Psychological Medicine

cambridge.org/psm

Original Article

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Cite this article: Edwards AC, Ohlsson H, Sundquist J, Crump C, Mościcki E, Sundquist K, Kendler KS (2024). The role of substance use disorders in the transition from suicide attempt to suicide death: a record linkage study of a Swedish cohort. *Psychological Medicine* **54**, 90–97. https://doi.org/10.1017/S0033291722002240

Received: 12 February 2022
Revised: 21 June 2022
Accepted: 28 June 2022
First published online: 9 November 2022

Key words:
cohort study; registry; substance use disorders; suicide attempt; suicide death

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The role of substance use disorders in the transition from suicide attempt to suicide death: a record linkage study of a Swedish cohort

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Abstract

Background. Suicidal behavior and substance use disorders (SUDs) are important public health concerns. Prior suicide attempts and SUDs are two of the most consistent predictors of suicide death, and clarifying the role of SUDs in the transition from suicide attempt to suicide death could inform prevention efforts.

Methods. We used national Swedish registry data to identify individuals born 1960–1985, with an index suicide attempt in 1997–2017 ($N = 74\,873$; 46.7% female). We assessed risk of suicide death as a function of registration for a range of individual SUDs. We further examined whether the impact of SUDs varied as a function of (i) aggregate genetic liability to suicidal behavior, or (ii) age at index suicide attempt.

Results. In univariate models, risk of suicide death was higher among individuals with any SUD registration [hazard ratios (HRs) = 2.68–3.86]. In multivariate models, effects of specific SUDs were attenuated, but remained elevated for AUD (HR = 1.86 95% confidence intervals 1.68–2.05), opiates [HR = 1.58 (1.37–1.82)], sedatives [HR = 1.93 (1.70–2.18)], and multiple substances [HR = 2.09 (1.86–2.35)]. In secondary analyses, the effects of most, but not all, SUD were exacerbated by higher levels of genetic liability to suicide death, and among individuals who were younger at their index suicide attempt.

Conclusions. In the presence of a strong predictor of suicide death – a prior attempt – substantial predictive power is still attributable to SUDs. Individuals with SUDs may warrant additional suicide screening and prevention efforts, particularly in the context of a family history of suicidal behavior or early onset of suicide attempt.

Introduction

Suicidal behaviors are a serious and persistent public health concern. Worldwide, approximately 700 000 individuals die by suicide on an annual basis (World Health Organization, 2021). Suicide attempts, defined by the National Institute of Mental Health as *non-fatal* events of suicidal intent (National Institute of Mental Health, 2019), outnumber suicide deaths by a factor of up to 30 (Han et al., 2016), and history of suicide attempt is one of the more reliable predictors of later suicide death (Franklin et al., 2017). Among individuals who survive an initial suicide attempt, risk for subsequent death by suicide is much higher than in the general population: In a longitudinal Swedish cohort study, 5.6% of those with an index attempt later died by suicide (Niederkrotenthaler, Mittendorfer-Rutz, Mehlum, Qin, & Bjorkenstam, 2020) while another Swedish study reported a prevalence of 0.7% in the general population (Edwards, Ohlsson, Sundquist, Sundquist, & Kendler, 2020a). Identifying predictors of the transition from suicide attempt to later suicide death has the capacity to reduce deaths by providing guidance to clinicians about who, among their patients with a history of suicidal behavior, may benefit most from direct efforts at prevention and intervention.

Substance use disorders [SUD; to include alcohol use disorder (AUD) and drug use disorders (DUD)] are strongly associated with suicidal behavior across multiple countries (Barak-Corren et al., 2017; Chai et al., 2022; Flensborg-Madsen et al., 2009; Gobbi et al., 2019; Hesse, Thylstrup, Seid, & Skogen, 2020; Lynch et al., 2020). Indeed, in a recent study that utilized electronic health records to predict suicide attempts and death, SUD exhibited the strongest association with suicidal behavior (Barak-Corren et al., 2017), and a more recent report specifically identified several substance-related ICD-9 codes (e.g. *poisoning by unspecified drug or medical substance*, *drug withdrawal syndrome*, *cocaine dependence*) as among

those most prominently associated with suicide attempt (Barak-Corren et al., 2020). Prior research demonstrates that co-occurrence of SUD and suicidal behaviors is due to familial factors (e.g. shared genetic and/or family environmental influences) (Colbert et al., 2021; Docherty et al., 2020; Edwards et al., 2020a, 2022; Mullins et al., 2022), non-familial shared liability (Edwards et al., 2021a), and a potentially causal relationship (Edwards et al., 2020a, 2022), underscoring the complexity of these associations.

While abundant evidence supports a role for SUD as an indicator of and/or causal risk factor for individual suicidal outcomes (e.g. ideation, attempts, or death), and previous research has found that the risk of suicide varies across specific substance use disorders (SUDs) (Crump, Sundquist, Kendler, Edwards, & Sundquist, 2021), little is known about the extent to which specific SUD – e.g., alcohol, cannabis, or opioids – are related to the *transition* from non-fatal suicide attempt to subsequent death by suicide. That is, within an already high-risk population of those with a history of suicide attempt, what is the utility of SUD status as an indicator of risk for suicide death? Understanding the features of individuals at highest risk could facilitate targeted prevention efforts and reduce the rate of suicide deaths.

With this in mind, the current study leveraged Swedish national registry data on suicide attempts, death, and SUD to test whether, among those with a history of suicide attempt, specific SUD were associated with suicide death. We further pursued a series of secondary research questions. First, given the heritable nature of suicidal behavior (Althoff et al., 2012; Brent & Mann, 2005; Brent & Melhem, 2008; Docherty et al., 2020; Edwards et al., 2021b; Glowinski et al., 2001; Mullins et al., 2022; Pedersen & Fiske, 2010) and prior evidence that high genetic liability for psychopathology can exacerbate the effects of other risk factors (Musliner et al., 2015; Peyrot et al., 2014; Polimanti et al., 2021; Wendt et al., 2021), we tested whether SUD status interacted with aggregate genetic liability to suicidal behavior (non-fatal attempt or death) when assessing risk of suicide death. Second, because earlier age of onset for suicidal behavior or other psychopathology for can be considered an indicator of severity (Kessler et al., 2007; Thompson, Dewa, & Phare, 2012), we tested whether effects of SUD registration on likelihood of suicide death differed as a function of age at index suicide attempt, an objective measure readily available in Swedish registries.

Both our primary and secondary analyses have the potential to be clinically informative through their identification of subgroups at particularly high risk for suicide death. Given the nationwide coverage of the data, these analyses are unique in their access to sufficient sample sizes to capture generally low-prevalence predictors (e.g. dependence on a specific substance) of a low-prevalence outcome (suicide death). Furthermore, the analyses do not rely on samples ascertained for other psychiatric illnesses (e.g. major depressive disorder), thereby increasing their generalizability.

Methods

Sample

We collected longitudinal information on individuals from Swedish population-based registers with national coverage linking each person's unique personal identification number which, to preserve confidentiality, was replaced with a serial number by Statistics Sweden. We secured ethical approval for this study from the Regional Ethical Review Board in Lund and no participant consent was required as the analyses were based on secondary data (No. 2008/409 and later amendments). In the database, we included all individuals born in Sweden between 1960 and 1985 with a suicide attempt registration any time during 1997–2017.

Measures

Suicide attempt was defined in the Swedish medical registers using the ICD-10 codes X60-X84 and Y10-Y34. We used the first date of registration of suicide attempt. Individuals with a recorded attempt prior to 1997 were not included in the study due to reduced data coverage. We also included records of suicide death from the Swedish Mortality register, using the same ICD-10 codes as for suicide attempt. Individuals registered with suicide death on the same date as suicide attempt were excluded to avoid misclassifying an attempt that did eventually lead to death as non-fatal ($N = 98$). In the database, we also included first registration of the following substance-specific SUDs: Alcohol Use Disorder, Cannabis, Cocaine/Stimulants, Hallucinogens, Opiates, Sedatives, Multiple Substance Abuse (MSA). A registration for MSA indicates that the individual has experienced problems with more than one substance and does not on its own provide information about which specific substances are of concern. We elected to include MSA registrations despite their inherent lack of specificity because this category included a large number of individuals with a suicide attempt ($N = 13\,733$), among whom $N = 5257$ (38.3%) did not have a registration for a specific SUD. ICD codes are provided in the Supplement.

We further included year of birth, sex and a family genetic risk score for suicide death ($FGRS_{SD}$) and suicide attempt ($FGRS_{SA}$); details on FGRS derivation, which we have reported previously (Kendler et al., 2021a; Kendler, Ohlsson, Sundquist, & Sundquist, 2021b; Kendler, Ohlsson, Sundquist, & Sundquist, 2021c), are provided in the supplement.

Analyses

We used Cox proportional hazards models to investigate, among those with a history of suicide attempt, the risk of suicide death as a function of substance-specific SUD registrations from date of suicide attempt until end of the follow-up (death, emigration, or 12–31-2017), while controlling for year of birth, sex, and age at index suicide attempt. We report the hazard ratio (HR) and 95% confidence intervals (CIs). The SUD registrations were treated as time-dependent covariates, so that an individual was considered free of SUD until the time of registration. Individuals registered with SUD prior to the index date of suicide attempt were considered exposed during the entire follow-up period. In multivariable analyses, all first-time registrations for each applicable SUD were included in the model, such that a subject with multiple registrations (e.g. for both AUD and cannabis use disorder) was coded as being affected accordingly.

For the secondary research questions, we included $FGRS_{SD}$ and $FGRS_{SA}$ in the models and interacted these variables, in separate models, with each specific SUD registration; this approach avoids the inclusion of multiple interaction terms, which would complicate interpretation. We evaluated the interactions with $FGRS_{SD}$ and $FGRS_{SA}$ on both the multiplicative and the additive scale. For the additive interaction, we present the relative excess

https://doi.org/10.1017/S0033291722002240 Published online by Cambridge University Press

risk due to interaction (RERI) (Knol, van der Tweel, Grobbee, Numans, & Geerlings, 2007). The RERI is calculated as the difference between the effect based on the summation of the separate effects included in the interaction term and the effect in the joint exposure category. In another secondary analysis, we tested the interaction between SUD registration and age at index suicide attempt. Conversion to the additive scale using the RERI requires a nuanced interpretation of effects given the typical conventions of the approach: namely, for both components of the interaction term, higher values are associated with poorer outcomes. Note that, to facilitate interpretation in the models including an additive interaction with age at attempt, we coded the data such that the parameter estimate for the interaction term reflects a one year *decrease* from the sample's mean age at index attempt. Correspondingly, assuming a positive effect of SUD registration, a positive parameter estimate would reflect an increase in risk among individuals with earlier age at index attempt. All analyses were performed using SAS 9.4 (©2002–2012 SAS Institute Inc., Cary NC US).

Results

Descriptive statistics

Details about the sample are provided in Table 1. A total of $N = 74\,873$ index suicide attempts (46.7% among females) were detected during the observation period [mean (s.d.) follow-up of 118.9 (66.4) months]. Of these, 3.0% later died by suicide. A slight majority (54.9%) of attempters did not have a registration for any SUD. The prevalences of suicide death among those with no SUD and those with a registration for each individual SUD are provided in Table 2 and online Supplementary Fig. S1. The prevalence of suicide death was considerably higher among those with SUD (4.8–6.5%) relative to those with no SUD registration (1.5%), though we did not observe pronounced differences in the rate of suicide death among those with different forms of SUD. Survival curves for each substance are provided in online Supplementary Fig. S2.

The correlations among suicide death and registrations for each SUD were wide-ranging (see online Supplementary Fig. S3). Suicide death was modestly correlated with each SUD category (tetrachoric correlations $r = 0.14$–0.24); substance-specific SUD registrations were moderately correlated ($r = 0.38$–0.58); and registration for MSA was more strongly correlated with substance-specific SUD registrations ($r = 0.58$–0.76).

Univariate analyses

We estimated the univariate associations between each category of SUD registration and suicide death. Hazard ratios (HRs) are presented in Table 3 (Model 1) and ranged from HR = 2.68, for cocaine/stimulants, to HR = 3.86, for opiates. We next tested, for each SUD, an interaction term between the focal SUD and sex. Hazard ratios ranged from HR = 0.87 (sedatives) to HR = 1.04 (cocaine/stimulants) but each case the 95% CIs included 1, indicating no significant sex differences (all $p > 0.05$). Subsequent models therefore retained sex as a covariate rather than stratifying analyses by sex.

Multivariate analyses

We next included all SUD registrations simultaneously as predictors of suicide death. Results are presented in Table 3 (Model 2). In this context, registrations for cannabis, cocaine/stimulants, and hallucinogens were no longer significantly associated with the transition to suicide death. HR estimates remained elevated for cannabis and hallucinogens, but were known quite imprecisely. For the other SUDs, HR estimates were attenuated (HR = 1.18–2.09) but remained significantly greater than 1. Because a subset of the cohort [$N = 10\,551$ females (30.2%); $N = 11\,398$ males (28.6%)] had multiple registrations for suicide attempt, we conducted a follow-up analysis to determine whether including a subsequent attempt as a time-varying covariate impacted HR estimates for SUDs (online Supplementary Table S3). While some HRs were modestly attenuated, overall findings were unchanged.

Secondary analyses

Effect of aggregate genetic risk

We tested whether FGRS for suicide attempt ($FGRS_{SA}$) or suicide death ($FGRS_{SD}$) contributed to risk for transition from attempt to death while accounting for the effect of SUD registration, and whether SUD registration and FGRS scores interacted (e.g. whether the joint effects of SUD registration and FGRS exceeded expectations given main effects). Complete results are presented in online Supplementary Table S1. Main effects HRs for $FGRS_{SA}$ ranged from 1.02–1.08 and differed from 1 for cannabis, cocaine/stimulants, hallucinogens, and sedatives. We did not observe significant interactions between SUD and $FGRS_{SA}$ on the additive scale (RERI = −0.01 to 0.40), though all but one estimate (for cocaine/stimulants) was positive. Similarly, interactions on the multiplicative scale were not statistically significant, and all but two (for cannabis and cocaine/stimulants) had HRs > 1. The consistency of direction of effect suggests that genetic liability to suicide attempt may exacerbate the effects of SUD on transition to suicide death, but the magnitude of the impact is weak.

When the FGRS for suicide attempt was replaced with an FGRS for suicide death ($FGRS_{SD}$), the main effects of $FGRS_{SD}$

Table 1. Descriptive statistics of sample. All individuals included in the sample were born 1960–1985.

	Total sample	Females	Males
Sample size (Individuals with non-fatal suicide attempt)	74 873	34 980 (46.7%)	39 893 (53.3%)
Suicide death *N* (%)	2283 (3.0%)	855 (2.4%)	1428 (3.6%)
Age at index attempt (s.d.)	33.4 (9.8)	32.5 (10.2)	34.1 (9.4)
Age at suicide death (s.d.)	37.1 (8.8)	37.2 (9.2)	37.0 (8.5)
Year of birth	1974 (7.7)	1974 (7.8)	1974 (7.7)
Time to suicide death since index attempt (months)	52.4 (54.8)	57.0 (57.9)	49.7 (52.8)

https://doi.org/10.1017/S0033291722002240 Published online by Cambridge University Press

Table 2. Prevalence of specific SUDs and frequency of suicide death within group

	Total sample		Females		Males	
	N (%)	% Suicide death	*N* (%)	% Suicide death	*N* (%)	% Suicide death
No SUD registration	41 097 (54.9%)	1.5%	20 485 (58.6%)	1.3%	20 612 (51.7%)	1.6%
AUD	24 590 (32.8%)	4.8%	9402 (26.9%)	3.9%	15 188 (38.1%)	5.3%
Cannabis	2180 (2.9%)	6.1%	491 (1.4%)	4.3%	1689 (4.2%)	6.7%
Cocaine/Stimulants	4075 (5.4%)	5.4%	1280 (3.7%)	4.0%	2795 (7.0%)	6.0%
Hallucinogens	617 (0.8%)	6.6%	180 (0.5%)	5.0%	437 (1.1%)	7.3%
Opiates	5282 (7.1%)	6.5%	1919 (5.5%)	5.3%	3363 (8.4%)	7.2%
Sedatives	7543 (10.1%)	6.2%	3843 (11.0%)	5.5%	3700 (9.3%)	6.9%
Multiple substance abuse	13 733 (18.3%)	5.9%	5330 (15.2%)	4.8%	8403 (21.1%)	6.7%

were positive (HR = 1.15–1.17), and in each case differed significantly from 1 (Table 4). All interactions on the additive scale were positive (RERI = 0.14–1.11); with the exception of cannabis and MSA, the RERI estimates were significantly different from the null expectation. Thus, the joint effects of SUD registration and high $FGRS_{SD}$ resulted in a higher likelihood of transition to suicide death than expected based on the sum of their main effects. We did not observe significant interactions on the multiplicative scale, with one exception [MSA × $FGRS_{SD}$; HR = 0.94 (0.89–0.996)].

Effect of age at index suicide attempt

Our primary analyses included age at index suicide attempt as a covariate. In this secondary analysis, we included an interaction term between SUD registration and age at index attempt, which tests whether the effect of an SUD registration varies as a function of the age at which an individual first exhibited medically serious suicidal behavior. Complete results are available in online Supplementary Table S2. With respect to main effects, the HRs for age at index attempt were <1, indicating that earlier age at index attempt was associated with an increased risk of subsequent suicide death, but CIs overlapped 1. However, the variable scale is a very modest increment – one year, with the potential range of 13–58 years – raising the possibility that even a small effect size could be meaningful when considered across the life course.

We did observe significant interactions between SUD and age at index suicide attempt (online Supplementary Table S2). The positive RERI estimates ranged from 0.03–0.14 and were statistically significant for all SUD except cannabis. Because these represent the effects of a one-year *decrease* in age at index attempt (relative to the mean age of 33.4), this indicates that the joint effects of SUD registration and earlier age at index suicide attempt on transition from attempt to death are worse than expected given the main effects of these predictors.

These effects are reproduced when testing interaction terms on the multiplicative scale (see Figure). We observed significant interactions with all SUD registrations other than AUD and cannabis, with corresponding HRs <1. For both scales, significant results indicate that the association between SUD and risk of suicide death is exacerbated among those with earlier age at index suicide attempt (i.e. during adolescence). The effect of SUD then declines among those whose first attempts occurred in early adulthood, and tapers further for later ages of onset. In some cases (e.g. among those with a registration for cocaine/stimulants), the HR for SUD registration does not differ significantly from 1 among those whose index suicide attempt occurred during later adulthood, as evidenced by CIs that overlap 1.

Table 3. Results from univariate (Model 1) and multivariate (Model 2) Cox proportional hazards models

	Model 1		Model 2	
	HR	95% CI	HR	95% CI
AUD	2.72	2.50–2.95	1.86	1.68–2.05
Cannabis	2.96	2.48–3.53	1.18	0.97–1.43
Cocaine/Stimulants	2.68	2.33–3.08	0.94	0.80–1.11
Hallucinogens	3.40	2.50–4.62	1.35	0.98–1.86
Opiates	3.86	3.44–4.34	1.58	1.37–1.82
Sedatives	3.56	3.22–3.94	1.93	1.70–2.18
Multiple substance abuse	3.72	3.72–4.05	2.09	1.86–2.35

AUD, alcohol use disorder; CI, confidence intervals; HR, hazard ratio.
Results are presented as HRs and 95% CIs. Both models include substance use disorder registration as a time-dependent covariate and are controlled for sex, year of birth, and age at index suicide attempt; multivariate models include all SUDs as joint predictors.

Discussion

In the current study, we explored the association between individual SUDs and risk for the transition from suicide attempt to suicide death, leveraging longitudinal Swedish national registry data. In multivariate analyses accounting for sociodemographic factors and registration for a range of SUD, we found that registration for alcohol use disorder, opiates, sedatives, and multiple substances (an aggregate ICD code) were associated with increased risk of suicide death among those with a previous suicide attempt. In secondary analyses, aggregate genetic risk scores for suicide attempt or death were largely positively associated with increased risk of this transition, and the impact of most SUD registrations was more pronounced among persons with higher genetic liability for suicide death. Furthermore, risk of suicide death was higher among those whose index suicide attempt occurred earlier in life, and this effect was exacerbated among those with any SUD registration other than for cannabis.

https://doi.org/10.1017/S0033291722002240 Published online by Cambridge University Press

Table 4. Main effects of, and interaction effects with, $FGRS_{SD}$

	Main effect		Interaction effect	
	SUD registration	$FGRS_{SD}$	Additive scale (RERI)	Multiplicative scale
AUD	2.69 (2.48–2.93)	1.17 (1.12–1.22)	0.14 (0.02–0.27)	0.96 (0.91–1.01)
Cannabis	2.90 (2.42–3.47)	1.16 (1.13–1.19)	0.25 (−0.06 to 0.56)	0.98 (0.90–1.08)
Cocaine/Stimulants	2.58 (2.23–2.98)	1.15 (1.12–1.19)	0.31 (0.08–0.53)	1.02 (0.94–1.11)
Hallucinogens	3.05 (2.29–4.27)	1.16 (1.13–1.19)	1.11 (0.36–1.86)	1.22 (0.98–1.53)
Opiates	3.80 (3.37–4.27)	1.15 (1.12–1.19)	0.35 (0.08–0.61)	0.98 (0.92–1.05)
Sedatives	3.49 (3.14–3.87)	1.15 (1.12–1.19)	0.34 (0.12–0.56)	0.99 (0.93–1.05)
Multiple substance abuse	3.70 (3.39–4.03)	1.17 (1.13–1.21)	0.18 (−0.01 to 0.38)	0.94 (0.89–0.996)

AUD, alcohol use disorder; SUD, substance use disorder; $FGRS_{SD}$, family genetic risk score for suicide death; RERI, relative excess risk due to interaction.
In each model, the predictors of interest were substance use disorder registration, $FGRS_{SD}$, and the corresponding interaction term; covariates were sex, year of birth, and age at index suicide attempt. Results are presented as HRs and 95% CIs.

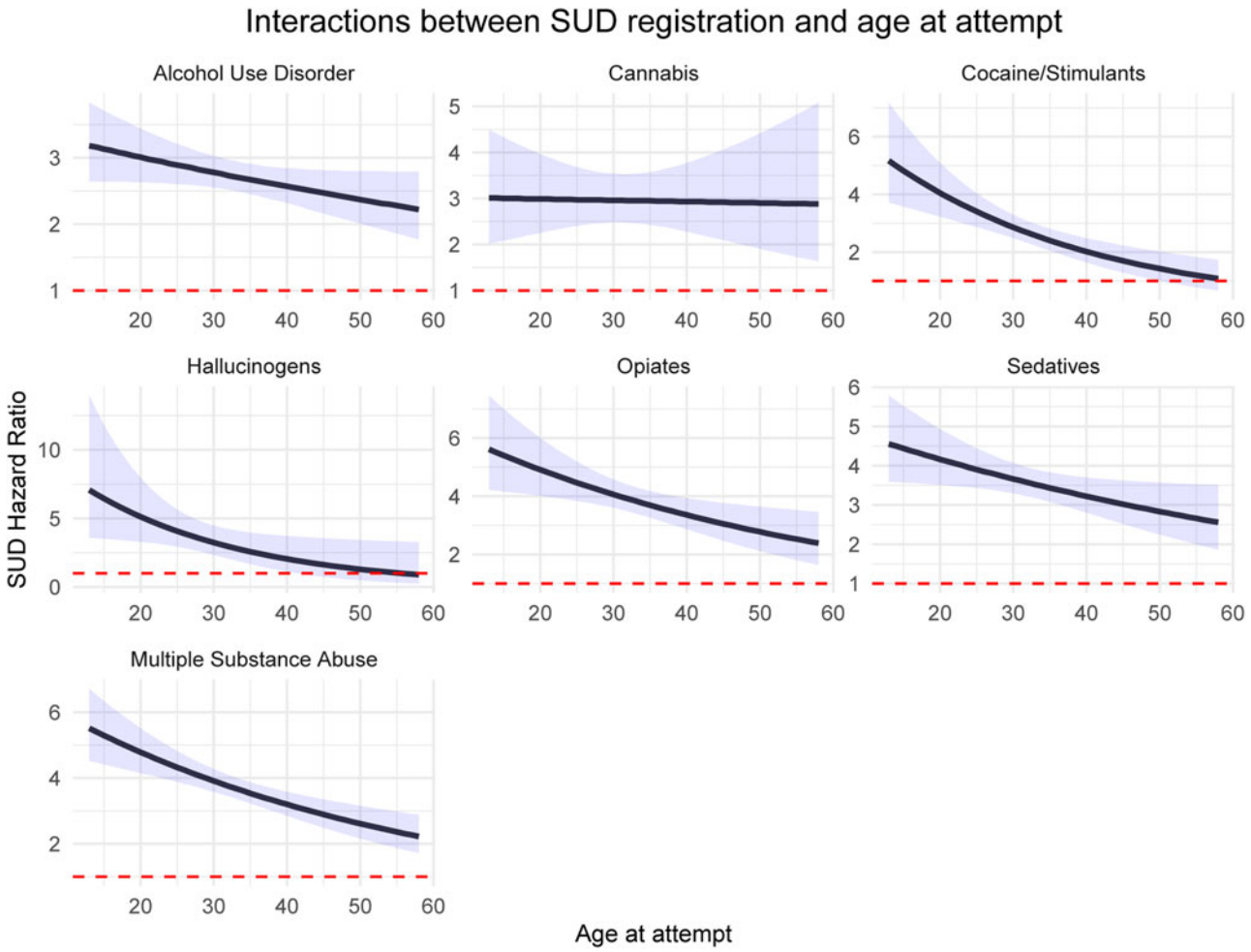

Fig. 1. Risk of transition to suicide death among individuals with specific SUD registrations, as a function of age at index suicide attempt. Results are HRs and 95% CIs (shaded area), based on estimates from regressions where the predictors of interest are an individual SUD registration, age at index suicide attempt, and the interaction between these predictors on the multiplicative scale; year of birth and sex are included as covariates. The red horizontal dashed line represents a HR of 1 (i.e. the null hypothesis).

While many individuals who survive an initial suicide attempt do not go on to die by suicide, a history of self-harm is a prominent risk factor for later death (Franklin et al., 2017). Substance use disorders have also been positively associated with risk for suicide death, and this study examined whether, even among the high-risk group of individuals with a prior attempt, that association remained. Indeed, we found that the prevalence of suicide death was 3–4 times greater among those with a SUD registration

https://doi.org/10.1017/S0033291722002240 Published online by Cambridge University Press

relative to individuals with no SUD who had previously attempted suicide. Thus, this group may be of particular interest to clinicians in the effort to reduce the burden of suicide.

We have previously shown that problems with opiates or sedatives are more strongly associated with risk for suicide death in the population at-large, with HRs of 4.62–6.39 in adjusted models (Crump et al., 2021). In the current study, these registrations, along with those for AUD and the aggregate category of 'multiple substance abuse', were prominently associated with risk of suicide death even within the high-risk group of people with a prior suicide attempt, albeit at attenuated HR estimates. Some other studies have also reported especially strong associations with opioid and polysubstance problems (Chai et al., 2022). Thus, while the time to transition from suicide attempt to suicide death did not differ markedly across substances, patients with opiate or sedative use disorders, in addition to those with AUD and MSA, likely warrant particular clinical attention. For example, use of assessments that explicitly address both prior attempts and SUDs, such as the Columbia-Suicide Severity Rating Scale (Posner et al., 2011), may be especially informative.

Overall, aggregate genetic liability to both non-fatal and fatal suicide outcomes, operationalized by our FGRS, were associated with an increased risk of transitioning from suicide attempt to suicide death. This likely reflects, in part, the substantial genetic correlation between non-fatal attempt and death, which has been previously reported (Edwards et al., 2021b; Mullins et al., 2022). However, the magnitude of effect was stronger for $FGRS_{SD}$ than for $FGRS_{SA}$ (HR = 1.15–1.17 *v.* HR = 1.02–1.08, respectively). This could reflect the differing levels of severity of suicide attempt *v.* suicide death, but an alternative explanation is that qualitative genetic differences between attempt and death result in an improved specificity/predictive utility of $FGRS_{SD}$ relative to $FGRS_{SA}$ for the transition from attempt to death. That the effects of most SUD interacted with $FGRS_{SD}$ on the additive scale is consistent with the diathesis-stress model of psychopathology (Kendler, 2020; van Heeringen & Mann, 2014) in that those with an elevated genetic propensity for suicide death are more sensitive to the risk of suicide conferred by manifestation of one or more SUDs. This could be due to differences in coping abilities among those with SUD (Cerea, Bottesi, Grisham, Vieno, & Ghisi, 2017; Van Gundy, Howerton-Orcutt, & Mills, 2015) or exposure to other stressors that are more common among this population, such as divorce (Franco et al., 2019; Kendler, Lonn, Salvatore, Sundquist, & Sundquist, 2017) or financial difficulties (Edwards, Ohlsson, Sundquist, Sundquist, & Kendler, 2020b; Franco et al., 2019).

Our findings must be considered in the context of several limitations. First, because we employ registry data rather than self-reported SUD and suicide attempt status, we are unable to capture less severe SUD cases and suicide attempts that do not necessitate medical attention. A substantial proportion of suicide attempts do not come to the attention of medical personnel (Piscopo, Lipari, Cooney, & Glasheen, 2016), and these attempters may be less likely to subsequently die by suicide. It is possible that inclusion of these cases would impact the observed effect sizes of SUD and/or the FGRS. Second, our analyses do not account for psychiatric comorbidity other than SUD. However, in our study examining the role of SUD and suicide in a previous context, we found that while inclusion of psychiatric comorbidity modestly attenuated effect sizes of SUD, it did not impact overall conclusions (Crump et al., 2021).

Third, we elected to include registrations for MSA despite the lack of specificity inherent to this category, which introduces a corresponding imprecision in our findings. Our rationale was that this category included a large number of individuals known to have SUD, many of whom (38.3%) did not otherwise have a specific SUD registration, and their exclusion was deemed inappropriate. In exploratory analyses, excluding this category in the multivariate model yielded slightly higher HRs for the remaining, specific SUD categories, with the only notable differences being that the CIs for cannabis and hallucinogens did not include 1 (i.e. differed from the null) in the less inclusive models. We therefore note that the substance-specific HRs reported herein are potentially conservative.

Fourth, our FGRS do not directly correspond to polygenic scores derived from individual genotype data. They rely on the manifestation of phenotypes (here, SA or SD) in relatives and corresponding registrations, and are sensitive to outcome prevalence. Fifth, we are unable to reliably identify substance abuse treatment in our nationwide study population, and could therefore not incorporate this information into our models. Sixth, we did not code individuals with a T40 registration ($N = 386$) as having a SUD: Due to lack of sufficient specificity in the ICD-10 codes to which we have access, we could not determine which substance was ingested. Because alcohol poisoning was included, this results in a slight imbalance in the severity of problems reflected across alcohol *v.* other substances. Finally, while our findings benefit from nationwide data on Swedish-born residents, they might not generalize to other countries or populations with different sociodemographic characteristics. In particular, Sweden's medical system is socialized, which might contribute to its superior access and efficiency relative to, for example, the United States (Schneider et al., 2021; Tandon, Murray, Lauer, & Evans, 2001) and impact who seeks treatment for SUD and/or suicidal behavior. However, the universal access to health care means that the confounding effect of unequal health care biases our findings to a lesser extent.

In summary, findings from the current study indicate that, even among a high-risk group of individuals with a history of suicide attempt, SUD remains a prominent predictor of transition to suicide death. The associations were most pronounced for individuals with MSA, AUD, or sedative dependence; they were further exacerbated among persons with high aggregate genetic liability to suicide death and those with earlier onset of non-fatal suicidal behavior. These results underscore the importance of assessment for SUD and family history of suicide among individuals with a history of suicidal behavior, as they warrant particular concern for future death by suicide. Recognizing the role of SUD in a population already at high risk for suicide can provide guidance for clinicians and highlight potential opportunities for preventive interventions and treatment to reduce suicide deaths.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722002240

Financial support. This study was supported by NIH grants MH129356, AA027522, AA023534, and DA030005; and by the Swedish Research Council.

Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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