Received: 2 December 2021 | Accepted: 13 May 2022

DOI: 10.1111/add.15965

RESEARCH REPORT

ADDICTION SSA

Risk of non-fatal suicide attempt in individuals with substance use disorder: the roles of aggregate genetic liability and environmental exposures in a Swedish population-based cohort

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Funding information
National Institute of Mental Health, Grant/Award Number: MH129356; National Institute on Alcohol Abuse and Alcoholism, Grant/Award Numbers: AA023534, AA027522; National Institute on Drug Abuse, Grant/Award Number: DA030005; Swedish Research Council; National Institutes of Health

Abstract

Background and Aims: Substance use disorder (SUD) is related to widespread adverse consequences, including higher suicidality. Shared genetic liability has been demonstrated between SUD and suicidality. Here, we measured the factors that contribute to increased risk of non-fatal suicide attempt among individuals with SUD by focusing upon aggregate genetic risks and both childhood and past-year environmental factors.

Design: Longitudinal study. Family genetic risk scores and environmental factors (childhood, aged from 0 to 15 years, and the year preceding SUD registration) were used to predict the relative risk of non-fatal suicide attempt using Cox proportional hazards models. Additional analyses employed a co-relative design, accounting for genetic factors and shared familial environment, to test for potential causality.

Setting and participants: Based on longitudinal Swedish registry data, 228 617 individuals with SUD registrations from 1991 to 2015 were included.

Measurements: SUD and suicide attempts were identified using medical records (International Classification of Diseases codes). SUD was also identified using pharmacy and criminal registries.

Findings: In multivariable analyses that jointly accounted for all the selected potential predictors, individuals with SUD were at higher risk for non-fatal suicide attempt if they had experienced a parental death [hazard ratio (HR) = 1.58; 95% confidence interval (CI) = 1.30, 1.93], were female (HR = 1.53, 95% CI = 1.49, 1.57), had low educational attainment (HR = 1.50, 95% CI = 1.46, 1.55), received social welfare (HR = 1.21, 95% CI = 1.17, 1.25) or had lived in a non-intact family (HR = 1.11, 95% CI = 1.08, 1.14). In co-relative analyses, low education was supported as a possible causal factor for suicide attempt. Aggregate genetic risks interacted with low education and being raised in a non-intact family, with increased prevalence of suicide attempt in people with high genetic risks and unfavorable environmental exposures.

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Conclusions: Aggregate genetic liability, childhood environmental experiences and specific socio-economic indicators are important risk factors for non-fatal suicide attempt among individuals with substance use disorder.

KEYWORDS
Alcohol, cohort study, drug, environment, gene, suicide attempt

INTRODUCTION

Substance use disorder (SUD) refers to the continuous use of substances (alcohol or drugs) despite significant impairments [1]. Excessive substance use is widespread, with SUD impacting more than 35 million individuals world-wide [2]. SUD increases the risk of severe psychopathology, including a 10-fold increase in the risk of suicide death [3]. Among individuals with SUD, up to 40% also reported a history of suicide attempts [4]. Suicidal behaviors are an important public health issue [5], particularly prevalent among individuals with SUD [6]. In line with previous studies [6, 7] showing significant risk of suicidal behaviors in both alcohol use disorder (AUD) and drug use disorder (DUD), we focused upon SUD to elucidate predictors of the first suicide attempt in this high-risk population.

The association between SUD and suicidal behaviors has been widely reported [6,8–10] and may be explained by shared genetic and environmental liability [11] and/or by a causal relationship [12]. We have previously reported evidence of a probable causal association between AUD and subsequent suicide attempt, even after accounting for the contribution of genetic and familial environmental influences [12]. This supports the hypothesis that AUD-related stress would increase the risk of suicide attempts [4]. However, the specific stressors that may generate or precipitate suicide attempts within the SUD population remain to be investigated and their causality supported.

Various environmental stressors have been documented in association to SUD and suicide attempts, and they can be broadly separated into two categories: childhood factors, referring to family history and early-life adversity; and proximal factors, referring to life events and behaviors temporally associated with suicide risk. As childhood factors, parental divorce, parental substance use and history of childhood adversities increase the risk of suicide attempt among SUD individuals [13–16]. With respect to environmental exposures during adulthood, prior works underscore the role of disruption in marital and interpersonal relationships, occupational and financial stressors and psychiatric disorders [4, 17]. Altogether, these studies offer important insights for the identification of risk factors among individuals with SUD. Nevertheless, relatively few studies have considered both childhood and proximal environmental exposures together with familial-genetic risk to predict suicide attempt. The possible causal role of environmental stressors, specifically among individuals with SUD, also remains to be investigated. In view of the strong genetic and familial influences in SUD and suicidality, causal associations can be evaluated using a co-relative design [18] which accounts for the contributions of familial confounding factors. Causality may be inferred if the association between a putative risk factor and an outcome remains significant in pair groups of increasing genetic correlation (full siblings) that are discordant for the risk factor, while non-significant associations would suggest that the relation between the risk and outcome is mainly explained by familial factors.

In view of the genetic liability, understanding how genetic risks moderate the role of environmental stressors is also critical. Interactions between genetic loci and SUD-related environment have been associated with suicidal ideations [19]. A recent well-powered genome-wide association study has also supported the existence of gene–environment interactions in self-harm risk [20]; this study indicates interactions between specific single nucleotide polymorphisms and socio-economic deprivation. However, much remains unknown about interactions between aggregate genetic risk for suicide attempt and environmental factors in the context of SUD.

In this study, we relied on large, representative and longitudinally available Swedish registries. We used familial genetic risk scores (FGRS), which have shown robust associations with psychiatric disorders and clinical features [21, 22], to quantify individual-level aggregate genetic liability. FGRS are calculated from the weighted rates of a disorder (e.g. AUD) in first- to fifth-degree relatives. FGRS are complementary to polygenic scores, but computed from the phenotypes of an individual's family. Calculated in the entire Swedish population, FGRS provide substantial information about genetic risk. We had four specific aims: (1) Evaluate the impact of aggregate genetic factors on risk for suicide attempt within individuals with SUD; (2) evaluate the impact of wide-ranging environmental factors on risk for suicide attempt in SUD; (3) account for familial confounding (genetic and environmental) to test whether the association between environmental risk factors and suicide attempt among those with SUD is potentially causal; and (4) determine whether genetic and environmental risks interact in the context of SUD.

MATERIALS AND METHODS

Participants

In Swedish population-based registers we selected all individuals born in Sweden between 1960 and 1995 to Swedish-born parents; individuals had been registered for SUD between 1991 and 2015 (n = 228 617). SUD was identified via medical, pharmacy and criminal records and included both AUD and DUD. We used the first registration of either AUD or DUD. We did not include tobacco use disorder from the registry data because of the inconsistency across clinical treatments, probably leading to false negatives. The outcome variable

was the first registration for non-fatal suicide attempt (as defined by the National Institute of Mental Health[1]), included from medical registries. In view of their distinct genetic and environmental etiologies [23], we excluded fatal suicide attempts that occurred within 14 days of the first attempt. Ethical approval was secured from the Regional Ethical Review Board in Lund and participant consent was not required. For more details, including ICD codes and registries used, see Supporting information.

Predictors

To investigate the risk of first suicide attempt among individuals with SUD, we selected several environmental variables according to prior results described in SUD populations. We evaluated the role of childhood environmental exposures considering parental divorce, number of parental hospitalizations and parental death before age 15 years. We also assessed whether an individual lived with an intact family (i.e. residing in the same household as both biological parents for more than 14 years) to account for separation, single-parent households or other non-documented familial settings. Additional factors were evaluated in the year preceding SUD registration and represented by marital and parenthood status, low educational attainment, unemployment, low income, social welfare and neighborhood deprivation. Low education was defined as fewer than 9 years of education, which corresponds to the minimum mandatory education in Sweden. These predictors were measured the year before SUD registration to infer their potential causal effect on suicide attempt risk. Furthermore, it was necessary to select a time-frame that could be equivalently applied among all members of the sample. This precluded focusing upon, for example, the year prior to suicide attempt, which would not apply to non-attempters. FGRS for suicide attempt ($FGRS_{SA}$), AUD ($FGRS_{AUD}$) and DUD ($FGRS_{DUD}$) were also included. The FGRS were derived from phenotypes of the individuals' families, from first- to fifth-degree relatives [18]. The risk for the phenotype was controlled for association with cohabitation for first-degree relatives and the total score was weighted by the number of relatives. FGRS are standardized *Z*-scores representing the level of genetic risk, with a mean score of 0 (i.e. a positive score indicates a genetic risk greater than the general population). According to previous studies [24] indicating unique genetic influences across AUD and DUD, we used separate FGRS for these phenotypes. We also controlled for the risk associated with AUD versus DUD in our models, as these may slightly differ in their association with suicidal behavior [7]. However, sensitivity analysis supported their inclusion in the same model. Finally, we included age at registration as an indicator of SUD severity [25]. For a detailed definition of all variables, see Supporting information.

A small amount of missing data was found for five of the proximal environmental risk factors (Supporting information). The predicted regression imputation method was used to predict missing values based on the other covariates. This single imputation approach was identified as reliable in previous studies with a low level of missing data [26].

Statistical analyses

To examine the association between the familial-genetic and environmental predictors and the first suicide attempt among individuals with SUD, we performed a series of univariable Cox proportional hazards models. Follow-up time in months was measured from date of SUD registration until time of first registration for suicide attempt, emigration, death or end of follow-up (31 December 2015). Individuals were followed for a mean of 9.2 years [standard deviation (SD) = 8.0] after their SUD registration. We tested the proportionality assumption and confirmed that results remained consistent over time (Supporting information). In Cox regression models, we included both cases (individuals with SUD who attempted suicide) and controls (individuals with SUD who did not attempt suicide) and evaluated the role of the predictors measured the year before SUD registration. We used hazard ratios (HR) to evaluate the likelihood of risk (HR > 1 as increased risk and HR < 1 as decreased risk, possibly protective) and 95% confidence intervals (CI) for significance. Together with the HR, we used the Akaike information criterion (AIC) to evaluate the strength of the included variables and model fit. For the univariable analyses, we observed how AIC decreased (improved balance of model fit and parsimony) when we included the predictor. Then, we ran a multivariable analysis with all variables included in the same model. Here we evaluated the effects of each variable by comparing the AIC from the full model with a model without the variable of interest. We thus observed how the AIC increased (poorer balance of model fit and parsimony) when we excluded the predictor. However, none of the variables were excluded based on the AIC. The use of AIC allowed us to complement the interpretation of the HR with a measure that can be compared across all the predictors (binary and continuous). All analyses were controlled for sex.

Next, we sought to assess the degree to which the association between the environmental predictors and suicide attempt reflect confounding by shared familial factors (genetic and/or environmental) using a co-relative design. From the Swedish Multi-Generation Register, we identified all full-sibling and first-cousin pairs where both in the pair were registered for SUD. Using a stratified Cox regression model with a separate stratum for each sibling/cousin pair, we refitted the univariable models. All environmental predictors were included in these analyses but comparisons between siblings were only performed for variables that vary between them (e.g. parental death was not included). FGRS were also excluded as their inclusion would be redundant with the co-relative design. Thereafter, we fitted a multivariable logistic model including all the factors that differ between siblings to the subset of the sample without any siblings (n = 194 468) as a training sample. Results from that model were applied to the second subset of the population (i.e. that which contained all siblings) and were evaluated using the receiver operating characteristic curve (ROC). From the logistic regression model, we created a risk score

[1]https://www.nimh.nih.gov/health/statistics/suicide

based on the deciles of the predicted probabilities and used it as a predictor in the next model [27]. The next model was a Cox regression model and we assessed the degree to which the association between the risk score and suicide attempt reflect confounding by familial risk factors using siblings that were discordant for the risk score (i.e. in different deciles). This approach was an additional effort to investigate the causality of the variables we had included in the models.

Finally, we investigated if familial-genetic risks for suicide attempt ($FGRS_{SA}$) moderate the impact of environmental factors. To inform public health perspectives, we used an Aalen's linear hazards model [28] and evaluated the interaction on an additive scale. Beyond the impact of the risk factors on their own, we sought to estimate the number of new suicide attempts that would occur if individuals were exposed to two of those risk factors [29]. The results from these models are presented as the excess number of cases per 10 000 person-years. We computed separate models (i.e. one for each environmental predictor), including $FGRS_{SA}$, the environmental risk factor and the interaction term. Beta (β) and 95% CI are presented; here, significance was determined when 95% CI did not overlap with 0.

Statistical analyses were performed using SAS version 9.4 [30] and the R-package Timereg [31, 32]. The code used in this study can be requested from the authors. This study was pre-registered through the Open Science Framework (https://osf.io/yt4ap).

RESULTS

Descriptive analyses

We identified 228 617 individuals with SUD registrations from 1991 to 2015. At their first SUD registration, the sample included 55.6% of individuals with DUD and 44.4% of individuals with AUD. At the end of the follow-up, the mean number of registrations was 13.1 (SD = 40.6) and 22.85% of the sample had both AUD and DUD registrations. The mean age for the first SUD registration was 26.2 years and 10.0% (n = 22 902) of individuals attempted suicide during the follow-up period. Suicide attempt risk over time was reported in Supporting information, Figure S1. Descriptive statistics for the predictors are provided in Table 1 and the distribution of the FGRS is reported in the Supporting information.

$FGRS_{SA}$ was correlated with both $FGRS_{AUD}$ (r = 0.41) and $FGRS_{DUD}$ (r = 0.38). FGRS for AUD and DUD were also correlated (r = 0.46).

TABLE 1 Univariable and multivariable models explaining risk for suicide attempt among SUD

		Univariable model		Multivariable model	
	% or mean (SD)	HR (95% CI)	AIC[a]	HR (95% CI)	AIC[b]
Female	26.4%	1.57 (1.53, 1.61)	955.03	1.53 (1.49, 1.57)	817.44
Age at SUD registration	26.2 (9.4)	1.01 (1.01, 1.01)	92.7	1.01 (1.01, 1.02)	190.1
DUD versus AUD	55.6%	1.23 (1.19, 1.26)	216.6	1.14 (1.11, 1.17)	83.9
Familial-genetic factors					
FGRS AUD	0.51 (1.3)	1.15 (1.14, 1.16)	1042.1	1.05 (1.04, 1.06)	94.5
FGRS DUD	0.52 (1.5)	1.11 (1.11, 1.12)	817.1	1.01 (1.00, 1.02)	1.0
FGRS SA	0.32 (1.3)	1.16 (1.16, 1.17)	1244,3	1.09 (1.08, 1.10)	316.8
Childhood environmental factors					
Divorce in childhood	1.8%	1.40 (1.31, 1.51)	73.3	0.91 (0.84, 0.99)	3.8
Parental death in childhood	0.2%	2.52 (2.10, 3.03)	64.2	1.58 (1.30, 1.93)	16.4
Parental hospitalization in childhood	0.30 (1.6)	1.02 (1.01, 1.02)	314.9	1.01 (1.01, 1.01)	75.2
Non-intact family in childhood	51.9%	1.35 (1.32, 1.39)	509.7	1.11 (1.08, 1.14)	48.0
Proximal environmental factors					
Married	5.7%	1.17 (1.10, 1.24)	24.0	1.24 (1.16, 1.32)	40.9
Child	26.6%	1.33 (1.30, 1.37)	385.8	1.32 (1.28, 1.37)	244.7
Neighborhood deprivation	0.29 (1.6)	1.04 (1.03, 1.05)	75.9	0.99 (0.98, 1.00)	2.8
Low education	27.6%	1.68 (1.64, 1.73)	1414.5	1.50 (1.46, 1.55)	791.7
Unemployed	27.4%	1.14 (1.11, 1.17)	83.7	1.05 (1.02, 1.08)	7.0
Social welfare	19.5%	1.55 (1.51, 1.59)	867.1	1.21 (1.17, 1.25)	135.3
Low income	25.0%	1.10 (1.07, 1.14)	43.3	0.94 (0.91, 0.97)	16.7

Note: Proximal environmental factors have been measured the year before SUD registration. FGRS are standardized values, with a mean of 0 (a positive score indicates a genetic risk greater than the general population).

Abbreviations: AIC, Akaike's information criterion; AUD, alcohol use disorder; DUD, drug use disorder; FGRS, family genetic risk scores; HR, hazard ratio; SA, suicide attempt; SD, standard deviation; SUD, substance use disorder.

[a]Decrease in AIC when predictor is added to the null model;

[b]increase in AIC when predictor is excluded from the full multivariable model.

Cox proportional hazards models

In univariable models (Table 1), every predictor was associated with increased risk of suicide attempt. Among the predictors included in our analyses, the strongest effect sizes were observed for parental death (HR = 2.52), low education (HR = 1.68), being a female (HR = 1.57) and social welfare (HR = 1.55). The decrease in AIC when each predictor was added to the model also highlighted the role of low education, $FGRS_{SA}$, $FGRS_{AUD}$, being a female, receiving social welfare and $FGRS_{DUD}$ in suicide attempt risk.

Sensitivity analyses were performed in AUD and DUD separately, as well as for a subset of individuals with no missing data (Supporting information); the results led to the same conclusions as those reported here.

We then performed multivariable analysis (Table 1) to consider all the predictors in a single model. Results indicated that sex (HR = 1.53), $FGRS_{AUD}$ (HR = 1.05) and $FGRS_{SA}$ (HR = 1.09) remained significant. Among childhood factors, divorce was no longer associated with suicide attempt, while other factors showed attenuated HR that remained > 1. Regarding the variables measured the year before SUD registration, having a child (HR = 1.32) and being married (HR = 1.24) were associated with higher risk for suicide attempt together with specific socio-economic variables, i.e. low education, social welfare and unemployment (HR = 1.50, 1.21 and 1.05). In the multivariable model, the increase in AIC when dropping a variable from the model supported the role of low education, $FGRS_{SA}$, having a child, receiving social welfare and $FGRS_{AUD}$.

Results from both univariable and multivariable models underscored marital and parenthood status as risk factors, such that being married and being a parent were associated with increased risk of suicide attempt. This is unexpected, and discrepant from previous literature. As these factors were measured in the year before SUD registration in our Cox models, we considered whether age might be an effect modifier. We conducted follow-up analyses to investigate the interaction between these predictors and age at SUD registration in risk for suicide attempt. Results are described in the Supporting information and showed that being married and having a child were associated with increased risk for those with younger ages at SUD registration but became associated with decreased risk (protective) for those whose SUD registration occurred after approximately ages 34 (marital status) and 35 (parenthood status).

Co-relative models

Co-relative analyses supported the role of familial factors in the association between risk for suicide attempt among SUD and having a child, a low education, being unemployed, receiving social welfare and neighborhood deprivation, as demonstrated by decreasing HR in groups of increased genetic closeness (cousins, siblings; Table 2). Regarding the evaluation of possible causal associations (HR > 1 in all groups), we found support for low education and possibly for marital and parenthood status as well as social welfare.

We then fitted our multivariable logistic regression model to the part of the cohort without siblings. We applied these results to the part of the population with siblings using a risk score based on the deciles of the predicted probabilities from the logistic model (Figure 1). The ROC value was 0.65, suggesting acceptable discrimination. The HR for suicide attempt per decile were 1.12 (95% CI = 1.11, 1.13) in the first population model and 1.08 (95% CI = 1.06, 1.09) in the second model accounting for sibling relatedness. While the co-sibling analysis led to an attenuated HR, the HR of 1.08 suggested that part of the association between the risk score (accounting for putative risk factors that differ between siblings) and suicide attempt was not confounded by familial factors and was potentially causal.

Interactions between aggregate genetic risk and environment

To examine the additive interactions between $FGRS_{SA}$ and environmental stressors, we used Aalen's linear hazard models. We targeted the most prominently implicated environmental factors, according to the literature [20, 33] and previous analyses (Table 3). We identified significant interactions between $FGRS_{SA}$ and non-intact family (β = 3.65; 95% CI = 0.95, 6.35) as well as low education (β = 8.80, 95% CI = 5.68, 11.9). For low education, results showed that one SD increase in the $FGRS_{SA}$ (i.e. higher family-genetic risk) led to 8.80 more cases per 10 000 person-years among individuals with low versus high education. That is, in people who did not have low education, one SD increase in $FGRS_{SA}$ led to 20.03[2] new cases while in people with low education, one SD $FGRS_{SA}$ increase led to 28.83[3] new cases. For an intact family, results indicated that one SD increase in $FGRS_{SA}$ led to 21.01[4] new cases while in people with a non-intact family, one $FGRS_{SA}$ increase led to 24.66[5] new cases (Table 3; Figure 2).

DISCUSSION

The analyses presented in this study evaluated predictors of the first suicide attempt among individuals with SUD, as they represent a population at especially high risk. The rate of suicide attempts in this population was 10%, a far higher prevalence than observed among population-based Swedish cohorts [12]. We examined the predictive role of aggregate genetic risks, childhood and proximal environmental factors, potential causality and the interaction between genetic and environmental risks. Our results underscore the important role of genetic risks together with specific childhood (non-intact family, parental death) and proximal (low education, social welfare)

[2]The β of the linear term plus the β of the quadratic term for low education = [21.1 + (−1.07)].
[3]The number of new cases for individuals who did not have a low education plus the interaction term = 20.03 + 8.80.
[4]The β of the linear term plus the β of the quadratic term for non-intact family = [22.0 + (−0.99)].
[5]The number of new cases for individuals with an intact family plus the interaction term = 21.01 + 3.65.

TABLE 2 Co-relatives analysis

	Population, *n* = 228 617 HR (95% CI)	Cousin, *n* = 24 309 HR (95% CI)	Sibling, *n* = 19 558 HR (95% CI)
Female	1.57 (1.53, 1.61)	1.54 (1.43, 1.66)	1.08 (0.99, 1.17)
Age at SUD registration	1.01 (1.01, 1.01)	1.01 (1.00, 1.01)	1.01 (1.01, 1.02)
DUD versus AUD	1.23 (1.19, 1.26)	1.29 (1.20, 1.53)	1.08 (0.99, 1.17)
Childhood environmental factors			
Divorce in childhood	1.40 (1.31, 1.51)	1.26 (1.02, 1.54)	–[a]
Parental death in childhood	2.52 (2.10, 3.03)	1.93 (1.22, 3.07)	–[a]
Parental hospitalization in childhood	1.02 (1.01, 1.02)	1.03 (1.01, 1.04)	–[a]
Non-intact family in childhood	1.35 (1.32, 1.39)	1.22 (1.14, 1.32)	–[a]
Proximal environmental factors			
Married	1.17 (1.10, 1.24)	1.18 (1.00, 1.39)	1.59 (1.34, 1.88)
Child	1.33 (1.30, 1.37)	1.20 (1.12, 1.29)	1.13 (1.04, 1.23)
Neighborhood deprivation	1.04 (1.03, 1.05)	1.03 (1.01, 1.05)	0.99 (0.96, 1.01)
Low education	1.68 (1.64, 1.73)	1.62 (1.51, 1.74)	1.35 (1.25, 1.45)
Unemployed	1.14 (1.11, 1.17)	1.09 (1.02, 1.17)	1.01 (0.94, 1.09)
Social welfare	1.55 (1.51, 1.59)	1.21 (1.13, 1.30)	1.09 (1.01, 1.18)
Low income	1.10 (1.07, 1.14)	0.96 (0.89, 1.03)	1.06 (0.99, 1.15)

Abbreviations: AUD, alcohol use disorder; CI, confidence interval; DUD, drug use disorder; HR, hazard ratio; SUD, substance use disorder.
[a]Comparisons between siblings have not been performed because these factors did not differ among siblings.

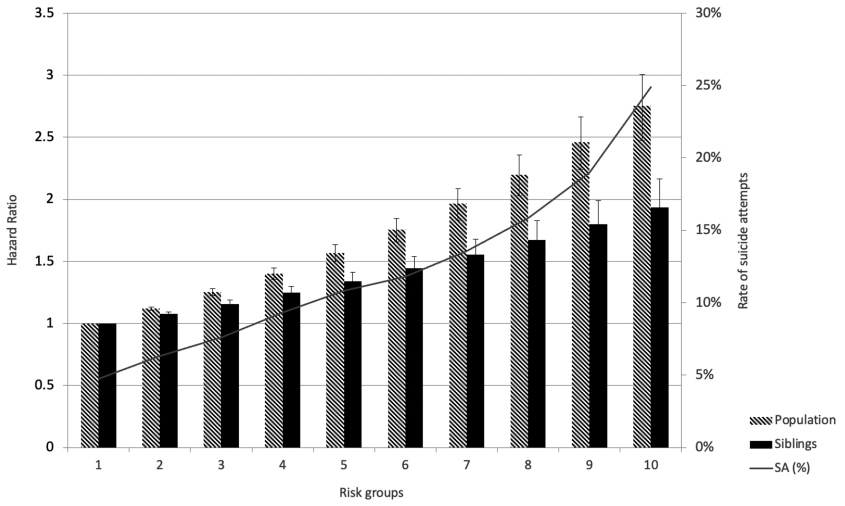

FIGURE 1 Multivariable regression model of risk for suicide attempt (SA). This figure illustrates results from our multivariable regression model, which has been fitted to the part of our cohort with no siblings, and then applied to the sibling sample: (1) without accounting for their relatedness (grey bars) and (2) co-sibling analysis (black bars). We divided the test sample into 10 risk groups, as shown in the *x*-axis. The *y*-axes represent hazard ratio (HR, left) and rates of suicide attempts (right) in the 10 groups. The receiver operating characteristic (ROC) curve was 0.65

TABLE 3 Results from Aalen's linear hazard models, illustrating the interaction between FGRS for suicide attempt and environmental predictors

Models		FGRS for suicide attempt	FGRS for suicide attempt (quadratic)	Environmental factors	Interaction between environment and $FGRS_{SA}$
Childhood environmental factors					
1	Parental death	26.2 (24.4, 28.2)	−1.21 (−1.71, −0.71)	145.0 (84.4, 206.0)	3.64 (−31.8, 39.1)
2	Non-intact family	22.0 (19.5, 24–5)	−0.99 (−1.49, −0.48)	22.7 (19.9, 25.0)	3.65 (0.95, 6.35)
Proximal environmental factors					
3	Low education	21.1 (18.9, 23.3)	−1.07 (−1.57, −0.57)	52.6 (49.0, 56.2)	8.80 (5.68, 11.9)
4	Low income	26.1 (23.9, 28.3)	−1.22 (−1.72, −0.72)	6.50 (3.34, 9.66)	0.50 (−2.40, 3.40)
5	Social welfare	23.3 (21.2, 25.4)	−1.11 (−1.62, −0.60)	41.6 (37.8, 45.4)	2.13 (−0.99, 5.25)

Table 3 includes both the linear and quadratic terms for family genetic risk scores for suicide attempt ($FGRS_{SA}$), the linear terms for environmental factors and the interaction terms. Interaction is measured with the linear term. A quadratic term has been added to account for potential extreme (FGRS) values.

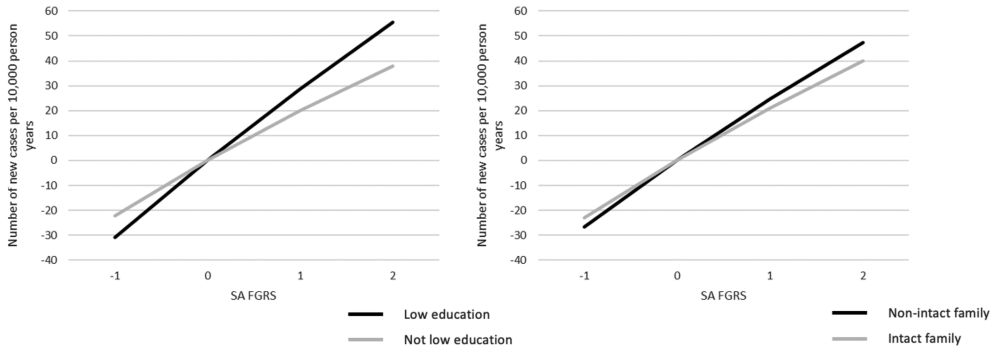

FIGURE 2 Interactions between family genetic risk scores for suicide attempt ($FGRS_{SA}$) and environmental stressors within individuals with substance use disorder (SUD). This figure illustrates interactions between family-genetic risk for suicide attempts and (A, left) educational attainment (≥ 9 years of education versus < 9 years) and (B, right) intact versus non-intact families. The *x*-axes indicate the standardized FGRS score (reference group = 0) and the *y*-axes represent the number of new cases of suicide attempt per 10 000 person-year. Negative values suggest that the effect of −1 FGRS [1 standard deviation (SD) below the mean] will lead to fewer cases per 10 000 compared to the mean FGRS

environmental factors. Findings indicate a possible causal role of low education and interactions between the overall genetic risk for suicide attempts with both non-intact family and low education.

First, we found that all FGRS were related to suicide attempt in univariable analyses. The association with FGRS for AUD and DUD is in line with previous molecular genetic studies showing that SUD and suicidal behaviors share some genetic liability [11, 19, 34], while we used a measure of aggregate genetic risks derived from family history and controlled for family environmental influences [21]. HR for FGRS as well as differences in AIC between models indicate that they were among the strongest predictors, emphasizing the usefulness of measures based on family history to predict clinical features [35].

Then, we assessed the impact of environmental factors in a model accounting for aggregate genetic risks, age and type of SUD at registration and sex. Consistent with prior studies [6, 13], we found that females and those with DUD were at higher risk for suicide attempts. Regarding childhood environmental exposures, our results show that parental death and the lack of an intact family during childhood are important predictors of suicide attempt risk. However, the number of parental hospitalizations was only weakly associated with later suicide attempt, and parental divorce slightly shifted (HR < 1) when accounting for other familial variables. This observation is surprising, but could be explained by the emotional context related to divorce. Indeed, divorce not only accounts for parental separation (as does non-intact family) and may also reflect the end of a conflicting relationship between parents [36]. This should, however, be interpreted with caution given the low prevalence of divorce in this sample. Overall, this suggests that among a high-risk population, early-life adversity is rather reflected by a lack of stability [37], including parental separation, being raised by a single parent and parental death. Experiences related to parental death also indicate the adverse role of unfavorable emotional experiences during upbringing. Parental death is recognized as an important risk factor for suicidal behaviors [38]; here, we show the significance of this event among those with SUD, even when accounting for a wide range of other risk factors. Moreover, while previous studies implicated 1–2 years after parental death as the most critical window for suicide risk [39], our analysis indicated that the risk may last considerably longer.

Concerning proximal environmental factors, our study reinforced the role of financial stressors [17], by specifically showing that being unemployed, receiving social welfare and having a low education the year before SUD registration were associated with the first suicide attempt among individuals with SUD. These variables are indicators of the economic situation, whereas low education might also be related to cognitive performance and personality traits [40]. Low education was significant in all models, with an effect size comparable to parental death. The role of low education has long been shown in both SUD and suicidal behaviors [41, 42], although sometimes confounded with other socio-economic variables. Our findings expand upon prior work, demonstrating that economic situation and low education are important predictors of suicide attempt in individuals with SUD, even after accounting for aggregate genetic risk, childhood factors and neighborhood deprivation.

Surprisingly, we found that being married and having a child were positively associated with suicide attempts. Our *post-hoc* analyses demonstrated the moderating role of age at SUD registration, emphasizing that these variables were risk factors with a younger age of SUD onset, but became protective among those with later onset of SUD. The protective effect is consistent with previous studies [17], while its inverse effect might be related to early age of onset, a measure of SUD severity [25]. Early age at sexual intercourse or marriage could also be indicators of externalizing behaviors and possible SUD severity [43, 44], suggesting that this population could be at higher risk for suicide attempts.

To test causality, we compared results from the population to groups of cousins and full siblings who were concordant for SUD and discordant in their exposure to risk factors. The attenuation of HR in cousin and sibling pairs, relative to the overall population, provides evidence that familial confounding contributes to the association between several putative risk factors and suicide attempt. Regarding

potential causality, low education was supported as being probably causally associated with suicide attempts in the SUD population. This result is in line with the study of Rosoff and colleagues [41] and further demonstrates that education is an important predictor, even among a group already at high risk for suicide. However, additional studies are needed to determine the factors underlying this association (e.g. economic factors, cognitive abilities, personality traits) and develop targeted suicide prevention. Similarly, co-relative analyses supported marital and parenthood status as possible causal predictors for suicide attempts, although this association shifts as a function of age at SUD onset. Nevertheless, the possible causal effect of risk factors shared among siblings still needs to be determined using complementary methods that enable causal inference, especially for parental death, which has the strongest effect size in the multivariable analysis.

The role of aggregate genetic risk is reinforced by significant interactions with environmental factors. Results indicated that individuals with SUD who had high $FGRS_{SA}$ and low education had an increased risk of suicide attempt compared to individuals with low education and low $FGRS_{SA}$. We also detected an interaction with non-intact family during childhood, showing that individuals with high $FGRS_{SA}$ who had lived in a non-intact family (less stable environment) and later developed SUD were at higher risks for suicide attempt than their peers with lower genetic liability. Our results suggest that genetic factors may partially explain the ways in which people respond to the environment [45] and strongly encourage the consideration of both genetic and environmental effects in future research and clinical efforts.

Some limitations must be noted to guide future research perspectives. In line with Rosoff et al. [41], we identified educational attainment as a predictor of suicide attempts. Future research, however, needs to evaluate the mechanisms involved in this association (e.g. cognitive abilities). Regarding childhood stressors, we have identified the role of parental hospitalizations, but did not examine the nature of these hospitalizations in detail. Limiting hospitalizations for life-threatening or psychiatric conditions could improve our understanding of this exposure, whose effect size was quite low. Beyond genetic and environmental risk factors, this study has not considered the role of psychiatric disorders that may also influence suicide attempt risk in SUD. Future studies should extend this question. In addition, our study design precluded investigating the effects of environmental exposures that occurred after an individual's SUD registration, which might have been differentially associated with suicide attempt. As our research relied upon registry data, we probably identified more severe cases of SUD and suicide attempts. Replications in other populations including less severe SUD and suicide attempts (e.g. those that may not have come to the attention of health-care providers) would reinforce our results and their generalizability.

To conclude, we considered both genetic and environmental factors and investigated their interaction in risk for the first suicide attempt among individuals with SUD. Genetic and socio-economic factors appear the most important, while childhood experiences continue to play a modest role later in life. After accounting for risk factors specifically related to SUD (age at registration, FGRS for AUD and DUD), we expand upon the literature by demonstrating that specific environmental variables previously implicated in suicide attempt risk in general samples are also important in individuals with SUD—a group already vulnerable to suicide. Altogether, these findings clarify our understanding of at-risk individuals and may be useful in clinical settings to evaluate suicide risk in SUD patients. Particular attention should be given to people with a family history of SUD or suicidal behaviors and low education. Additional risks can be expected when people are in financial difficulties and have experienced childhood instability. We also strongly encourage consideration of whether being married and having children are perceived as protective or additional stressors beyond SUD itself, as our findings showed their distinct roles as a function of SUD age of onset and support their potential causal influence in suicide attempt risk.

ACKNOWLEDGEMENTS

This study has been supported by the National Institutes of Health (National Institute on Alcohol Abuse and Alcoholism: grant numbers AA027522, AA023534; National Institute of Mental Health: grant number MH129356; and National Institute on Drug Abuse: grant number DA030005) and by the Swedish Research Council to J.S.

DECLARATION OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Séverine Lannoy: Conceptualization; writing - original draft presentation. **Henrik Ohlsson:** Conceptualization; formal analysis. **Mallory Stephenson:** Conceptualization. **Kenneth Kendler:** Funding acquisition. **Jan Sundquist:** Funding aqcuisition; resources. **Kristina Sundquist:** Funding acquisition; resources. **Alexis Edwards:** Conceptualization; funding acquisition; supervision; writing - original draft presentation. All authors: Writing - review & editing.

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How to cite this article: Lannoy S, Ohlsson H, Stephenson M, Kendler KS, Sundquist J, Sundquist K, et al. Risk of non-fatal suicide attempt in individuals with substance use disorder: the roles of aggregate genetic liability and environmental exposures in a Swedish population-based cohort. Addiction. 2022;117(11):2943–52. https://doi.org/10.1111/add.15965