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Unexpected adverse childhood experiences and subsequent drug use disorder: a Swedish population study (1995–2011)

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Abstract

Aims—Exposure to extraordinary traumatic experience is one acknowledged risk factor for drug use. We aim to analyse the influence of potentially life-changing childhood stressors, experienced second-hand, on later drug use disorder in a national population of Swedish adolescent and young adults (aged 15–26 years).

Design—We performed Cox Proportional Hazard regression analyses, complemented with co-relative pair comparisons.

Setting—Sweden

Participants—All individuals in the Swedish population born 1984 to 1995, who were registered in Sweden at the end of the calendar year they turned 14 years of age. Our follow-up time (Mean: 6.2 years; Range 11 years) started at the year they turned 15 and continued to December 2011 (N=1,409,218).

Measurements—Our outcome variable was drug use disorder, identified from medical, legal and pharmacy registry records. Childhood stressors, as per DSM-IV stressor criteria, include death of an immediate family member and second-hand experience of diagnoses of malignant cancer, serious accidental injury, and victim of assault. Other covariates include parental divorce, familial psychological well-being, and familial drug and alcohol use disorders.

Findings—After adjustment for all considered confounders, individuals exposed to childhood stressors ‘parental death’ or ‘parental assault’ had over twice the risk of drug use disorder than those who were not (HR = 2.63 (2.23–3.09) and 2.39 (2.06–2.79), respectively).

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Conclusions—Children under 15 who experience second-hand an extraordinary traumatic event (such as a parent or sibling being assaulted, diagnosed with cancer, or dying) appear to have approximately twice the risk of developing a drug use disorder than those who do not.

Introduction

Exposure to extraordinary traumatic events, as defined by DSM-*J*(i.e. physical and/or sexual abuse in childhood, adulthood sexual assault, or combat) is one of several acknowledged risk factors for drug use disorder (1, 2). Over 90% of drug users report one or more traumatic event in their lifetime (2, 3); however, mechanisms behind this association remain unclear, with three schools of thought prominent in substance use literature. Firstly, there is the 'self-medication' hypothesis (4), which stipulates that the traumatic event precedes drug use, with individuals illicitly 'self-prescribing' to cope with feelings of stress associated with past trauma. Secondly, is the theory that drug use precedes the traumatic event, that drug use is a high-risk behaviour, which could lead to increased risk of exposure to future traumas (5–7). Lastly, is the 'artefact hypothesis', the assumption being that associations between traumatic events and drug use are non-causal, they being confounded (or mediated) by unmeasured factors, for example psychological wellbeing (8, 9), or shared genetic and environmental factors (10).

Research focusing on the 'self-medication' and 'artefact' hypotheses gives special attention to adverse childhood experiences (11–15), as children are considered highly vulnerable to any potential long-term negative influences that adversity may have on future health behaviours and outcomes (16–18). Many studies investigating adverse childhood experiences and psychopathology focus predominantly on the traumas of physical and emotional abuse, neglect and sexual abuse (for examples see: (8, 9, 19–21)). Researchers have also considered environmental and potential genetic factors (such as parental drug and alcohol use disorders) as confounding risk factors for future substance abuse (17, 18).

However, past research gives less attention to events that could be termed 'unexpected' adverse childhood experiences. This term is our attempt to define potentially life-changing childhood events not categorised as forms of abuse or neglect, which also operationalize DSM-*IV* stressor criterion. Such events are subdivided into: i) trauma experienced 'first-hand' and ii) trauma experienced 'second-hand', i.e. learning of trauma that occurred to an immediate family member (parent/sibling) (22, 23). This study shall focus on the latter group.

Being guided by DSM-*IV* stressor criterion (22, 23), we identified four suitable proxies for second-hand traumatic childhood experiences from Swedish registry data. These included an immediate family member: i) being diagnosed with malignant cancer, ii) being assaulted, iii) suffering severe accidental injury leading to permanent disability, and iv) dying. We hypothesise that second-hand experiences of trauma during childhood are also capable of evoking emotional stress and, therefore, have the potential to affect later drug use.

Illicit substance use often starts during adolescence (12–19 years of age) (24). Children exposed to adverse experiences have an even greater risk for early substance use debut (25).

The aim of this longitudinal study was to investigate the associations between experiences of second-hand childhood traumas (between the ages 0–14 years) and future drug use disorder in a national population of Swedish adolescent and young adults (aged 15–26 years). By further considering familial drug and alcohol use disorders, and psychological wellbeing, our study aimed to test the 'self-medication' hypothesis (4), whilst investigating the degree to which the association between 'second-hand' childhood traumas and drug use disorder are causal.

Methods

Drug use disorder is a multifactorial syndrome influenced by genetic risk factors, a broader vulnerability to a range of externalizing disorders, and by an array of environmental risk factors (26). We used identical data sources described in several previous publications on drug abuse in Sweden (26–28). In short, we used linked data from multiple Swedish nationwide registries and healthcare data. Linking was achieved via the unique individual 10-digit personal ID number assigned at birth or immigration to all Swedish residents. The following sources were used to create our drug use disorder database: the Swedish Hospital Discharge Register, containing all hospitalizations for all Swedish inhabitants from 1964–2010; the Swedish Prescribed Drug Register, containing all prescriptions in Sweden picked up by patients from 2005 to 2009; the Outpatient Care Register, containing information from all outpatient clinics from 2001 to 2010; the Primary Health Care Register, containing outpatient diagnoses from 2001–2007 for 1 million patients from Stockholm and middle Sweden; the Swedish Crime Register, containing national data on all convictions from 1973–2011; the Swedish Suspicion Register, containing national data on all individuals strongly suspected of crime from 1998–2011; and the Swedish Mortality Register, containing all causes of death.

Dependent variable – drug use disorder

We identified drug use disorder cases from Swedish medical registries via *ICD* codes: *ICD8*: drug dependence (304); *ICD9*: drug psychoses (292) and drug dependence (304); *ICD10*: mental and behavioural disorders due to psychoactive substance use (F10–F19), except those due to alcohol (F10) or tobacco (F17)); in the Crime Register by codes: 3070 (driving under the influence of narcotics), 5010, 5011 and 5012 (possession and use of an illicit substance), and by references to laws covering narcotics (law 1968:64, paragraph 1, point 6 (possession, use or other charges in relation to illicit substances)) and drug-related driving offences (law 1951:649, paragraph 4, subsection 2 and paragraph 4A, subsection 2).

Drug use disorder was further identified in individuals (excluding those suffering from cancer) in the Prescribed Drug Register who had retrieved (on average) more than four defined daily doses of either Hypnotics and Sedatives (Anatomical Therapeutic Chemical (ATC) Classification System N05C and N05BA) or Opioids (ATC: N02A) over a twelvemonth period. This study was approved on 30th November 2011 by the regional ethical review board in Lund, Sweden (Dnr 2011/675).

Study population

We sampled all individuals in the Swedish population born 1984 to 1995, who were registered in Sweden at the end of the calendar year they turned 14 years of age. Our follow-up time (mean: 6.2 years; range 11 years) started at the year they turned 15 and continued to the year 2011 (N=1,409,218).

Independent variables

Unexpected adverse childhood experiences—We identified four second-hand childhood traumas using *ICD* codes from the Swedish Hospital Discharge Register, with such events occurring to immediate family members of our study sample (parents/full-siblings - see appendix for *ICD* codes). These included diagnoses of malignant cancer; accidental injury leading to permanent disability (spinal cord injury or full/part loss of limb(s)); victim of assault; and death.

Firstly, we created a cumulative 'unexpected adverse childhood experience' variable by summing responses to all four events. This variable represented direct trauma to the parents of our study population only, not their siblings (1/0). We also created a dichotomous (1/0) variable for each of the four stressor events and stratified them by affected family member (parent or full-sibling). Any second-hand childhood stressor (as defined above) must have occurred to an immediate family member whilst our study population were 0–14 years old.

We included parental divorce as a covariate in our analyses. Though divorce does not qualify as a DSM-*IV* stressor, previous studies have found associations between family structure and drug use disorder (29–32). As cohabitation without marriage is common in Sweden, we defined the year of 'divorce' as the year that individuals discontinued to reside with both their parents.

Other considered covariates were the gender of our study population, and their parents' education, psychological wellbeing, drug and alcohol use disorders, as defined by *ICD* codes (17, 18, 33, 34). Among siblings, only drug (not alcohol) use disorder was considered a potential confounder (34). As the mean age of initial alcohol use disorder diagnosis in our sample was 41.9 years, we assumed that such behaviour later in life would have little or no influence over their siblings' drug use between ages 15–24 years. Furthermore, past research suggests no significant association between sibling alcohol use disorder on other sibling's drug use disorder (35, 36).

We measured all covariates whilst our study population was aged 0–14 years (see *dependent variable* definitions and appendix for all *ICD* codes).

Statistical analysis

Due to different exposure periods based on year and month of birth, in order to examine the associations between childhood stressors and subsequent drug use disorder, we utilized Cox Proportional Hazard regression to investigate all individuals from age 15 years until: i) the time of first registration of drug use disorder; ii) until death; or iii) until end of follow-up (year 2011), whichever came first. As full-siblings could be included in the analysis, we

adjusted for non-independence with a robust sandwich estimator. We investigated the proportionality assumption in all models; if this was not fulfilled, we included an interaction term between the variable of interest and the logarithm of time. We tested the proportional hazards assumption for all other variables both before and after the inclusion of the interaction term. The main predictor variable in the analysis was 'unexpected adverse childhood experiences'.

Model 1 was a crude analysis of our cumulative 'parental' childhood stressor variable. Model 2 adjusted for parental divorce, parental education and the gender of our study population. Model 3 further adjusted for parental genetic and or environmental factors (by excluding individuals with parental drug and alcohol use disorders, and psychological disorders from the analysis). Model 4 further adjusted for *familial* genetic and or environmental factors by also excluding individuals with full-sibling drug use disorder.

We performed separate analyses to investigate effects of each of the four separate stressor categories, Models A1a–A1d testing events that occurred to parents and/or full-siblings. Models A2a–A2d repeated the analysis in A1a–A1d, whilst adjusting for *all* potential confounders considered in Model 4.

As a sensitivity test, by means of the Swedish Multi-Generation Register, we identified all first cousin and full-sibling pairs that were discordant for drug use disorder and our cumulative 'unexpected adverse childhood experience' variable ($N_{(\text{first cousins})}$ = 25,522 pairs; $N_{(\text{full-siblings})}$ = 5772 pairs). This meant that we compared cousin and sibling pairs where one (aged 0–14 years) experienced the stressor, while the other either did not (as not yet born at the time of the stressor event, or experienced it aged 15 years or more). The Cox proportional hazards model adjusts for the cousin/sibling cluster and therefore accounts for an array of unknown shared genetic and environmental factors. Model S1 provided a crude analysis; Model S2 further adjusted for parental divorce. All statistical analyses were performed using SAS 9.3 (37).

Results

Table 1 shows the frequency and percentages of our study population, who experienced trauma as a child 'second-hand', i.e. learned of trauma to an immediate family member. The traumas are presented as i) a cumulative measure and ii) as separate categories, all results being stratified by drug use disorder. Table 2 presents results from Models 1–4. Individuals (aged 15–26 years) in our study population, exposed to one or more childhood stressor (between ages 0–14 years), were more than twice as likely to be registered with drug use disorder (Model 1, HR = 2.12 (95% confidence interval (CI) 1.96–2.30)). The relative risk increased after adjustment for parental education and sample population gender (Model 2, HR = 2.39 (2.16–2.65)). After adjustment for parental drug and alcohol use disorders, and psychological disorders (Model 3) and full-cousin and full-sibling drug use disorder (Model 4), the relative risk decreased (HR = 1.98 (1.73–2.27) and 1.94 (1.67–2.25), respectively)). There was a significant interaction term between our cumulative stressor variable and gender in Model 2 only (0.87 (0.81–0.94)). The proportionality assumption was not fulfilled; the HR for the interaction term between 'log time' and the cumulative stressor variable was

0.85 (0.80–0.89) in Model 1, suggesting that the effect of childhood stressors on drug use disorder decreased over time.

Table 3 presents results from Models A1a–d and A2a–d (effects of individual childhood stressors on later drug use disorder). After adjustment for *all* considered confounders (Models A2a–d), the highest relative-risk categories for drug use disorder were death and assault of parents (HR = 2.63 and 2.39, respectively), and assault of siblings (HR = 1.93).

Tables 4a and 4b show results from the first cousin and sibling-pair sensitivity analyses. After adjustment for parental divorce (Models S2), the relative risk of drug use disorder after exposure to our cumulative 'unexpected adverse childhood experience' variable was 1.65 for first cousins and 1.46 for full-siblings. After stratifying for age difference, the largest risk was seen in those cousin/full-sibling pairs whose difference in age was greater than 5 years (see Tables 4a–b).

Discussion

The aim of this longitudinal study was to investigate the associations between experiences of second-hand childhood traumas (between the ages 0–14 years) and later drug use disorder in the Swedish adolescent and young adult population (aged 15–26 years). Our results showed that individuals, who experienced any childhood stressor second-hand, had approximately twice the risk of drug use disorder than those who did not. The association between our cumulative stressor variable and drug use disorder was attenuated in the first cousin and sibling-pair analysis (HR = $1.55_{(c)}$ and $1.46_{(s)}$, respectively); however, in cousins/siblings whose difference in age was greater than 5 years, the relative risk remained high (HR = $1.72_{(c)}$ and $1.92_{(s)}$, respectively). To our knowledge, this is the first nationwide study that specifically investigated the effects of second-hand adverse childhood experiences on drug use disorder, and our results add strength to the increasing body of evidence suggesting that environmental effects within families impact on risk for drug use disorder (26, 27, 31, 34, 38). Of the individual stressor categories investigated (Table 3), death of a parent had the highest relative risk of drug use disorder (HR = 2.63). We identified parental death from all-cause Mortality Registers. However, we could not ascertain whether death was an indirect result of another trauma category (i.e. prior diagnosis of malignant cancer, serious assault or accidental injury).

Parental/full-sibling assault was associated with higher relative risk for later drug use disorder (HR = 4.80 and 4.49, respectively, see Table 3). These values were attenuated after adjustment for all considered confounders ($HR_{(P)} = 2.39$, $HR_{(S)} = 1.93$). The extent of attenuation most likely reflects the degree of correlation between risk of assault, the psychopathology of substance use disorders, poor mental health status and lower levels of education. These factors could even be indicative of an underlying behaviour type, which could potentially confound associations between second-hand childhood trauma and later drug use disorder. However, that risk remains after adjustment for these factors (and in our co-relative sensitivity analyses), lends support to the hypothesis that second-hand experience of trauma during childhood increases the risk of later drug use disorder in adolescence/adulthood.

Of the other considered covariates, being male was consistently associated with a higher relative risk for drug use disorder (Model 4, Table 2; HR = 3.32). This is in line with previous findings that men are typically twice as likely to try (and become dependent upon) illicit substances than women (39, 40). Similarly, our results showed an increased relative risk of drug use disorder later in life if a child experienced parental divorce (HR = 2.07), which mirrors past research investigating drug use disorder and the family structure (26, 29–32). Though there is extensive research investigating adverse childhood experiences (e.g. sexual or physical abuse, or neglect) and detrimental health behaviours in later life (11–18, 41), research specifically investigating effects of second-hand stressor events on drug use disorder is sparse. A PubMed search revealed only two drug use studies that included similar stressor events as covariates. Both papers tentatively supported our results: Newcomb and Harlow (42) grouped traumatic events stemming from: i) family and parents, ii) accidents and illness, and iii) relocation, labelling such occurrences as ‘uncontrollable stressful events’. They concluded that these events had both a direct and mediated impact on substance use on young adults if they occurred during late adolescence (sample aged 12–18 years, N= 376). The second study by Reed et al. (43), used retrospective data from young adults, as defined by DSM-*IV* stressor events. Their results suggested that early life traumas, if coupled with a subsequent diagnosis of post-traumatic stress disorder (PTSD), were associated with increased risk for drug use (N = 998).

In an attempt to test the conclusions made by Reed et al. (43) (that associations between childhood stressors and drug use could be mediated by a diagnosis of PTSD), we further identified all individuals in our study population who had a diagnosis of PTSD: i) between ages 0–14 years (N = 532), and ii) between 0–26 years (N= 5045) using ICD codes (*ICD*10 F43; *ICD*9 308,309) from the Swedish Hospital Discharge Register. After excluding these individuals from our analysis, those who experienced childhood stressors were still more than twice as likely to be registered as drug abusers (0–14 years PTSD: HR = 2.17 (1.93–2.35) and 0–26 years PTSD: HR = 2.12 (1.92–2.34)). Though these results do not appear to support the mediation theory of Reed et al., it should be noted that rates of PTSD derived solely from hospital discharge records are most likely to be much lower than those obtained from in-depth interviews (43).

The issue of causal inference is extensively debated in epidemiology (44), some even arguing that in the absence of experimental data, causal interpretation is impossible. As the risk for drug use runs strongly in families, offspring of affected parents will share risk factors for drug use disorder (34). Therefore, employment of a co-relative comparison (which dramatically reduces the number of environmental confounds compared to standard comparisons of unrelated individuals), can provide support for the hypothesis that unexpected childhood stressors contribute significantly to the aetiology of drug use disorder in later life. As per our definition, discordant cousins/siblings could have either: i) never experienced a stressor event (not yet born); or ii) experienced it at an age older than 14 years; therefore, it is probable that we underestimated the risk for drug use disorder in these analyses.

The risk for drug use disorder was stronger in co-relative probands whose age difference was 6 years or more. This may be due to the fact that cousin/sibling pairs, whose age

difference was 5 years or less, controlled for a larger amount of environmental factors (34). However, it is also possible that a major component of the risk difference reflects how much of the period of vulnerability for drug use disorder onset each cousin/sibling has already survived.

Strengths and Limitations

A major strength of our study is its annual sampling of a national population from 1995–2011 and the employment of multiple data sources to capture drug use disorder cases. Our data are nearly 100% complete for drug use disorder and all other medical diagnoses used as covariates in this study. For all hospitalisations, only 0.4% of personal identification numbers and 0.9% of all main diagnoses were missing. This enabled us to perform the first nationwide study to investigate the effects of unexpected childhood stressors on drug use disorder. Despite this, there are several limitations of our study that should also be discussed.

We identified drug use disorder from medical, pharmacy and criminal records, utilising *ICD* codes to capture cases within our study population. While this method has the important advantage of not requiring accurate respondent recall and reporting, the risk for misclassification bias remains. Furthermore, individuals captured in Swedish registers most likely belong to a sub-group of more severe drug users, labelled ‘drug use disorder’ cases by us. However, studies conducted in Norway reported rates of drug use and dependence of 3.4%, assessed using DSM-*III*-R criteria, which is identical to that found by our registry-based study (45, 46).

Though we were guided by DSM-*IV* traumatic events and stressor criterion (specifically, learning about trauma to immediate family members) (22), we created our variables based solely on our interpretation of stressors that could be readily identified with ICD codes from medical records. This made it difficult to validate our second-hand trauma exposures. However, we are reassured by an external audit of the Swedish Hospital Discharge Register, which suggests that the vast majority of diagnoses are 85–95% valid (47).

This study is based upon Swedish population data. As levels of drug use in Sweden are considered low compared to other Western countries, and that the Swedish population has free access to many aspects health care and support systems and resources, it is not readily apparent how transferrable these results are to other populations, whose access to such resources is limited.

Finally, as the study period spans sixteen years, secular trends (such as period and cohort effects) may have had some impact on our findings. However, a recent study of drug abuse in Sweden over four decades revealed that from 1997–2010, period and cohort effects on hospitalisations due to drug abuse have remained relatively stable (48).

Conclusions

The results of this study show that associations between unexpected adverse childhood experiences and later drug use disorder remain, even after adjustment for *familial* psychological disorders, and drug and alcohol use disorders. We, therefore, cannot reject the

hypothesis that early-life exposure to such stressors is one possible precursor to drug use disorder. Furthermore, results from our co-relative sensitivity analyses cast doubt on theories suggesting that associations between unexpected adverse childhood experiences and drug use disorder are non-causal. Based on our results, current and future policy may further benefit from new initiatives to identify early the more vulnerable members of the population to drug use disorder.

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Appendix

Unexpected adverse childhood experiences: ICD Codes

Malignant cancer

*ICD*8: 140–49, 150–59, 160–63, 170–74, 180–89, 190–99, 200–09; *ICD*9: 1400–2089; *ICD*10: C000–C970.

Permanent disability (full/part loss of limb(s))

*ICD*8/9: 887.x, 896.x, 897.x; *ICD*10: S48.0,1,9, S58.0,1,9, S68.4,8,9, S78.0,1,9, S88.0,1,9, S98.0,4, T13.6, T11.6, T05.1,2,3,4,5,6.

Permanent disability (spinal cord injury)

*ICD*8: 806.x, 958.x; *ICD*9: 952.x, 806.x; *ICD*10: S12, S12.1, S12.2, S12.7, S12.9, S14, S14.1, S24, S24.1, S34.0, S34.1, S34.3, G82.x, T06.1, T09.3, T91.1, T91.3, S22.0, S22.1, S32.0, S32.1, S32.2, S32.7, S32.8.

Assault

*ICD*8/9: E960–E969; *ICD*10: X850–Y099 Y87.1.

Familial genetic factors

Parental mental health status

*ICD*8: 295.xx, 296.xx, 298.xx, 297.xx, 299.xx, 300.xx 301.xx; *ICD*9: 295–316; *ICD*10: F20–29, F30–39, F50–59, F60–69.

Parental alcohol use disorder

*ICD*8: 291, 980, 571, 303; *ICD*9: 291, 303, 305A, 357F, 425F, 535D, 571A–D, 980, V79B; *ICD10*: F10 (excluding acute alcohol intoxication: F10.0), Z50.2, Z71.4, E24.4, G31.2, G62.1, G72.1, I42.6, K29.2, K70.0–K70.9, K85.2, K86.0, O35.4, T51.0–T51.9; Anatomical Therapeutic Chemical (ATC) codes in the Prescribed Drug Register: disulfiram (N07BB01), acamprosate (N07BB03), or naltrexone (N07BB04). Additionally, we identified individuals with at least two convictions of drunk driving (law 1951:649) or drunk in charge of maritime vessel (law 1994:1009) in the Crime register. We used the Cause of Death Register to obtain data on alcohol-associated death and used the same codes as above.

Parental/Full-sibling drug use disorder codes were the same as described for the dependent variable in the main text.

Table 1

Frequencies and percentages (%) of sample population who experienced unexpected adverse childhood experiences (UACE), stratified by drug use disorder (DUD) *N* = 1,409,218; follow-up time: mean 6.2 years; range 11 years

	No DUD	DUD
***N* (total)**	**1,350,239 (95.8)**	**58,979 (4.2)**
Cumulative UACE variable: Parent (P) and sibling (S)	69,880 (93.6)	4,811 (6.4)
UACE (P)	60,331 (93.5)	4,228 (6.6)
UACE (S)	13,474 (92.4)	1,103 (7.6)
Individual UACE variables		
Malignant Cancer (P)	35,070 (95.4)	1,708 (4.6)
Malignant Cancer (S)	4,300 (95.9)	183 (4.1)
Permanent disability through injury (P)	4,728 (94.1)	295 (5.9)
Permanent disability through injury (S)	1,580 (94.5)	92 (5.5)
Death (P)	25,462 (92.1)	2,200 (7.9)
Death (S)	2,542 (94.7)	143 (5.3)
Victim of Assault (P)	4,725 (87.6)	667 (12.4)
Victim of Assault (S)	5,710 (88.9)	714 (11.1)
Covariates		
Divorce (P)	395,736 (93.6)	27,048 (6.4)
Women	671,363 (98.0)	13,665 (2.0)
Men	678,867 (93.7)	45,313 (6.3)
Low education (P)	80,069 (92.8)	6,223 (7.2)
Middle education (P)	386,447 (94.6)	22,028 (5.4)
High education (P)	883,723 (96.6)	30,728 (3.4)
Mental Health (P)	61,137 (90.2)	6.620 (9.8)
DUD (P)	49,386 (85.5)	8,379 (14.5)
DUD (S)	58,014 (84.0)	11,089 (16.1)
Alcohol Use Disorder (P)	32,684 (89.2)	3,948 (10.8)

Table 2

Hazard ratios (HR) with 95% confidence intervals (95% CI) of future drug use disorder after exposure to our cumulative 'unexpected adverse childhood experience' variable (UACE) between ages 0–14 years, and other considered covariates (*N* = 1,409,218)

	Model 1 HR (95 % CI)	Model 2 HR (95 % CI)	Model 3* HR (95 % CI)	Model 4 ** HR (95 % CI)
UACE (P)	2.12 (1.96; 2.30)	2.39 (2.16; 2.65)	1.98 (1.73; 2.27)	1.94 (1.67; 2.25)
UACE (P) * Log(time)	0.85 (0.80; 0.89)	0.85 (0.81; 0.90)	0.84 (0.79; 0.90)	0.86 (0.80; 0.93)
Divorce (P)		2.13 (2.09; 2.17)	1.98 (1.94; 2.02)	2.07 (2.03; 2.11)
Low Education (P)		1.84 (1.79; 1.90)	1.69 (1.63; 1.75)	1.44 (1.39; 1.50)
Middle Education (P)		1.45 (1.42; 1.48)	1.34 (1.31; 1.37)	1.31 (1.28; 1.34)
High Education (P)		1.0	1.0	1.0
Gender (M vs. F)		3.26 (3.19; 3.32)	3.44 (3.46; 3.51)	3.32 (3.23; 3.40)
UACE * gender		0.87 (0.81; 0.94)	0.94 (0.86; 1.04)	0.95 (0.85; 1.05)

*Excluding individuals with parents registered with drug and alcohol use disorders, Mental Health problems (n=119,827)

**Excluding individuals with parents registered with drug and alcohol use disorders, Mental Health problems and Siblings registered with drug use disorder (*N*=176,916)

(P) – Parents

Table 3

Hazard ratios (HR) with 95% confidence intervals (95% CI) of future drug use disorder after exposure to individual stressor variables (between ages 0–14 years) and other considered covariates ** (N = 1,409,218)

Stressor variable	**Model A1 a–d* HR (95 % CI)**	**Model A2 a–d** HR (95 % CI)**
a) Death (P)	2.51 (2.24; 2.80)	2.63 (2.23; 3.09)
Death P * Log(time)	0.83 (0.78; 0.89)	0.80 (0.72; 0.88)
b) Permanent disability (P)	1.67 (1.48; 1.88)	1.21 (1.01; 1.45)
c) Victim of assault (P)	4.80 (3.97; 5.82)	2.39 (2.06; 2.79)
Assault (P) * Log(time)	0.86 (0.75; 0.98)	
d) Malignant Cancer (P)	1.30 (1.14; 1.48)	1.54 (1.31; 1.80)
Cancer (P) * Log(time)	0.91 (0.84; 0.98)	0.88 (0.80; 0.98)
a) Death (S)	2.07 (1.37; 3.12)	1.29 (1.05; 1.60)
Death (S) * Log(time)	0.71 (0.54; 0.94)	
b) Permanent disability (S)	1.47 (1.20; 1.82)	1.26 (0.93; 1.70)
c) Victim of assault (S)	4.49 (3.72; 5.41)	1.93 (1.66; 2.23)
Assault (S) * Log(time)	0.81 (0.71; 0.93)	
d) Malignant Cancer (S)	0.96 (0.82; 1.12)	0.97 (0.81; 1.17)

* Each stressor was investigated in separate models.

** Each stressor was investigated in separate models. All models were adjusted for parental education and divorce, plus study sample gender and excluded individuals with parents registered with drug and alcohol use disorders, and MH problems, and individuals with full-siblings with drug use disorder.

Parent (P); sibling (S)

Table 4a

Hazard ratios (HR) with 95% confidence intervals (95% CI) of future drug use disorder (DUD) in a first cousin-pair analysis, they being discordant for unexpected adverse childhood experience (UACE) and DUD (*N* = 25,522 pairs)

	Model S1 HR (95 % CI)	Model S2* HR (95 % CI)
UACE (P)	1.55 (1.50; 1.59)	1.65 (1.60; 1.70)
UACE (P) (cousins 1–5 years apart)	1.53 (1.48; 1.58)	1.63 (1.58; 1.69)
UACE (P) (cousins > 5 years apart)	1.66 (1.53; 1.80)	1.72 (1.59; 1.87)

*Adjusted for parental divorce

Parent (P)

Table 4b

Hazard ratios (HR) with 95% confidence intervals (95% CI) of future drug use disorder (DUD) in a sibling-pair analysis, they being discordant for unexpected adverse childhood experience (UACE) and DUD (*N* = 5772 pairs)

	Model S1 HR (95 % CI)	Model S2* HR (95 % CI)
UACE (P)	1.46 (1.34; 1.60)	1.46 (1.34; 1.59)
UACE (P) (siblings 1–5 years apart)	1.36 (1.23; 1.49)	1.36 (1.23; 1.49)
UACE (P) (siblings > 5 years apart)	2.04 (1.66; 2.51)	1.92 (1.55; 2.38)

*Adjusted for parental divorce

Parent (P)