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Re-examining the link between childhood maltreatment and substance use disorder:

A prospective, genetically informative study

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Abstract

Childhood maltreatment is considered a risk factor for substance use disorders (SUD), but this is largely based on retrospective self-reports that are subject to recall bias, designs that do not control for familial confounding, or both. The specific contribution of childhood maltreatment to SUD risk thus remains unclear. Here, we evaluated this contribution in a prospective cohort with objectively recorded childhood maltreatment, using a design that allows controlling for familial confounding. We used medical records and registers to study 525 young adults (20-37 years) with prospectively and objectively documented severe maltreatment exposure, 1,979 clinical controls (unexposed former child and adolescent psychiatry patients), 1,388 matched healthy controls; and their siblings and cousins. We examined the association between maltreatment and SUD using Cox regression models in the population, as well as stratified within siblings in the same family. SUD risk was significantly increased with childhood maltreatment exposure (crude HR: 6.61, 95%CI: 5.81-7.53; HR adjusted for sex, birthyear, externalizing problems, parents' SUD and socioeconomic factors: 3.50, 95%CI 2.95, 4.16). An approximately 3-fold elevated SUD risk remained when comparing exposed individuals with their unexposed siblings (adjusted HR: 3.12, 95%CI 2.21, 4.42). We provide estimates of the association between childhood maltreatment and SUD accounting for possible confounds of both recall bias and familial factors. When familial confounding is controlled for, SUD risk attributable to severe childhood maltreatment is decreased, but nevertheless considerable. These findings establish a specific contribution of childhood maltreatment to SUD, underscoring the need for SUD prevention in young people exposed to maltreatment.

Key words:

early life trauma; childhood maltreatment; addiction; drug; alcohol

Introduction

It is widely held that childhood maltreatment (CM) is a major risk factor for subsequent substance use disorders (SUD).[1-5] This association appears to be quantitative: Severe maltreatment, including physical, sexual and emotional abuse, is associated with increased SUD risk and severity.[2, 3, 6] Furthermore, the more CM subjects report, the higher their rates of substance use before age 14, and SUD in adulthood.[5] Multiple brain mechanisms through which CM may mediate SUD risk have been proposed.[7] However, while the statistical association of CM with SUD risk is indisputable, interpreting this association faces two major challenges.

First, associations of CM and SUD largely rely on retrospective self-report of maltreatment.[4] Retrospective self-reports are subject to multiple sources of error, including recall and selection bias (e.g. self-selection into samples),[8, 9] intentional false reporting,[10] but also minimization or denial of past maltreatment.[11] Agreement between prospectively and retrospectively recorded CM is poor.[12] Retrospective self-report of CM shows a weaker association with objectively assessed life outcomes than do prospective measures.[13] Accounting for these potential sources of error is critically important, as illustrated by one of the few studies assessing CM – SUD association with prospectively and objectively recorded CM. Using prospective follow-up of court records, authors did not find increased SUD risk associated with CM; while, in the same population, retrospective self-report indicated 2.5 – 3 times elevated risk.[14]

Second, even when CM is prospectively and objectively recorded, associations between childhood events and subsequent outcomes are subject to familial confounding. This refers to the combined influence of factors shared between family members, that are distinct from CM exposure. Both genetic and environmental factors contribute to familial risk. For instance, a robust statistical association was found between CM and violent offending, in what was famously labeled “the cycle of violence”.[15] However, genetically informative analyses showed that this association is largely explained by familial confounding.[16]

Controlling for familial confounding is critical for interpreting the statistical association between CM and SUD. SUD has a significant heritability.[17] Genetic risk factors for SUD overlap with those for externalizing disorders that are likely to increase the risk for perpetrating CM, such as antisocial personality disorder.[18] Accordingly, reported rates of childhood sexual and physical abuse are 2-fold elevated in the offspring of a parent with SUD, and this association is further

strengthened if both parents have SUD.[19] Accounting for environmental factors that contribute to familial confounding is equally important. For instance, it has been reported that the association between CM and alcohol use disorders (AUD) largely reflects environmental factors common to members of twin pairs.[20] Finally, while genetic and environmental risk factors are commonly considered distinct, there is in fact a substantial genetic influence on environmental measures.[21]

Thus, despite multiple replications and statistical robustness, the nature of the CM – SUD association remains unclear. Establishing a causal contribution of CM to SUD risk would require large randomized controlled studies that for obvious reasons cannot be carried out. Quasi-experimental, observational studies may help infer causality when randomized controlled trials are not possible,[22] but this requires designs that control for potential confounds. To our knowledge, no prior study of the association between CM and SUD has concurrently addressed the potential confounds of retrospective self-report and shared familial factors.

We therefore examined whether prospectively and objectively documented severe CM is associated with an increased risk for SUD in adulthood. Using a sibling comparison design, we also determined to what extent any such association is explained by unmeasured confounding from genetic and environmental familial factors. [23, 24]

Methods and Materials

Study population

Patients with prospective childhood trauma exposure were identified from a specialized child- and adolescent psychiatric outpatient clinic (CAP-TU) in Linköping, using the regional health care register for Östergötland County, Sweden, containing practically all health care visits in the region since 1999[25], and the National Patient Register (NPR).[26]

From the regional register we identified: i) 470 persons, now young adults (age >18 years), (male n=188; 40%), exposed to severe physical or sexual abuse or severe neglect before age 18; ii) for each of these, we identified from the same local register three sex and age matched controls. After merging with data from the national registers (Supplementary Table 1), and removing five individuals with NPR maltreatment diagnosis before age 18, we obtained a sample of 1 388 controls (male=556; 40%) with no child and adolescent psychiatry contact. We also identified iii) a clinical control group comprising all former general child and adolescent psychiatry outpatients in Östergötland born 1980 - 1997, but with no contact with the CAP-TU (n=2029, male n=947; 47%). Clinical controls included all children and adolescents with ADHD, and individuals with depression and anxiety disorders in need of a specialist referral, thus comprising former patients with both externalizing and the more severe internalizing problems from the region.

For all participants, we also identified maltreatment diagnoses documented in the NPR before age 18 (Supplementary Table 2). Because CAP-TU did not use ICD codes for CM, these individuals had CM exposure of sufficient severity to be diagnosed by other healthcare providers. Nine participants in the group with prior CAP-TU contact, 5 individuals initially selected to be healthy controls, and 50 clinical controls had NPR CM diagnoses, and were thus re-assigned to the CM exposed group. The study population (N=3 887, male 1 691, mean age 28.6 years), thus comprised 525 individuals with prospectively documented CM, 1 383 healthy controls, and 1 979 clinical controls with no documented trauma (Table 1).

To address possible familial confounding in the association between prospectively recorded CM and SUD, we used the Swedish Multi-Generation Register,[27] connecting individuals born in Sweden to their biological parents, to identify parents, half and full siblings, and cousins to the study population. Thus, the study population and their identified relatives comprised 35 206

individuals, mean age in 2017, 34.7 years, range 0-93 years. In the final analysis we excluded the parental generation, to avoid exposure and outcome misclassification due to large differences in diagnostic routines, healthcare access etc. between generations. This resulted in a population of 28 733 individuals, mean age 29.5 years in 2017, (range 0-67 years).

We identified that subjects in the study population (N=3 887) had on average of 1.2 (range 0 to 10) siblings, 0.9 half-siblings (range 0-10) and 5.5 cousins (range 0 to 55). Of those exposed to CM, 122 had full-siblings, 28 had half siblings also subjected to CM. Among siblings and cousins, we found 168 with NPR maltreatment diagnoses before age 18.

Description of national registers [26, 28, 29] and International Classification of Diseases (ICD-8 to 10) and Anatomical Therapeutic Chemical (ATC) codes used is presented in (Supplementary Tables 1-4). Data was cross-linked using the Swedish national identity number.[30] National register data were de-identified after extraction to mask participants' identity and protect their integrity. The study was approved by the regional ethics review board in Linköping, Sweden (Dnr 2015/256-31, and 2017/41-32).

Variables

Childhood maltreatment (CM) was defined as contact with the CAP-TU (n=470) and/ or NPR maltreatment diagnosis before age 18 (n=55 in the population identified in the regional health records, and additional 168 individuals among their siblings and cousins). CAP-TU admission required severe reported trauma leading to involvement of child protective services. We examined the medical records of a CAP-TU subsample (n=81), who had given informed consent when participating in an ongoing clinical study. Medical records indicate that CM in this population was mainly sexual and physical abuse and severe neglect (Supplementary Table 4).

Substance use disorder (SUD) was coded as present if any of the following was found: i) ICD-8 to ICD-10 SUD diagnoses other than nicotine (F1-; Supplementary Table 2); ii) SUD medical complications (e.g., liver cirrhosis or acute alcohol induced pancreatitis); iii) SUD medication (for alcohol dependence, or opioid maintenance treatment); iv) SUD-related deaths; v) SUD-related criminality, and/or vi) involuntary treatment for SUD. For the initial sample (N= 3 887) we also included participants' contact with specialized SUD clinics in Östergötland County, using the Regional Health Care register, between 1998 and 2017.

Socioeconomic factors - we used education level as a proxy for socioeconomic status.

Externalizing problems were coded as present if ADHD and/or externalizing behavior problems were present that resulted in involuntary placement outside the home before age 18 (most commonly aggressive behavior, and/ or drug related juvenile offences). ADHD was defined as either NPR ADHD diagnosis and/or ADHD medication in the PDR. In Sweden, these medications can only be prescribed by a specialist in psychiatry or child and adolescent psychiatry thus being a good proxy for ADHD diagnosis [31].

Statistical analysis

We used Cox proportional hazard models to estimate the association between prospectively recorded CM and SUD later in life. The models calculate hazard ratios (HRs) for time to SUD diagnosis in those exposed to CM compared to unexposed, using age at first SUD related event as the underlying timescale. In 11 subjects (6 males), including 1 maltreated individual (male), age at first SUD was missing; these were not included in the final analysis. We used cluster robust standard errors to adjust 95% confidence intervals (CIs) for family clustering in the analyses in the population. Moreover, we adjusted models for: sex, education, externalizing problems in participants, parents' SUD, and birthyear as categorical variable. We also present separate estimates by sex. To examine possible sex differences in the association between CM and SUD we used Cox models stratified by sex, and tested the difference using Wald-type tests.

To account for possible familial (genetic and environmental) confounding in the association between CM and SUD later in life, we fitted Cox models stratified by sibling groups (i.e., stratified by an identification variable, with values shared between siblings in a family), comparing differentially exposed siblings within the same family. These models were also adjusted for sex, externalizing problems and birthyear [23]. Similarly, we fitted Cox models stratified by first-degree cousin groups.

Sensitivity analyses

To test the robustness of our findings and explore the role of possible confounds such as different types of maltreatment, placement outside the home during childhood, or carryover effects between siblings, we performed several sensitivity analyses described in Supplementary Table 5.

Data management was performed in MATLAB (Copyright 1994-2020 The MathWorks Inc.), and statistical analyses in STATA 15.1 (Copyright 1985-2017 StataCorp LLC).

Results

Study population characteristics are displayed in Tables 1 and 2. More than one third (36.2%) of those exposed to CM had lifetime SUD, compared to only 5.6% in controls without prior child psychiatry contact. Clinical controls also had higher SUD prevalence (26.8%) compared to healthy controls, but significantly lower (chi2, $p<0.001$) compared to those exposed to CM. In the CM exposed participants, we also found significantly more externalizing and socioeconomic problems (chi2, $p<0.001$) and participants were more likely to have parents with SUD and/or ADHD (Table 2) compared to both clinical and population controls.

Cumulative incidence for SUD for those exposed, versus population- and clinical controls unexposed to CM is presented in figure 1.

Insert figure 1 here

The crude association in Table 3 (HR 6.61, 95% CI 5.81, 7.53, $p<0.001$) indicates that individuals exposed to CM had increased risk for developing SUD later in life. Estimates decreased when adjusting for sex, externalizing problems, socioeconomic factors indexed by education level, parents' SUD and birthyear, but nevertheless indicated significantly increased risk for SUD in those exposed to CM (HR 3.50, 95%CI 2.95, 4.16, $p<0.001$). HRs were in general higher for women (Table 3) compared to men, and the difference was statistically significant in both the crude ($p=0.007$) and the adjusted model above ($p=0.026$).

Within the same family, siblings exposed to maltreatment had significantly higher risks for SUD compared to their unexposed siblings, as indicated by HR obtained from analyses in 28 525 individuals stratified within 24 249 sibling groups, containing 296 informative families with differentially exposed sibling groups (total 865 individuals) (HR 3.12, 95%CI 2.21, 4.41, $p<0.001$). The association remained statistically significant after adjusting for sex, externalizing problems and birthyear (HR 3.20, 95%CI 2.20, 4.66, $p<0.001$) (Table 3). Hazard ratios within cousin groups were similar to those in the population analysis (Supplementary Table 5).

Sensitivity analyses

Repeating within family analysis in families with only two children (130 differentially exposed sibling pairs) rendered similar estimates as above: HR crude 3.18, 95%CI 1.86, 5.44, $p<0.001$ (Supplementary Table 5).

In families with only two children, we also tested for possible carryover effects between siblings in the same family. Carryover effect for exposures and/ or outcomes, typically occur either from older to younger, or from younger to older siblings.[24] We found no significant differences for SUD risks when the older versus when the younger child was exposed to CM (p=0.31). (Supplementary Table 5). This argues against any significant carryover effects, regarding the role of CM in developing SUD later in life.

Sensitivity analysis within sibling groups aged 20-40 in 2017 (n=19 199) gave similar results as the full sample (HR crude 3.01, 95%CI 2.07, 4.36, p<0.001). (Supplementary Table 5)

Participants with a childhood NPR maltreatment diagnosis had significantly more SUD compared to former CAP-TU patients. A sensitivity analysis comparing only previous CAP-TU patients (n=470) with those unexposed to any CM showed a lower but nevertheless significantly increased risk for SUD in CAP-TU (HR adjusted as above 1.96 (95%CI 1.60, 2.40, p<0.001). (Supplementary Table 5).

We also found increased SUD risk in those exposed to CM when excluding those with childhood placement outside the home (HR crude 7.46, 95%CI, 6.47, 8.59, p<0.001). A stratified analysis indicated that both maltreatment and placement outside the home were associated with increased SUD risks. We also found a significant reduction in relative SUD risk between individuals with CM exposure and placement outside the home, vs those with CM exposure but not placed outside the home (HR= 0.14, p<0.001 (95%CI, 0.10 – 0.20). This suggests that removing the child from a harmful environment may decrease the relative risk increase due to maltreatment (Supplementary Table 5).

Discussion

We evaluated the specific contribution of CM to SUD risk, while addressing two main sources of potential error: bias related to retrospective self-report, and confounding by familial factors encompassing genetic susceptibility and the influence of shared family environment distinct from CM. To achieve this objective, we identified a unique cohort with prospectively and objectively documented CM, used the extensive system of Swedish registers to follow up this cohort with virtually no attrition, and used sibling data to address familial confounding, in a quasi-experimental, sibling comparison design.

Using this approach, we find a robust association between CM and SUD. This association is weakened when controlling for familial confounding. However, a robust, approximately 3-fold increase in SUD risk remains in individuals exposed to maltreatment compared to their unexposed siblings. This is consistent with a causal interpretation, although some potential for residual genetic confounding remains since siblings only share 50% of their co-segregating alleles.

Prior work has largely been based on retrospective self-report of maltreatment, which is subject to multiple sources of potential bias.[1-6, 9] Among these, recall bias is most likely to inflate estimates of CM contributions to SUD risk. Maltreatment is generally underreported, but individuals who experience negative outcomes such as SUD are more likely to report early life trauma. For instance, a study asked nearly 8,000 adults to recall CM at two separate timepoints, 12 years apart. In 39% of the participants, reporting was inconsistent[9]. Increasing levels of psychological distress, chronic stress[9] as well as neuroticism[13] were associated with increased likelihood of retrospectively reporting childhood adverse events.

Prospective follow-up of objectively recorded CM allows recall bias to be eliminated, but studies with this approach are rare. The few prior reports of prospectively followed CM victims have not consistently found an association of CM with SUD, or have found only a modest, approximately 1.5-fold increase in SUD risk.[14, 32, 33] As discussed below, the robustness of the association in our study may be related to the fact that we primarily captured severe CM.

A strength of our study stems from the stability of the population and the homogeneity of the health care system. During the follow up period, only three CAP units and three addiction services operated in the catchment area, all using the same medical records register. All identified

former CAP-TU patients could be followed through the regional and national registers. Data transfer to national registers is mandatory for Swedish health- and social welfare providers, and the unique Swedish personal identity number allows registers to be cross-linked. This enabled us to assess our clinical cohort with virtually no loss to follow-up.

Our sample included two subgroups of prospectively documented CM: those with CAP-TU contact, and participants with NPR maltreatment diagnosis before age 18. We found that, compared to former CAP-TU patients, persons identified through the NPR were more likely to have SUD problems. In this subgroup, reverse causation, i.e. that SUD leads to higher risk for maltreatment, cannot be ruled out. Substance related problems in teenagers may increase risks for victimization. This is, however, unlikely to significantly influence our findings, since sensitivity analyses restricted to CAP-TU subjects yield similar results, indicating increased SUD risk in those exposed to severe CM.

In accordance with prior literature, we also found externalizing disorders to be a strong predictor of SUD later in life.[34] Externalizing problems were more common in both the CAP-TU and the clinical controls compared to population controls. As expected, clinical controls also had an increased risk for SUD later in life, compared to the general population controls, albeit significantly lower compared to those exposed to CM, in line with prior research indicating childhood psychiatric problems as risk factors for SUD.[34, 35]

Placement outside the home was associated with increased risk for SUD but did not further increase risk in those maltreated. Results suggest that removing the child from a harmful environment may decrease the relative risks due to maltreatment. However, this should be interpreted with caution, since it is difficult to know to what extent removal from the home environment is independent from exposure or outcome.

Some limitations of our study should be considered. Prior studies have found that SUD risk is influenced by maltreatment type.[2, 3] We lack information on CM type for individual participants. Medical records for a subsample of 81 participants show that a majority (84%) was exposed to sexual abuse, physical abuse, or both (Supplementary Table 4). We do know that participants with CAP-TU contact were exposed to CM severe enough to require assistance from child protective services, while participants identified through the NPR had CM severe enough to seek and receive medical help. Prior literature suggests a link between CM severity and the risk and

severity of SUD.[5, 6] Selection of participants with severe CM could therefore contribute to the strong association between CM and SUD in our study. We also lack information on exposure to emotional abuse, previously linked with alcohol use disorder.[2] Because of these limitations, we do not know to what extent our findings can be generalized to less severe CM, or CM types less commonly represented in our study.

There is also a possibility that exposed participants were misclassified as unexposed because of reluctance to report CM.[36] However, Swedish child protection laws mandate that health care providers report all CM to the social services.[37] If severe maltreatment had been suspected in children with ongoing specialist contact, they would likely have been reported. While this makes severe trauma in the clinical controls less likely, the presence in some cases, especially of less severe maltreatment cannot be excluded. This type of misclassification could erroneously weaken our estimates of the association between CM and SUD. If anything, the estimates we provide are therefore conservative.

Healthy controls more often had at least one parent born outside of Sweden. We defined healthy controls as individuals without any child and adolescent psychiatry contact. Families with immigrant background are less likely to seek help from specialist psychiatric services.[31] It is therefore possible that some participants in need of child psychiatry or exposed to CM were misclassified as healthy controls. Such misclassification could also weaken the measured association between CM exposure and SUD, once again rendering our estimates of this association conservative.

Our SUD classification was based on multiple sources, including in- and outpatient diagnoses, treatment, and medical as well as legal consequences of SUD. Each of these sources has limitations. In Sweden, only about 20% of people with SUD seek medical treatment[38] and formal SUD diagnoses are typically recorded only late in the disease process, resulting in register data underestimating the population-based prevalence of AUD.[39, 40] On the other hand, including all F1- diagnoses (except nicotine) may have resulted in inclusion of individuals with only one health care contact for an episode of alcohol or drug intoxication. We believe that we for the most part captured the more severe end of the SUD spectrum, but may also have included some patients with only brief health care contact. Because of these limitations, we cannot draw conclusions about the severity of SUD associated with CM.

Despite these limitations, our study fills a major knowledge gap, and has important implications. We provide robust evidence in support of an association between prospectively and objectively recorded CM and subsequent SUD. We establish that this association is in part due to factors shared between siblings, that include the aggregated influence of shared genetics and familial environment. However, our data also provide robust support for CM as an independent, specific risk factor for SUD. This risk factor is preventable. Every effort possible should be made to prevent its occurrence, as well as its consequences.

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Competing Interests statement

Andrea J Capusan has received speaker's fees, and/ or scientific advisory board compensation from Lundbeck, Indivior and Camurus, all outside the scope of the current project.

Markus Heilig has received speaker's fees, research funding and/ or scientific advisory board compensation from Lundbeck, Aelis Farma, Indivior, Brainsway Technologies and Janssen Pharmaceuticals, all outside the scope of current project.

Per A Gustafsson has received speaker fees and scientific advisory board compensation from Lilly and Shire pharmaceutical companies all outside the scope of the current project.

Ralf Kuja-Halkola, Kajsa Igelström, and Leah Mayo have no conflicts of interest to declare.

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Figure 1. Cumulative incidence of substance use disorder (SUD) in those exposed to childhood maltreatment versus unexposed clinical and population controls. Solid lines are (1 - Kaplan Meyer estimates); dotted lines are 95% confidence intervals (CI). **A)** Full cohort; **B)** Males; **C)** Females

Table 1. Distribution of study population exposed to childhood maltreatment (CM), healthy controls and controls with previous contact with general child and adolescent psychiatry (CAP) by sex, age, substance use disorder (SUD), externalizing problems.

	Entire cohort including relatives (siblings, half siblings, cousins) n	(%)	Exposed to childhood maltreatment in the study population [1] n	(%)	Matched healthy controls n	(%)	Test, healthy controls vs exposed to CM	Clinical controls 2 n	(%)	Test, Clinical controls vs exposed to CM
	28 733		525		1 383			1 979		
Sex (male)	14 558	(50.7)	217	(41.3)	551	(39.8)	χ^2 (1) =0.4, p=0.55	923	(46.6)	χ^2 (1) =4.7, p=0.03
Age in Jan 2017, mean (SD, range)	29.5	(10.54, 0 – 67)	28.4	(4.09, 20-37)	28.3	(4.09, 20-37)	t (1906) = -0.3, p=0.75	28.8	(3.95, 20-37)	t (2502) = -2.3, p=0.02
One or both parents born outside of Sweden[c]	4 524	(15.7)	145	(27.6)	471	(34.1)	χ^2 (1) =7.2, p = 0.007	438	(22.1)	χ^2 (1) =7.0, p = 0.008
SUD [3]	2 994	(10.4)	190	(36.2)	77	(5.6)	χ^2 (1) = 296.5, p<0.001	531	(26.8)	χ^2 (1) = 17.7, p<0.001
Age at first SUD[d] reported event (mean, SD, range)	21.6	(6.51, 9 – 55)	18.4	(3.61, 12-31)	21.5	(3.73, 15-31)	t (263) = 6.3, p<0.001	20.0	(4.08, 12-34)	t (709) = 4.7 p<0.001
Externalizing problems	1 891	(6.58)	104	(19.8)	16	(1.2)	χ^2 (1) =224.6, p<0.001	437	(22.1)	χ^2 (1) = 1.26, p = 0.26
ADHD	1 709	5.9	84	16	14	(1.0)	χ^2 (1) = 175.4 p< 0.001	387	19.6	χ^2 (1) = 3.4 p= 0.06

[1] Maltreatment = Contact with child and adolescent psychiatry trauma treatment unit (CAP-TU) or diagnosis of maltreatment before age 18; **[2]** clinical controls = childhood contact with child and adolescent psychiatry (CAP) with no documented exposure to CM;

[3] SUD (Substance Use Disorder) = contact with SUD clinic and/or SUD diagnosis and/or drug related criminal offences and/or diagnosis for medical complications to SUD and/or medication for SUD and/or drug related deaths, as well as compulsory treatment for SUD.

[e] Externalizing = ADHD and/or Compulsory placement for own misconduct

Table 2. Socioeconomic and family factors for the study population exposed to childhood maltreatment (CM), matched healthy controls and controls from general child and adolescent psychiatry (CAP) without documented trauma

	Exposed to CM[1]		Matched healthy controls		Test group, Healthy controls vs exposed to CM	Clinical controls[2]		Test group, Clinical controls vs exposed to CM
	n	(%)	n	(%)		n	(%)	
Total = 3 887	525	(100)	1 383	(100)		1 979	(100)	
Father SUD[3] (N=694)	162	(32.4)	134	(12.1)	$\chi^2(1) = 94.1$ p <0,001	398	(21.2)	χ^2 (1) = 27.48 p<0.001
Mother SUD (N=338)	87	(17.1)	45	(4.0)	χ^2 (1) = 81.0 p< 0.001	206	(10.8)	χ^2 (1) = 14.99 p < 0.001
ADHD in any parent (N=166)	42	(8.0)	17	(1.2)	χ^2 (1) = 58.2 p< 0.001	107	(5.4)	χ^2 (1) = 4.99 p = 0.026
Social economic welfare[4] (N=559)	163	(32.9)	113	(10.6)	χ^2 (1) = 115.8 p< 0.001	283	(15.2)	χ^2 (1) = 80.46 p<0.001
Foster care placement due to of family environment[5] (N=135)	76	(14.5)	7	(0.5)	χ^2 (1) p<0.001	52	(2.6)	χ^2 (1) p<0.001
Teenage mother (N=148)	49	(9.6)	37	(3.3)	χ^2 (1) = 28.3 p< 0.001	62	(3.2)	χ^2 (1) = 37.2 p< 0.001
Single mother (N=1146)	252	(50.9)	211	(19.8)	χ^2 (1) = 156.9 p< 0.001	683	(36.6)	χ^2 (1) = 33.4 p< 0.001

[1] Childhood Maltreatment (CM) = Contact with child and adolescent psychiatry trauma treatment unit (CAP-TU) or register diagnosis of maltreatment before age 18; [2] Clinical controls = childhood contact with general child and adolescent psychiatry with no documented maltreatment; [3] SUD (Substance Use Disorder) = SUD diagnosis, and/or SUD medical complications, and/or SUD medication, and/or substance related deaths, and/or contact with SUD clinic, and/or compulsory treatment for SUD and/or drug related criminal offences. [4]Economic support from social services when the index subject was 10 years of age; [5] Foster care between 0-17 years of age. Obs. Number of individuals in each row is indicated in parentheses.

Table 3. Relative risks for substance use disorder (SUD) in those exposed to childhood maltreatment for the whole population, separately in males and females and stratified within sibling clusters in the same family

	Population [1]		Males [2]		Females [3]		Stratified for siblings[d]	
	HR[4]	(95% CI[5])	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Crude	6.61	(5.81, 7.53)	5.92	(4.90, 7.17)	8.41	(7.05, 10.03)	3.12	(2.21,4.41)
Adjusted for covariates[6]	3.71	(3.13, 4.42)	3.18	(2.49, 4.07)	4.39	(3.43, 5.62)	3.32 [7]	(2.30,4.79)
Adjusted as above and for birthyear	3.50	(2.95, 4.16)	3,12	(2.44, 3.99)	3.88	(3.04, 4.94)	3.20 [8]	(2.20,4.66)

Individuals at risk: [1] Total population included in the survival analysis N = 28 525; [2] Males N= 14 461; [3] Females N=14 064; [d] N=865 individuals in 296 families with >1 child differentially exposed to CM

[4] HR= hazard ratio estimated using Cox regression; [5] CI 95% confidence intervals in brackets; [6] Covariates: sex, substance use disorder in parents, socioeconomic status indexed by education level, and externalizing problems (ADHD and/or severe conduct problems resulting in enforced placement outside the home) in the individual; [7] Within sibling group comparisons were adjusted for sex, externalizing problems in the individual and in the last comparison [8] also for birthyear

Supplementary Table 1

Swedish regional and national registers used in the study to obtain demographic, diagnostic, treatment and social welfare data for the study population and their relatives. Data was cross-linked using the Swedish national identity number.[1]

Register	Definition	Utilized to identify
Regional Health Care Register for the County of Östergötland, Sweden [2]	Contains practically all health care visits in the region since 1999.	Populations with child psychiatry trauma treatment unit (CAP-TU) contact, matched psychiatrically healthy controls and clinical controls
National Patient Register (NPR) [3]	Contains diagnosis codes for inpatients (since 1973) - and outpatients (since 2001) based on the International Classification of Diseases (ICD-8 to 10) diagnoses, from the whole of Sweden.	ICD codes indicating substance use disorders (SUD) and related medical diseases, ADHD and childhood maltreatment before age 18 (Supplementary Table 2)
Swedish Prescribed Drug Register (PDR),[4]	Information on Anatomical Therapeutic Chemical (ATC) codes of all medication prescribed in Sweden since 2005.	Medication for SUD and ADHD (Supplementary Table 3)
Swedish Total Population Register[5] and Migration Register	Contains all Swedish residents born since 1932. Dates of all registered migrations to and from Sweden since 1969	Demographic information regarding sex, dates of birth, education etc.
Swedish Multi-Generation Register,[6]	Connects individuals born in Sweden to their biological parents.	To identify parents, siblings, and cousins to the study population
National Cause of Death Register	Provides data on cause of death.	SUD related deaths.
Swedish National Council for Crime Prevention Register	Containing data on all prosecutions.	SUD related criminal offenses (drunk driving, using/selling illicit drugs etc.).
National Social Welfare Register (National Board of Health and Welfare).	Information on the need for social welfare payments and need for child protective services	Social welfare payments during the index persons' childhood, and need for mandatory placement outside the home

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Supplementary Table 2 International classification of disease (ICD) codes from the Swedish National Patient Register (NPR)[1] used to extract diagnose data from the Swedish National Registers in the study

Diagnoses extracted	ICD codes for	ICD-10 (fr o m 1999)	ICD-9 (1987-1998)	ICD-8 (1969-1986)
Alcohol Use disorders and related medical diseases	Alcohol-induced pseudo-Cushing syndrome	E244	E2550	
	Mental and behavioral disorders due to alcohol	F100-109	2910,2911, 2912, 2913, 2914, 2915, 2918, 2918, 2919, 2922, 303, 3050	2910,2911, 2919, 2912,2913, 3039,2943, 3031, 3032, 3039
	Degeneration of nervous system due to alcohol	G312	303	3031,3032,3039
	Alcoholic polyneuropathy	G621	3575	3039
	Alcoholic myopathy	G721	3594	3039,9779,9899
	Alcoholic cardiomyopathy	I426	4255	425
	Alcoholic gastritis	K292	5353	3032
	Alcoholic liver disease	K700-709	5710, 5711, 5712, 5713, 5728	5710, 572, 573
	Alcohol-induced acute pancreatitis	K852	5770	5770
	Alcohol-induced chronic pancreatitis	K860	5771	5771
	Maternal care for (suspected) fetal abnormality and damage, unspec.	O354	6554	6349
	Toxic effect of alcohol	T510-511	9800,9801	9800,9801
	Alcohol rehabilitation	Z502	V578	Y39
	Alcohol abuse counselling and surveillance	Z714	V654	Y79

	Alcohol use	Z721	V658	missing
Illicit drug use disorders and related medical conditions	Mental and behavioral disorders due to substance use	F110–F160, F180, F190	2920,2921,2922, 2928, 2929,2940, 3040, 3041, 3042, 3043, 3044,3045, 3046, 3047, 3048, 3049, 3052, 3053,3054,3055, 3056,3057, 3059	299,969,971,2911,294, 3040,3041, 3042, 3043 ,3046,3047, 3049, 3049, 9650, 9670, 9679, 9701, 9709,9745,9778,9779
	Maternal care for (suspected) damage to fetus by drugs	O355	6555	6449
	Fetus and newborn affected by maternal use of drugs of addiction	P044	7607	7617
	Poisoning with psychostimulants with abuse potential	T436	9697	971
	Drug rehabilitation	Z503	V578	Y39
	Drug abuse counselling and surveillance	Z715	V654	Y79
	Drug use	Z722	V628	Y110,Y119,Y19
ADHD	Attention deficit hyperactivity disorder and subtypes	F900A, F900B, F900C, F900X	3140, 3141, 3142, 3148, 3149	308
Childhood Maltreatment	Other maltreatment including mental cruelty, sexual, physical abuse	Y071, Y078	E9670, E9671, V612	E968, Y79
	Problems related to alleged physical abuse of child	Z616		

ICD=International classification of disease
National Patient Register (NPR), contains International Classification of Diseases (ICD-to 10) diagnose codes for inpatients (since 1973) and outpatients (since 2001)

Supplementary Table 3. Anatomical Therapeutic Clinical (ATC) classification codes and categories of medication from the Swedish Prescribed Drug Register (PDR)1, used to extract data on treatment

Medication for		ATC-code[2]	Name of substance
Substance use disorder (SUD)	Alcohol dependence	N07BB01	Disulfiram
		N07BB03	Akamprosat
		N07BB04	Naltrexon
		N07BB05	Nalmefen
	Opioid maintenance therapy	N07BC01	Buprenorfin
		N07BC02	Metadon
		N07BC05	Levometadon
		N07BC51	Buprenorfin, combinations
ADHD		N06BA01	Amfetamin
		N06BA02	Dexamfetamin
		N06BA04	Metylfenidat
		N06BA09	Atomoxetin
		N06BA11	Dexmetylfenidat
		N06BA12	Lisdexamfetamin
		C02AC02	Guanfacin

[1] PDR contains information on Anatomical Therapeutic Chemical (ATC) codes of all medication prescribed in Sweden since July 2005;

[2]ATC=Anatomical Therapeutic Chemical

Supplementary Table 4.

Type of childhood maltreatment in the former child and adolescent psychiatry trauma treatment unit (CAP-TU) based on patient records of a significant subsample

Type of trauma*	**Female**		**Male**		**Total**	
	n	(%)	n	(%)	n	(%)
Sexual abuse	34	(65.4)	4	(13.8)	38	(46.9)
Sexual abuse and neglect	1	(1.9)	0	(0)	1	(1.2)
Sexual- and physical abuse	6	(11.5)	1	(3.4)	7	(8.6)
Sexual-, physical abuse and neglect	5	(9.6)	2	(6.9)	7	(8.6)
Physical abuse	3	(5.8)	8	(27.6)	11	(13.6)
Physical abuse and neglect	2	(3.9)	2	(6.9)	4	(4.9)
Neglect	0	(0)	1	(3.4)	1	(1.2)
Type of trauma not specified	1	(1.9)	11	(37.9)	12	(14.8)
Total	52	(100)	29	(100)	81	(100)

* No ICD or other diagnose codes for childhood maltreatment were used by the CAP-TU, data is based on authors reading of patient records

Supplementary Table 5. Sensitivity Analyses - Risks for substance use disorder (SUD) in those exposed to childhood maltreatment (CM) compared to those unexposed, expressed in Hazard Ratios (HR) obtained from Cox proportional hazard models, using age at first SUD as underlying time scale, and using cluster robust standard errors to estimate 95% confidence intervals (CI), crude and adjusted for covariates [8]

Analysis	Population Individuals(clusters)	Estimate HR	95%CI	P value
Within families with only two children (130 discordant sibling pairs) [1]				
Crude	2 851 (1 430)	3.18	1.86, 5.44	<0.001
Adjusted for sex, externalizing problems[9] and birthyear	2 851 (1 430)	3.53	1.90, 6.57	<0.001
Testing for carryover effects [2]				
Calculates risk for SUD in sibling pairs when the older sibling is exposed (crude)	123 (63)	2	0.95, 4.19	0.066
Calculates risk for SUD in sibling pairs when the younger sibling is exposed (crude)	116 (58)	3.57	1.53, 8.32	0.003
Difference between the above	239 (121)	0.56	0.18, 1.71	0.310
Within cousin group analysis, stratified by cousins [3]				
Crude	28 525 (9 947)	6.09	4.89, 7.58	<0.001
Adjusted for sex, externalizing problems, SUD in parents, education and birthyear	24 144 (8 686)	4.38	3.27, 5.86	<0.001
Within birth restricted sibling cohort [4] (sibling groups, aged 20-40 year in 2017)				
Crude	19 199 (15 581)	3.01	2.07, 4.36	<0.001
Adjusted for sex, externalizing problems, SUD in parents, birthyear	19 199 (15 581)	3.19	2.15, 4.75	<0.001
Comparing CAP-TU contact with no prospectively registered trauma [5]				
Crude	28 302 (24 095)	3.37	2.84, 4.01	<0.001
Adjusted for sex, externalizing problems, education and birthyear	23 943 (20 203)	1.96	1.60, 2.40	<0.001
Stratified within siblings in the same family crude	28 302 (24 095)	1.75	1.19, 2.58	0.004
Stratified within siblings in the same family adjusted for sex, externalizing problems, birthyear	28 302 (24 095)	1.73	1.13, 2.65	0.012
Individuals placed outside the home during childhood [6]				
Those with childhood placement outside the home excluded- crude	27 773 (23 709)	7.46	6.47, 8.59	<0.001
Those with childhood placement outside the home - adjusted for sex, birthyear, education	23 523 (23 153)	4.71	3.93, 5.64	<0.001
Those with childhood placement outside the home stratified by sibling group, crude	27 773 (23 709)	3.94	2.65, 5.85	<0.001
Difference of SUD risks, between those placed and not placed outside the home – Wald type tests	28 525 (24 249)	0.14	0.10, 0.20	<0.001
Placement due to family environment, those placed for behavior reasons excluded– crude	28 258 (24 084)	7.45	6.47, 8.58	<0.001
Placement due to family environment, crude (interaction term)	28 258 (24 084)	0.14	0.08, 0.24	<0.001
Placement due to behavior problems, those placed for behavior reasons excluded – crude	28 014 (23 866)	7.42	6.44, 8.54	<0.001
Placement due to behavior problems, crude (interaction term)	28 014 (23 866)	0.19	0.11, 0.33	<0.001
Adjusting for welfare payment to mother when participant 10 years old [7]				
Analysis in index population (crude)	3 876 (3 630)	2.37	2.01, 2.80	<0.001
Adjusted for sex, externalizing, social welfare payment to mother when child 10years old and birthyear.	3 415 (3 178)	1.89	1.57, 2.28	<0.001

[1] Family clusters included a few families with a high number of siblings, less common in Sweden, who may not be representative for the general population. Therefore, we fitted Cox models in families with only two children.

[2] Carryover effects between siblings may involve both exposures and/ or outcomes, and typically occur either from older to younger, or from younger to older siblings. Using information about birth order we therefore performed stratified Cox regression comparing outcomes in informative families with two children (i.e. exposure discordant families) when the older versus when to the younger child was exposed.

[3] Analysis stratified by first degree cousins, crude and adjusted by sex, externalizing problems, parents' SUD and birthyear as a categorical variable.

[4] HRs for SUD comparing those with childhood trauma treatment unit contact (CAP-TU) (n=470) with those unexposed to maltreatment in any register.

[5] Sensitivity analysis repeating the analysis in a birth year restricted sibling cohort aged 20-40 in 2017 (dates of birth between 1977-1997), to explore potential misclassification bias due to large age difference between siblings. This could be caused by that older siblings: a) may not be recorded in these registers with diagnoses given that the outpatient register (since 2001) and the PDR (since 2005) are relatively new; b) were not offered treatment to the same extent, since diagnostic and treatment procedures and availability of SUD services have improved over the decades.

[6] Since placement outside the home may alter family and sibling environment, we performed additional sensitivity analyses a) removing those placed outside the home (n=752); b) stratified by placement outside the home and tested for differences using Wald type tests; c) Stratified analyses were performed separately if placement outside the home occurred due to harmful family environment; or d) due to severe behavioral problems in the child/ adolescent.

[7] In a sensitivity analysis we controlled for low socioeconomic status during childhood comparing indexed by social welfare payments to the mother when the subject was 10-year-old only those exposed, matched healthy controls and clinical controls.

[8] Covariates: sex, externalizing problems, education, birthyear as categorical variable; Covariates within sibling comparison analyses: sex, externalizing problems, birthyear as categorical variable

[9] Externalizing problems were considered present if either ADHD and/ or severe conduct problems resulting in placement outside the home were present.

[10] Population size varies depending on size of the nested subsample for the sensitivity analysis and on possible missing values for different covariates in the adjusted analyses;