug use to broadly poor psychosocial development. Previous research, however, has focused on antecedent environmental factors, which in all probability confound the effects of substance use when studying the later life outcomes outlined above (Fergusson et al., 2005; Pope et al., 2003). One such category of antecedent environmental factors is adverse life events (ALEs) in childhood, a broad category of potentially stressful experiences that have received particular attention in the field of addiction. However, there is an important ongoing debate on how to quantify ALEs. One of the first epidemiological studies investigating the association between adverse childhood events and substance use in adulthood measured adversity as threatening childhood experiences like physical or sexual abuse (Felitti et al., 1998). Also included, however, were household dysfunction categories such as domestic violence, parental substance misuse, and incarceration as well as physical and emotional neglect. These events were termed adverse childhood experiences (ACEs) and

thus an ACE score could be assigned to a given person reflecting how many events from the list they underwent. Using this cumulative measurement of adversity, a vivid dose-response relationship with substance use emerged, as studies reported adverse childhood events to increase the risk of early substance use before age 14 by a factor of two to four times (Dube et al., 2003). This finding has now been replicated in community samples (Felitti et al., 1998; Leban & Gibson, 2020), economically disadvantaged youth (Fagan et al., 2015), and urban minority samples (Mersky et al., 2013). Different categories of substances (i.e., early initiation of tobacco, alcohol, and illicit drug consumption) were also found to have qualitatively different associations with specific adverse life events (Anda et al., 1999; Mersky et al., 2013).

Although the original ACE measurement remains popular for clinical, research, and legislative purposes, researchers have promoted moving past the original ACE terminology and studying broader early adverse life events (ALEs; Compton et al., 2023; McLennan et al., 2020). This included studying events such as serious childhood illness, illness, or death in the immediate family and repeating a grade at school (Amone-P'Olak et al., 2009). Using this more inclusive measurement of ALEs, a positive association was still reported with substance use, albeit with an attenuated effect size (Wills et al., 2001). Following this line of research, some authors have argued that physically violent traumatic events (e.g., sexual abuse, domestic violence) should not necessarily be given a special role above other experiences when using questionnaires to count adverse life events (Finkelhor et al., 2005). Others point out different types of abuse load on a complex multifactor structure according to characteristics such as physical threat to health (Mersky et al., 2017). Specifically, Mersky et al. (2017) demonstrated that events of a different physical threat (e.g., emotional parental neglect versus physical assault) should not be collapsed into a single score to avoid losing unique and sometimes contradictory associations to outcomes such as substance use. This is backed up by empirical evidence, as adolescents with experiences of assaultive traumatic events also report more frequent binge drinking compared to those reporting non-interpersonal trauma (Cisler et al., 2011). Likewise, adolescents living in dysfunctional families (i.e., severe parental psychopathology, economic adversity, and unemployment) were more likely to report higher drug dependance regardless of whether they were also abused or not, however, the effect size was considerably higher for the former group (Benjet et al., 2013). The manner of grouping and summing adverse life events remains a topic under evolving discussion. Investigating multiple classifications of ALEs according to physical threat is thus an important avenue to explore in studying the onset of early substance use.

The dimension of timing

After the early seminal work on cumulative adversity, researchers are also taking interest in which age periods of childhood are most sensitive to adversity (Dunn et al., 2020; Schroeder et al., 2020). These age periods are described as functionally-coherent phases of childhood during which specific brain regions mature and biobehavioral systems are particularly malleable. Neurodevelopmental theory has guided research investigating time-sensitive brain maturation, producing findings that very early life stress between the ages 3 and 5 is linked with reduced hippocampal size (De Bellis et al., 2000); the age of 10 to 11 corresponds to peak amygdala sensitivity (Pechtel et al., 2014); and

adolescent stress around age 14 distinctively affects the prefrontal context (Casey & Jones, 2010). Based on such findings, neurodevelopmental theory maps out various time-dependent routes in which dysfunctional changes in neuroanatomy (i.e., changes in the amygdala, hippocampus, and prefrontal cortex specifically) could lead to early and problematic substance use (Andersen, 2019). There is a striking lack of epidemiological evidence, however, to inform whether adversity early or later in life is a better predictor of substance use. One study focusing exclusively on neglect (Dubowitz et al., 2019) and one study which used incarcerated populations (Rich et al., 2016) have both tentatively reported that adolescent adversity around age 16 as opposed to earlier had a most impactful effect on risky substance use. Life course theory is another framework that addresses the timing of adverse events; general consensus is that events in early childhood should have maximal impact on later health outcomes and behaviors (Halfon et al., 2014). This prediction is based on reasoning that early adverse events determine the trajectory of a life course in later years and are therefore more impactful on how a person interacts with their environment. One recent study investigating timing of adversity found childhood maltreatment around ages 5–9 is most associated with increased psychopathology at age 15 (Dunn et al., 2023). Little empirical evidence exists, however, to substantiate similar corroboration with early substance use.

Thus, the present study set out to investigate how adverse life events, defined broadly as a variety of potentially stressful life events or more narrowly as experienced physical and sexual abuse, impact substance use in a cohort of high-risk adolescents. We hypothesized that there is a positive association between the occurrence of adverse life events and lifetime substance use consisting of measured alcohol, tobacco, marijuana use, and six other illicit substances. We further categorized adverse life events according to a set of age periods they occurred in, grouping them as events occurring before the age of 3; between 3 and 8; between 8 and 12; and finally those occurring after 12. As theory on the effects of timing is in early stages of development and empirical research so far remains inconclusive, we propose provisional hypotheses on which age windows should be associated with substance use. First, according to life course theory, early adversity (before age 8) should have the largest effect on substance use. Second, in accordance with preliminary empirical literature, we predicted later adversity in adolescence (after age 12) is associated with more substance use. We additionally explored whether adverse life events are specifically linked with tobacco, alcohol, and marijuana use in adolescence.

Methods

Setting and study population

The iBerry (Investigating Behavioral and Emotional Risk in Rotterdam Youth) cohort consists of 1,022 adolescents selected based on their high risk of developing emotional and behavioral problems (Grootendorst-van Mil et al., 2021). For the cohort selection, 16,758 adolescents in their first year of high school (aged 13) were screened using the self-report Strengths and Difficulties Questionnaire (Goodman, 1997). Adolescents with the highest 15% problem scores and a random sample from the lowest 85% problem scores were selected, resulting in a 2.5:1 ratio. The current cross-sectional analysis uses data from the baseline measurement (mean age 14.9 years) of the cohort. The final sample consisted of 909 out of the 1,022 adolescents due to missing data on non-confounder variables.

Materials

Adverse life events

Information on exposure to adverse life events during childhood was obtained via the childhood adversity interview from The Tracking Adolescents' Individual Lives Survey (Ormel et al., 2012). A trained research assistant asked the accompanying parent or caregiver whether each of 14 events occurred in the adolescent's life and how old the adolescent was at the time of the event. These events were: hospitalization of the adolescent; serious illness or hospitalization of the mother, father, sibling, or close friend; death in the family or outside of family (e.g., of friend); parental divorce; moving houses; repeating class; switching school; extended living outside the household; physical violence and sexual abuse. Counts and percentages of each ALE are presented in Appendix Table 1. We categorized whether each event happened in the following four age periods: 0 to 3 years old; 4 to 8; 9 to 12; 12 or later. These intervals were chosen to balance theoretically meaningful maturation windows which are considered particularly susceptible to the effects of adverse life events (Andersen, 2019; see Appendix Figure 1A) and to also keep in line with adverse life event timing literature so far (Dunn et al., 2020; see Appendix Figure 1B). Based on those considerations, we came up with age groups corresponding to infancy (up to 3 years), early childhood (4–8), middle childhood (8–12), and late childhood (older than 12). A cumulative sum score theoretically ranging between 0 (no events experienced) and 14 (all events experienced) was created. Additionally, cumulative sum scores for each of the four age periods were created (e.g., four events occurred in the 4 to 8 years old period). By definition, however, school-related ALEs could not factor into the earliest age group, as school age in the Netherlands starts at age 5. Finally, the same sum scores were applied for only physical and sexual abuse events to create a sum score of physical adverse events ranging from zero to two (both physical and sexual abuse occurred). These events were isolated as a physically threatening type of adversity, as they are interpersonal, assaultive, threaten bodily integrity, and are generally outside what is considered by societies as developmental adversity within the normal range (Charuvastra & Cloitre, 2008). Sexual abuse in children and adolescents overwhelmingly consists of molestation, statutory rape, prostitution, pornography, exposure, incest, or other sexually exploitative activities and thus we consider it violates bodily integrity by its nature (Negriff et al., 2014).

Substance use

We used data from three instruments to identify which substances adolescents have ever used. Those instruments were the semi-structured Mini International Neuropsychiatric Interview for Children and Adolescents (Sheehan et al., 2010), the Self-Report Delinquency scale (SRED; Moffitt & Silva, 1988), and an additional three questions tapping into alcohol and tobacco consumption as used in The Tracking Adolescents' Individual Lives Survey (Ormel et al., 2012). Example questions include "How many times have you drank alcohol" from the SRED scale and "Do you smoke or have you ever smoked" from the three substance use questions. See the appendix for detailed information on how data from the three instruments were combined. As we expect drug use underreporting even in the Dutch context (Knibbe et al., 2007), we counted a positive response on any one of the three instruments as a substance having been used.

For the final substance use outcome variable, we created a lifetime count of how many substances the adolescent has used which could theoretically range from 0 (no substances tried) to 10 (taken all possible substances, i.e., alcohol, tobacco, marijuana, inhalants, stimulants, hallucinogens, tranquilizers, narcotics, cocaine, and other unspecified drugs). The lifetime count score was calculated, as it is an established measure in childhood maltreatment research (Sadeh et al., 2021), while also being indicative of adult substance use and later problems in living (Brecht et al., 2008; Chassin et al., 2002). Additionally, three items from the SRED were used to determine the frequency of alcohol, tobacco, and marijuana lifetime use. The response options were "Never," "Once," "two–three times," "four–six times," and "seven or more times," which were collapsed into "Never," "A few times," and "Many (7+) times to maximize the distribution of adverse events among categories.

Confounders

Adolescents self-reported their sex and age via a general demographics questionnaire. An accompanying parent of the adolescent provided information on national origin (Dutch; non-Dutch) based on where the parent was born, and household monthly income, which was categorized into less than 1599 euros; 1600–2399; 2400–4399, more than 4400. Urbanicity of living environment was determined from the number of addresses per km^2 surrounding home address, each adolescent was categorized as living rural, suburban, or urban neighborhood (defined as <1000, 1000–1500, and >1500 addresses/km^2, respectively). Self-reported psychopathology of the primary caregiver was measured using the Brief Symptom Inventory (BSI, Derogatis & Melisaratos, 1983). The BSI is a self-report general measure consisting of 53 items with 5 Likert-scale response options each, measuring psychological symptoms in various domains such as depression, anxiety, somatization, hostility, psychoticism, and paranoid ideation. A weighted mean global severity index measuring the general psychological functioning was calculated and used for the current analysis. Parental illicit substance use was a single self-report question that inquired from the primary caregiver whether they have ever taken any illicit drugs (including marijuana which is legal to consume in the Netherlands), with a binary "Yes/No" response option.

Statistical analysis

The primary analysis was focused on the association of childhood adverse life events with lifetime number of substances used in adolescence. Initially, two models were created – one where ALEs were measured as a cumulative score of a broad range of potentially stressful events, and one where the cumulative score consisted only of physical and sexual abuse, i.e., physical ALEs. Secondary, the adverse life events predictors also indicated in which age period the cumulative events occurred. All models were adjusted for key confounders, which consisted of age, sex, national origin, urbanicity of living environment, household income, parental psychopathology, and parental drug use. Selection of variables to adjust for was based on theoretical considerations of which confounders could introduce spurious associations (Amone-P'Olak et al., 2009; Verweij et al., 2013). As an additional exploration, we investigated the association of ALEs and their timing with the frequency of individual substances used (alcohol, tobacco, marijuana) in adolescence, thereby fitting three additional models with the

frequency of use variables as outcomes. Sex-stratified models were not carried out due to limited number of physical ALEs.

To model the substance use count outcome, a Poisson generalized linear model as implemented in the R base statistical package (v. 4.1.1; R Core Team, 2021) was used. We report on incidence rate ratios (IRR) obtained from exponentiated betas, 95% confidence intervals (CIs), and *p*-values obtained from the Poisson regressions. Nagelkerke's pseudo R^2 determined the proportion of variance explained (Nagelkerke, 1991). To provide an intuitive quantity of effect size, we compare the model estimated effect of adverse life events to that of age. In other words, we present how every additional adverse life event experienced affected substance use comparable to growing up a given amount of years using estimated marginal means, identical to the means typically used for effect plot visualizations. Model diagnostics were assessed in the following way: zero inflation was checked by comparing the ratio of observed zero responses to the model-estimated zero responses. Overdispersion was checked using a significance test of difference between the mean and variance of the outcome (Gelman & Hill, 2006, pp. 115–116). Finally, for the additional analyses on frequency of individual substance use, we used ordinal logistic models as implemented in the R package "MASS" (Ripley et al., 2022) in order to model the individual item Likert responses for how often adolescents used alcohol, tobacco, and marijuana. For this last set of models, we report on the same estimates as above and also plot estimated conditional probabilities. To maximize distribution of physical events across Likert responses, a dummy variable for sexual or physical abuse was created for this analysis, indicating whether any event occurred or no physically threatening event occurred.

Two sensitivity analyses were carried out. First, to asses if the results were subject to multicollinearity, we reran the analyses with a single dummy variable for sexual or physical abuse timing as used in previous literature (Dunn et al., 2020). This variable coded when physical ALEs were experienced for the first time (i.e., "experienced first time before age 3," "experienced first time age 4–8," "experienced first time age 8–12," and " experienced first time after age 12"), as opposed to separate continuous variables for each timing period. This approach also ruled out chronic accumulation of stress as a plausible mechanism behind associations. Second, to investigate the possibility that the patterns we observed were due to the recency of adverse life events, the ALE timing variables were replaced with two variables: 1) a variable counting how many recent events occurred in the past two years and 2) a variable counting events that happened earlier in life.

Data were missing on parental psychopathology (17.6% missing); household income (14.6%); adverse life events (11.1%); national origin (10.4%) and the alcohol, tobacco, and marijuana frequency use items (5.9%). For those missing values, multiple imputation as implemented in the "MICE" R package (van Buuren & Groothuis-Oudshoorn, 2011) was used creating five imputed datasets. We used auxiliary variables associated with the missing data to impute with more precisions and to relax the missing-at-random assumption. These auxiliary variables included: subscale scores of anxiety, depression, stress, withdrawal, aggressive and social problems, rule breaking, and aggressive behavior as measured by the Youth Self-Report questionnaire (Achenbach & Rescorla, 2001). Convergence was assessed using trace plots.

All analysis files are available at https://osf.io/kxuw5

Results

Sample characteristics are presented in Table 1. The study sample consisted of 909 adolescents with a mean age of 14.9 years (range 12–18); of those 436 (48%) adolescents were male and 473 (52%) female. The majority of adolescents were of Dutch background (77%). A majority of adolescents (58.0%) had used at least one substance, which was most often alcohol (94.9%) and tobacco (5.1%). Of the remaining adolescents, 21.4% had used at least two substances, 9.2% had used at least three substances, and 1.2% had used at least four substances. Only one adolescent in the sample had used five types of substances. Distribution of number of substances used and frequency of use of specific substances is presented in Appendix Figure 2. Next, Poisson bivariate associations equivalent to correlations were significant between the broad operationalization of lifetime adverse life events and number of substances used (IRR = 1.07 [95%CI = 1.03, 1.12], $p < .001$). This was also the case, but with a larger incidence rate ratio, between physical lifetime ALEs (including only sexual and physical abuse) and substance use (IRR 1.27 [1.11, 1.45], $p < .001$).

Broad and physical operationalizations of adverse life events and number of substances used

All adjusted primary estimates are presented in Table 2. When adjusting for confounders, the association with cumulative broad ALE did not remain significant (IRR 1.03 [0.98, 1.07], $p = .25$). Broad ALE occurring within specific age windows were likewise all nonsignificant in their association with substance use count (all $p > .19$). The full coefficient estimates for all variables in the broad ALE models can be found in Appendix Table 2. Nagelkerke's R^2 indicated 12.9% variance was explained by the final model. Turning to physical ALEs, after adjustment for confounders, the association remained significant (IRR 1.18 [1.03; 1.35], $p = .018$). By modeling physical adverse life events occurring at specific age windows, an association between physical and sexual abuse experienced after the age of 12 and higher number of substances used was found (IRR 1.36 [1.13, 1.63], $p < .001$). To quantify the effect size using estimated marginal means, we calculated the difference between an adolescent with a single physical ALE and an adolescent with no events (estimated mean difference of 0.30). This difference was identical to the substance use difference between a 12-year-old and a 14-year-old (0.30). Similarly, the difference between no events and two physical events (0.71) is close to the estimated difference between a 12- and 16-year-old (0.80). All estimated marginal means are visualized in Figure 1. Experience of physical adverse life events at younger ages was not significantly associated with substance use (Appendix Table 3). Nagelkerke's R^2 from the final model indicated 14.9% explained variance. The sensitivity analysis in which we dummy-coded physical life events as to which period they occurred in for the first time supported these results. Only adolescents who experienced adverse life events for the first time after the age of 12 were more likely to report more substances used compared to those who have never experienced physical events (IRR 1.52 [1.22, 1.91], $p = .002$). Full coefficients from this sensitivity analysis are reported in Appendix Table 4. Finally, we looked at recency of physical events instead of the defined age categories when they occurred. Recent physical and sexual abuse (in the past two years) was significantly associated with substance use (IRR 1.33 [1.06, 1.67], $p = 0.015$), whereas earlier abuse was not (see Appendix Table 5).

Table 1. Characteristics of the sample (*N* = 909)[1]

Sex	
Male	436 (48%)
Female	473 (52%)
Age, years	14.86 (12.67–18.11)
Urbanicity of living environment	
Rural	183 (20%)
Suburban	169 (19%)
Urban	557 (61%)
Net monthly household income, euro's	
<1599	102 (12%)
1600–2399	132 (16%)
2400–4399	411 (50%)
>4400	178 (22%)
Educational level[2]	
Special needs secondary education	34 (4.0%)
Combined education level	71 (8.3%)
Prevocational secondary education	381 (45%)
Higher general secondary education	191 (22%)
Preuniversity education level	175 (21%)
National origin	
Netherlands	656 (77%)
Other Western	51 (6.0%)
Other non-Western[3]	144 (15.7%)
Parental illicit drug use	29 (3.5%)
Parental psychopathology, score (BSI)	0.16 (0.00–1.62)
Adolescent number of substances used	0.86 (0.00–5.00)
Alcohol	493 (54%)
Tobacco	157 (17%)
Marijuana	101 (11%)
Other drugs	34 (4%)
Number of any adverse life events	2.27 (0.00–10.00)
Number of physical adverse life events	0.27 (0.00–2.00)

[1]Data are presented as *n* (%) or mean (range).
[2]Combined educational level refers to participants who have not yet reached the stage of choosing their educational degree. Prevocational, higher general and preuniversity educational levels in that order increasingly focus away from practical vocational education and towards higher academic education.
[3]Category includes Surinamese (5.6%); Asian (3.3%); Dutch Antilles (2.1%); Cape Verdean (1.9%); Moroccan (1.3%); Turkish (1.3%); African (0.8%); and South-American (0.8%).

Physical adverse life events and frequency of specific substances used

We modeled the association of timing of physical ALEs and the frequency of alcohol, tobacco, and marijuana usage using ordinal models, adjusting for confounders. There was no significant association of physical ALEs and tobacco use frequency (all $p > 0.22$). For marijuana use, a physical ALE occurring between the ages of 4 and 8 was significantly associated with more frequent use (OR 0.80 [0.49, 1.12], $p < .001$). A physical ALE after the age of 12 was no longer associated with marijuana frequency (OR 0.67 [−0.08, 1.36], $p = .07$). For alcohol use, there was a significant association for an event occurring before the age of 3 and less

Table 2. Incidence rate ratios (IRR) of primary interest from modeling the effect of adverse life events (ALE) on number of substances used. Results presented separately for broad operationalization of ALEs and for physical ALEs consisting exclusively of sexual and physical abuse. All estimates adjusted for age, sex, national origin, urbanicity of living environment, household income, parental psychopathology, and parental drug use

	Broad ALEs			Physical ALEs		
	IRR	95% CI	*p*-value	IRR	95% CI	*p*-value
ALEs lifetime	1.02	[0.98, 1.07]	0.285	1.18	[1.03, 1.35]	0.018
ALEs up to 3	1.01	[0.92, 1.10]	0.879	0.59	[0.33, 1.07]	0.085
ALEs 4 to 8	0.98	[0.91, 1.06]	0.585	1.22	[0.95, 1.57]	0.12
ALEs 9 to 12	1.01	[0.94, 1.08]	0.804	0.92	[0.73, 1.17]	0.509
ALEs older than 12	1.05	[0.98, 1.14]	0.184	1.36	[1.13, 1.63]	<.001

frequent alcohol use (OR −1.86, [−3.76, −0.50], $p = .02$). All coefficients from the three frequency use models are presented in Appendix Table 6. To further investigate the associations, estimated probabilities were plotted against physical adverse life events in Figure 2. For marijuana use, an adolescent who had not experienced a physical ALE between the ages of 4 and 8 had an 85.0% estimated probability of never having used marijuana compared to 71.5% of adolescents who had experienced a physical ALE in that period. Those with physical ALEs had an estimated 8.5% higher probability of having tried marijuana a few times (i.e., one to seven times) and 4.9% higher probability to have used it often (7+ times). The associations were in the opposite direction for alcohol use, in that if an adolescent had experienced a physical ALE before the age of 3, there was a higher estimated probability (81.7%) of having never drunk alcohol compared to if there were no experienced events in that period (42.6%).
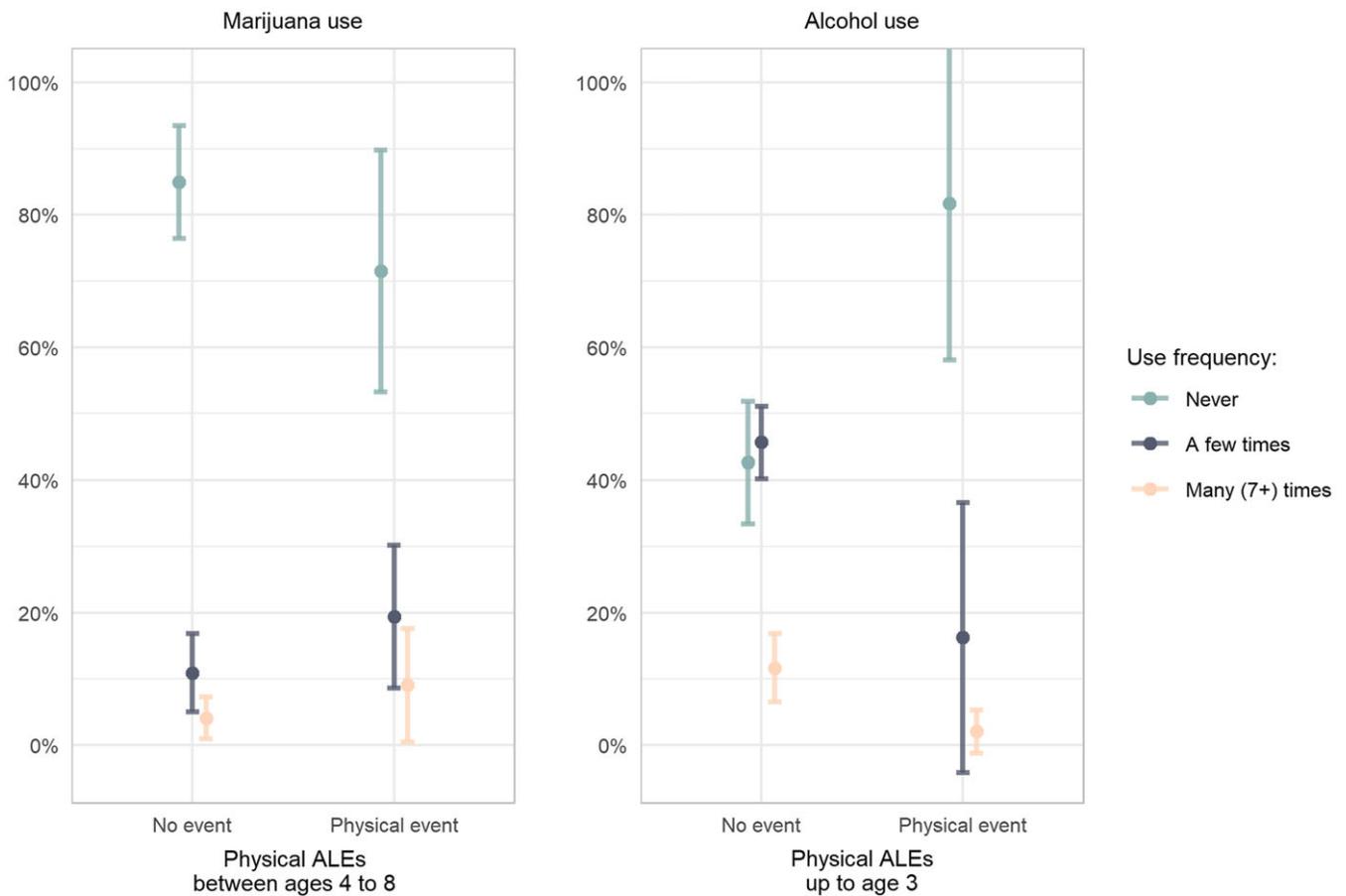
Estimated probabilities for substance use frequency responses (marijuana and alcohol) according to how many physical adverse life events have occurred in an age period. Presented only age periods with significant association to frequency of substance use. For a visualization of all estimates from this analysis refer to Appendix Figure 3.

Discussion

In the current study, we investigated the occurrence of adverse life events, as well as the dimensions of timing and type of adverse life events, and their association with substance use in a population-based adolescent sample with a high risk of psychopathology. First, when all adverse life events, including those considered less physically threatening, were included, no association with substance abuse in adolescence was observed. However, we did find associations between physical adverse life events (i.e., physical and sexual abuse) and an increased risk of substance use in adolescence, which remained after controlling for several socioeconomic and parental confounders. When investigating adverse life events occurring at specific developmental periods, it was found that physical ALEs occurring after the age of 12 were robustly associated with number of substances used. While the IRR appeared low, we estimated that a 12-year-old adolescent exposed to sexual and physical abuse in that period was estimated to use as many substances as a 16-year-old without a history of abuse. In
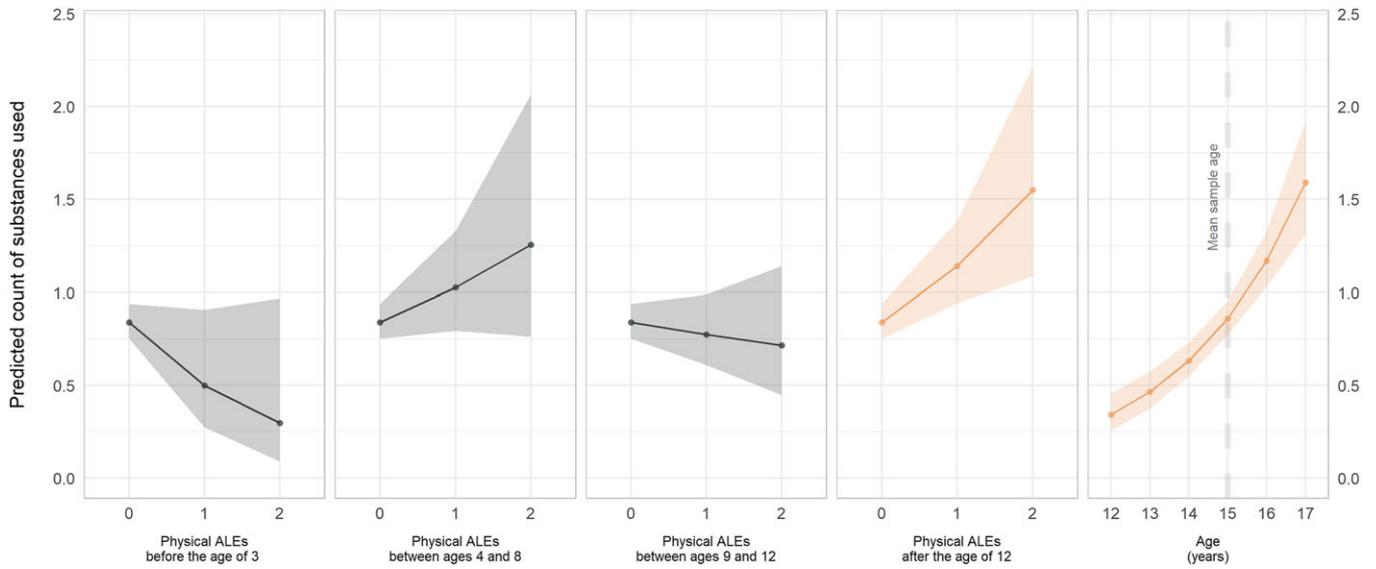
Figure 1. Estimated marginal means of substance use according to physical adverse life events (physical and sexual abuse) occurring at four age periods. Significant effects shaded in orange. For intuitive comparison of effect size, we also depict on the rightmost panel the predicted count of substances used as a function of age.

Figure 2. Estimated probabilities for substance use frequency responses (marijuana and alcohol) according to how many physical adverse life events have occurred in an age period. Presented only age periods with significant association to frequency of substance use. For a visualization of all estimates from this analysis refer to Appendix Figure 1.

contrast to our hypothesis based on theory, early life adversity was not associated with lifetime substance use. Additionally, exploratory findings point to sexual or physical abuse between the ages of

4 and 8 being particularly associated with more frequent marijuana use and abuse before the age of 3 was negatively associated with alcohol use. The considerable width of the confidence intervals

should be taken into account to interpret those latter findings with appropriate uncertainty.

Theoretical implications

The type of adversity mattered, as physical and sexual abuse predicted substance use, whereas a broader accumulation of adverse life events did not. This was particularly so for marijuana use as opposed to drinking alcohol, presumably the former signifying a more problematic early substance use while use of alcohol in adolescence is a normative part of development (Rich et al., 2016). Theoretical frameworks that address timing of adversity agree with the prediction that early negative experiences are most potent in launching people down unfavorable life trajectories, including falling into later problematic substance use (Andersen & Teicher, 2009; Perry, 2006). Research empirically testing this prediction has focused on general functioning outcomes so far, which combine in a single index score a wide range of symptoms and behavioral problems meant to reflect an overall disordered development (Hambrick et al., 2019; Hambrick, Brawner, Perry, et al., 2019). There was no evidence in our results to support that early life stress, including physical and sexual abuse, is predictive of frequent or polysubstance use in the current sample of high-risk adolescents. Recall bias could be a major factor for this absence of effect, as even abuse happening a decade ago could go unreported by the parents due to a lapse in memory or underreporting due to other factors.

On the contrary, we found more proximal events of sexual or physical abuse to equate the substance use profile of a 12-year-old to that of a 15-year-old. The current findings may follow more analogously along the research line of investigating substance use as coping mechanism for proximal traumatic events (Resnick et al., 1997). These studies typically employ adult victims of physical and sexual trauma to consistently report heightened maladaptive substance use after recent events compared to less maladaptive use if trauma is reported earlier in life (Acierno et al., 1996; Griffin et al., 2013; Walsh et al., 2012). The major deviation thus is a focus not on specific developmental windows during which impairments are particularly conducive for later substance use, but maladaptive coping mechanisms used to relieve the overwhelming state of distress following traumatic events (Khantzian, 2003). The current study is unable to confidently distinguish whether impairments in specific neurodevelopmental periods or maladaptive coping strategies mediate the trauma pathways. However, post-hoc analyses which provided evidence for an association between substance use and recent trauma regardless of age point towards the latter interpretation. We should also mention the work done in accelerated maturation following early adversity (Herzberg et al., 2021). In the current context, this hypothesis would suggest early substance use is the consequence of an adaptive neuro-restructuring response to a hostile environment (Callaghan & Tottenham, 2016). Further studies with neurological data available would be crucial to place the current findings in the arena of neurodevelopmental theories. Regardless, the current results advance theoretical models by favoring late as opposed to early trauma resulting in heightened substance use.

Past empirical findings

In comparing results to past research, it is important to consider that substance use in the current high-risk sample consisted primarily of alcohol, tobacco, and marijuana (58%) as opposed to very low rates of using other illicit drugs (3%). While there is little empirical literature to directly compare the current findings in terms of adolescent substance use and timing of adverse life events, there are several other lines of research of similar context. In their study on childhood neglect and adulthood substance use, Dubowitz et al. (2019) used latent class analysis to report that one class of adult participants with late neglect (around age 16) had the highest use of alcohol, marijuana, cocaine, and heroin. This finding highlights that although many studies, ours included, have not measured neglect and its timing, its developmental effects on substance use could conceivably be just as adverse. The closest methodology to the current study investigated the timing of physical or sexual abuse (past year versus lifetime) and its effect on marijuana and alcohol in a sample of incarcerated adolescent girls (Rich et al., 2016). Despite the selective nature of the sample, the results were remarkably similar in that number of substances used was particularly associated with recent abuse. To add context to these similar results, the adolescents reported the experiences themselves, while the current study used parent-reported adversity. Concurringly, Thornberry et al. (2001) used latent class analysis to find that maltreatment between 12 and 17 as assessed by child protective services, but not earlier in childhood, is associated with higher drug use and alcohol-related problems. Yet another finding from a cohort study corroborates that later (after age of 6) as opposed to early maltreatment predicted adults receiving alcohol abuse diagnoses and lifetime antisocial personality disorders as assigned via diagnostic interviews (Kaplow & Widom, 2007). Finally, it should be noted that Cowell et al. (2015) found neurocognitive functioning, as measured by inhibition control and memory tasks, was only impaired after reported abuse during infancy but not later in life. Therefore, their findings on a theoretically important mediating factor, namely inhibition control, do not easily map onto the current results. Nevertheless, taken together past studies offer provisional evidence that the associations found in the current sample are not completely contingent on auxiliary factors, as older age groups and diverse operationalizations of physical maltreatment and substance use produced similar conclusions to the ones reported here.

Strengths and limitations

Several limitations of the current study should be noted. First, parents instead of the adolescents themselves were asked to indicate which life events occurred and when. Events like physical and sexual abuse in particular could be undercounted if the interviewed parent was unaware or indeed the perpetrator of abuse, even though we asked for no identifying details beyond if abuse happened and when. Sexual and physical abuse in particular might be something children choose not to share with their parents, who themselves might have been directly or indirectly involved. Interviewing the adolescents themselves could have resulted in more reported events in the later years, but life events in the early years, and traumatic ones in particular, would be at higher risk of being unavailable for verbal recall or otherwise forgotten (Goodman et al., 2019). Recall bias remains an issue, especially when parents are asked to provide a specific age when an event occurred. We addressed this issue like in previous literature by classifying events into wider age periods, instead of using a more memory-demanding continuous measure (Dunn et al., 2020). It should also be noted there is still no consensus on which specific adverse life events need to be included or excluded in a cumulative stress score (Devaney et al., 2021). As such, we did not have data on

categories of neglect and deprivation (e.g., poverty, parent in prison, emotional neglect), which could operate through separate mechanisms to again push adolescents toward problematic substance use (McLaughlin & Sheridan, 2016). Finally, different life events (e.g., sickness in family) affect children differentially according to how old they are. This is not something the current measurement of adversity accounted for.

Relatedly, however, the current results did contribute to the discussion of measuring adverse life event by studying both a broad conceptualization of early stress and a narrow definition of threatening sexual or physical abuse. A particular strength of the current study is the measurement of substance use using two self-report and one interview instrument. This multimodal procedure alleviates social desirability bias that could have arisen in any individual response, thus producing an exceedingly reliable substance use measurement (Stacy et al., 1985). On the other hand, measuring lifetime substance use comes with two disadvantages. First, it is a crude measure of risky substance use. It should be noted that lifetime use is often used in adolescent research and is consistently found to be a robust predictor of negative psychological and social outcomes like emotional problems, academic achievement, and risky sexual activity (Hallfors et al., 2002; McDermott et al., 2013). Second, lifetime measures provide no information on temporality. Even though the adolescent population is young, it is an unverifiable assumption that substance use occurred after the adverse events. The direction of effect is thus assumed and not empirically verified here, which can be considered a major limitation of the study. Next, while the sample was not strictly representative of the Dutch adolescent population, we were able to adjust for several important socioeconomic and parental factors which is more pertinent than representativeness for explanatory research questions like ours (Rothman et al., 2013). Additionally, adverse life events and problematic substance use are of relatively low prevalence in the general population of adolescents, thus making the current high-risk cohort ideal for studying how and when those two relate. Such associations can only be studied in an observational design, however, making any causal claims subject to strong assumptions.

Implications

The current study may have several implications. First, studies investigating adverse life events should measure and investigate the dimensions of type and timing, as those were found to be important driving factors in explaining how adversity translates to increased substance use. Recent theoretical commentaries on stress and psychological functioning, as well as newly developed instruments already lay emphasis on studying those dimensions (Devaney et al., 2021; Hawes et al., 2021); the current study drives this point further by demonstrating the importance of measuring timing of adverse life events for the specific outcome of substance use. Second, the current study specifically describes an important factor behind substance use. Previous studies have documented early adversity as a consistent predictor of impaired mental health (Dunn et al., 2020; Hambrick et al., 2019; Thornberry et al., 2001), while here we also demonstrated the importance of late childhood adversity as an important risk factor of substance use. Preventive strategies for curtailing substance use already strongly advocate for the screening of negative life events in an individual's history (Stanis & Andersen, 2014). It is worth noting that while there is high enthusiasm among institutions and lawmakers to introduce community-based screening for childhood abuse and adversity, the empirical body of evidence in support for such individualized use of adversity sum scores is still in its very infancy (Anda et al., 2020). Further work investigating the dimensions of adversity instead of cumulative scores is required to meaningfully improve screening initiatives. The present results thus address which events and what timing could particularly be considered red flags for an adolescent to be classified as at high risk of problematic substance use.

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