Psychological Medicine

cambridge.org/psm

Shared genetic and environmental etiology between substance use disorders and suicidal behavior

Alexis C. Edwards[1], Henrik Ohlsson[2], Séverine Lannoy[1], Mallory Stephenson[1], Casey Crump[3,4], Jan Sundquist[2,3,4], Kristina Sundquist[2,3,4,*] and Kenneth S. Kendler[1,*]

[1]Department of Psychiatry, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University School of Medicine, Richmond, VA, USA; [2]Center for Primary Health Care Research, Lund University, Malmö, Sweden; [3]Department of Family Medicine and Community Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA and [4]Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Original Article

*Joint senior authors.

Cite this article: Edwards AC, Ohlsson H, Lannoy S, Stephenson M, Crump C, Sundquist J, Sundquist K, Kendler KS (2023). Shared genetic and environmental etiology between substance use disorders and suicidal behavior. *Psychological Medicine* **53**, 2380–2388. https://doi.org/10.1017/S0033291721004256

Received: 9 June 2021
Revised: 28 September 2021
Accepted: 30 September 2021
First published online: 12 November 2021

Key words:
Alcohol use disorder; drug use disorder; substance use disorders; suicidal behavior; suicide attempt; suicide death; twin modeling; shared liability

Author for correspondence:
Alexis C. Edwards,
E-mail: alexis.edwards@vcuhealth.org

Abstract

Background. Previous studies have demonstrated substantial associations between substance use disorders (SUD) and suicidal behavior. The current study empirically assesses the extent to which shared genetic and/or environmental factors contribute to associations between alcohol use disorders (AUD) or drug use disorders (DUD) and suicidal behavior, including attempts and death.

Methods. The authors used Swedish national registry data, including medical, pharmacy, criminal, and death registrations, for a large cohort of twins, full siblings, and half siblings ($N = 1\,314\,990$) born 1960–1980 and followed through 2017. They conducted twin-sibling modeling of suicide attempt (SA) or suicide death (SD) with AUD and DUD to estimate genetic and environmental correlations between outcomes. Analyses were stratified by sex.

Results. Genetic correlations between SA and SUD ranged from rA = 0.60–0.88; corresponding shared environmental correlations were rC = 0.42–0.89 but accounted for little overall variance; and unique environmental correlations were rE = 0.42–0.57. When replacing attempt with SD, genetic and shared environmental correlations with AUD and DUD were comparable (rA = 0.48–0.72, rC = 0.92–1.00), but were attenuated for unique environmental factors (rE = −0.01 to 0.31).

Conclusions. These findings indicate that shared genetic and unique environmental factors contribute to comorbidity of suicidal behavior and SUD, in conjunction with previously reported causal associations. Thus, each outcome should be considered an indicator of risk for the others. Opportunities for joint prevention and intervention, while limited by the polygenic nature of these outcomes, may be feasible considering moderate environmental correlations between SA and SUD.

Introduction

Alcohol and drug use disorders [AUD and DUD, respectively; substance use disorders (SUD) collectively] are strongly associated with the risk of suicidal thoughts and behaviors (Agrawal et al., 2017; Barak-Corren et al., 2017; Conner, Bridge, Davidson, Pilcher, & Brent, 2019; Conner, Duberstein, & Conwell, 1999; Flensborg-Madsen et al., 2009; Hesse, Thylstrup, Seid, & Skogen, 2020; Lynch et al., 2020; Lynskey et al., 2012; Morin et al., 2013; Ostergaard, Nordentoft, & Hjorthoj, 2017; Polimanti et al., 2021; Westman et al., 2015). Both SUD and suicidal behavior represent substantial public health concerns: AUD and DUD account for over $500 billion in annual costs (Birnbaum et al., 2011; Florence, Zhou, Luo, & Xu, 2016; National Drug Intelligence Center, 2011; Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015) and 165 000 annual deaths (Centers for Disease Control and Prevention, 2020; National Institute on Drug Abuse, 2020), while suicide was the 10th overall leading cause of death in the USA in 2018 (Centers for Disease Control and Prevention) and suicide attempts (SA) and suicide deaths (SD) led to an estimated $93.5 billion in annual costs (Shepard, Gurewich, Lwin, Reed, & Silverman, 2016). Clarification of the etiology of these outcomes and the mechanisms underlying their association has the potential to inform treatment and intervention efforts.

The relationship between SUD and suicidal thoughts and behaviors can be due to both causal pathways and non-causal effects such as familial confounders. Using Swedish national registry data, we have previously investigated the association between AUD and SA (Edwards et al., 2021*a*, 2021b) and SD (Edwards, Ohlsson, Sundquist, Sundquist, & Kendler, 2020). Those studies suggested that the observed association among outcomes was

CAMBRIDGE UNIVERSITY PRESS

due in part to shared familial liability as well as a potentially causal pathway (i.e. AUD→SD). Unlike traditional twin-family models, the co-relative approach employed in those studies does not result in heritability or co-heritability estimates. Instead, it extends the cotwin control method (Kendler et al., 1993) to account for confounding familial factors that might jointly influence the risk of two outcomes, one of which is conceptualized as a potential risk factor for the other, thus aiding with causal inference. Further evidence of a causal association was reported by Orri et al. (2020), who used Mendelian randomization and found that lifetime cannabis use may increase the risk for SA, though it should be noted that this finding may not generalize to a clinical outcome such as cannabis use disorder.

A non-mutually exclusive alternative to a causal model for the SUD–suicidality association is that of shared liability: genetic and/or environmental factors that jointly increase the risk for both outcomes. Studies of familial aggregation of SUD and suicidality largely support the role of familial factors in comorbidity (Bridge, Brent, Johnson, & Connolly, 1997; Kim et al., 2005; Roy, 1983, 2000), with some exceptions (Ballard et al., 2019). However, to our knowledge, twin-family studies have not been previously employed to estimate the genetic and environmental correlations between SUD and suicidal behavior. Such an approach would complement previous efforts: (i) it provides direct estimates of genetic and shared environmental correlations; and (ii) it enables the examination of unique (non-shared by family members) environmental correlations, which are not accounted for in co-relative models, studies of familial aggregation, or molecular genetic studies. These factors may be important predictors, as environmental stressors such as divorce (Edwards, Larsson Lonn, Sundquist, Kendler, & Sundquist, 2018; Fjeldsted, Teasdale, Jensen, & Erlangsen, 2017; Kendler, Lonn, Salvatore, Sundquist, & Sundquist, 2017; Roskar et al., 2011) or unemployment (Henkel, 2011; Nordt, Warnke, Seifritz, & Kawohl, 2015) are associated with increased risk of both SUD and suicidality. They could also constitute targets for prevention or intervention, e.g. reducing environmental stressors may help to improve SUD-related consequences and suicidality.

In the current study, we use national Swedish registry data and a twin-family model to investigate the latent genetic and environmental relationships between SUD and suicidality. We have previously reported on shared liability between AUD and DUD in twins born 1958–1991 (Kendler et al., 2016), and found modest but significant outcome-specific genetic and environmental influences; therefore, the current study does not combine these outcomes into a single SUD variable. Similarly, we have reported that SA and SD are etiologically different (Edwards et al., 2021*a*, 2021b; Kendler, Ohlsson, Sundquist, Sundquist, & Edwards, 2020) and should not be collapsed into a single outcome. Our primary analyses focused on non-fatal SA, with additional but less well-powered analyses where SD replaced SA. Given prior evidence that familial factors contribute to co-aggregation of SUD and suicidal behavior, we hypothesized that we would observe moderate to substantial genetic correlations across outcomes. Although previous studies have not directly addressed the extent to which non-familial environmental risk factors jointly contribute to SUD and suicidal behavior, we expected to observe environmental correlations given the existence of plausible shared risk factors. We did not establish hypotheses regarding how suicidal behavior would be differentially etiologically related to AUD *v.* DUD, or whether we would observe differences as a function of suicidal outcome (SA that did not end in death *v.* SD).

Methods

Sample

We collected 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 of Lund University (No. 2008/409, 2010/476, 2012/795, and 2016/679). For the analysis, we double entered from the Swedish Twin Registry all same-sex twin pairs with known zygosity and birth years between 1960 and 1980, and from the Swedish Multi-Generation Register all Swedish-born same-sex full- and half-sibling pairs born between 1960 and 1980 and within 5 years of each other. An individual could be included several times if he/she had several siblings or different type of siblings. Zygosity was assigned using standard self-report items, which, when validated against biological markers, were 95–99% accurate.

Using the Swedish national census and population registers, we assessed cohabitation status for same-sex full- and half-sibling pairs as the proportion of possible years they lived in the same household until the oldest turned 16. Among monozygotic (MZ) and dizygotic (DZ) twins and full siblings, we only included pairs reared together for ⩾80% of their possible years. For half siblings, we included pairs reared together for ⩾80% and pairs reared together ⩽20% of the possible years, classifying these as pairs reared together or apart, respectively (see below for implications within the twin/family model).

Phenotypes

SA, SD, AUD, and DUD were defined at the individual level using information from Swedish population-based registers. The variables were treated as binary, and the registration could occur at any time during the follow-up period. SA were identified using the Swedish Hospital Discharge Register (coverage 1973–2015) and Outpatient Care Register (national coverage 2001–2015). Consistent with NIMH terminology, 'suicide attempt' is used to refer to non-fatal events (National Institutes of Mental Health, 2019). SD were determined using the Swedish Mortality Register (coverage 1969–2016). AUD and DUD were identified using the Swedish Hospital Discharge Register (coverage 1973–2015); Outpatient Care Register (national coverage 2001–2015); Primary Care Registry (partial coverage from 1999 to 2017); the Swedish Drug Register (2005–2017); the Swedish Mortality Register; the Swedish Criminal Register (1973–2017); and the Swedish Suspicion Register (1998–2017). ICD and legal codes for each phenotype are provided in the online Supplementary material.

Statistical analyses

To investigate the latent genetic and environmental relationships between SA, AUD and DUD, we used trivariate twin/sibling modeling, which assumes three sources of liability: additive genetic (A), shared environment (C), and unique environment (E). The model assumes that MZ twins share 100% of their genes; DZ twins and full siblings share, on average, 50% of their genes; while half siblings share, on average, 25% of their genes. The model also assumes that the shared environment, which reflects family and community experiences, is equal between MZ twins,

https://doi.org/10.1017/S0033291721004256 Published online by Cambridge University Press

Table 1. Sample size and prevalence of each outcome by sex and sibling pair type

	Sibling pair type				
	Monozygotic twins	Dizygotic twins	Full siblings	Half siblings reared together	Half siblings reared apart
Sample size and prevalence					
Females					
Number of pairs	4664	3974	348 654	12 440	28 680
Suicide attempt	3.1%	3.5%	3.4%	6.6%	6.7%
Alcohol use disorder	2.6%	2.8%	2.8%	5.9%	5.9%
Drug abuse	1.7%	1.7%	1.9%	4.4%	4.8%
Suicide death	0.2%	0.2%	0.2%	0.4%	0.4%
Males					
Number of pairs	3820	3484	395 308	13 132	32 224
Suicide attempt	2.9%	2.9%	3.2%	6.3%	6.0%
Alcohol use disorder	4.7%	5.8%	6.8%	14.1%	14.2%
Drug abuse	2.7%	2.2%	3.6%	9.0%	9.1%
Suicide death	0.3%	0.3%	0.6%	1.1%	1.0%
Mean (s.d.) age at registration					
Females					
Suicide attempt	26.8 (9.5)	28.4 (9.6)	25.6 (9.4)	24.8 (9.3)	25.5 (89.9)
Alcohol use disorder	31.0 (10.9)	33.7 (11.7)	29.9 (11.2)	29.0 (10.8)	30.5 (11.1)
Drug abuse	31.0 (10.0)	32.1 (10.0)	28.9 (9.5)	28.0 (9.0)	30.2 (9.8)
Suicide death	36.5 (8.6)	29.1 (11.6)	31.7 (10.1)	29.3 (9.0)	30.7 (10.3)
Males					
Suicide attempt	29.5 (8.8)	30.1 (8.8)	28.1 (9.6)	27.4 (9.4)	28.5 (10.3)
Alcohol use disorder	29.9 (10.0)	31.5 (10.9)	28.6 (10.4)	26.6 (9.5)	27.6 (10.2)
Drug abuse	27.2 (7.6)	29.4 (8.3)	26.9 (8.1)	26.6 (7.9)	28.0 (8.5)
Suicide death	32.8 (8.6)	32.8 (8.7)	30.9 (9.2)	31.5 (8.7)	30.9 (9.6)

DZ twins, and full siblings, while for half siblings C equaled 1 for pairs reared together and 0 for pairs reared apart. Finally, the unique environment reflects experiences not shared by twins/siblings, random developmental effects, and random measurement error. The model is based on the idea of an underlying unobserved distribution of liability to SA, AUD, and DUD, measured as binary outcomes. The correlation within each twin/sibling pair corresponds to the proportion of variance explained by the genes (A) and environment (C) they share. Thus, each model yields estimates of the proportion of variance in a given outcome that can be attributed to A (i.e. heritability), C, and E. The model was built using the Cholesky decomposition where the first factor loads on SA, AUD, and DUD, the second loads only on AUD and DUD, while the third only loads on DUD. We replicated the models using SD instead of SA, as prior research indicates that these outcomes do not represent different levels of severity on a single liability continuum (Kendler et al., 2020). In the multivariate context, these models also enable the estimation of genetic and environmental correlations and bivariate variance decomposition between phenotypes (Røysamb & Tambs, 2016). The correlations provide insight to the *degree* of shared liability between outcomes, e.g. the extent to which a shared set of genetic factors jointly impacts the risk of SA and AUD. The bivariate decomposition estimates indicate the *proportion* of the observed phenotypic correlation accounted for by each source of variance. Note that even where two phenotypes exhibit a high genetic correlation, if heritability is low, this will be reflected in a low estimate for A in the bivariate variance decomposition. All analyses were stratified by sex. The OpenMx package (Boker et al., 2020; Neale et al., 2016) was used in R to fit the models.

Results

Descriptive statistics

Table 1 presents the number of pairs and lifetime prevalence of AUD, DUD, and SA, by sibling type (MZ twin, DZ twin, full sibling, half sibling raised together, and half sibling raised apart) and sex. Age at first registration is also included in Table 1. Overall, AUD and DUD were more common among males, while SA was more common among females. The prevalence of all three outcomes was higher among half-siblings.

Figure 1 illustrates tetrachoric correlations within individuals across outcomes, alongside sibling correlations within and across outcomes for each type of sibling pair (see online Supplementary Table S1 for more details). As expected, and

https://doi.org/10.1017/S0033291721004256 Published online by Cambridge University Press

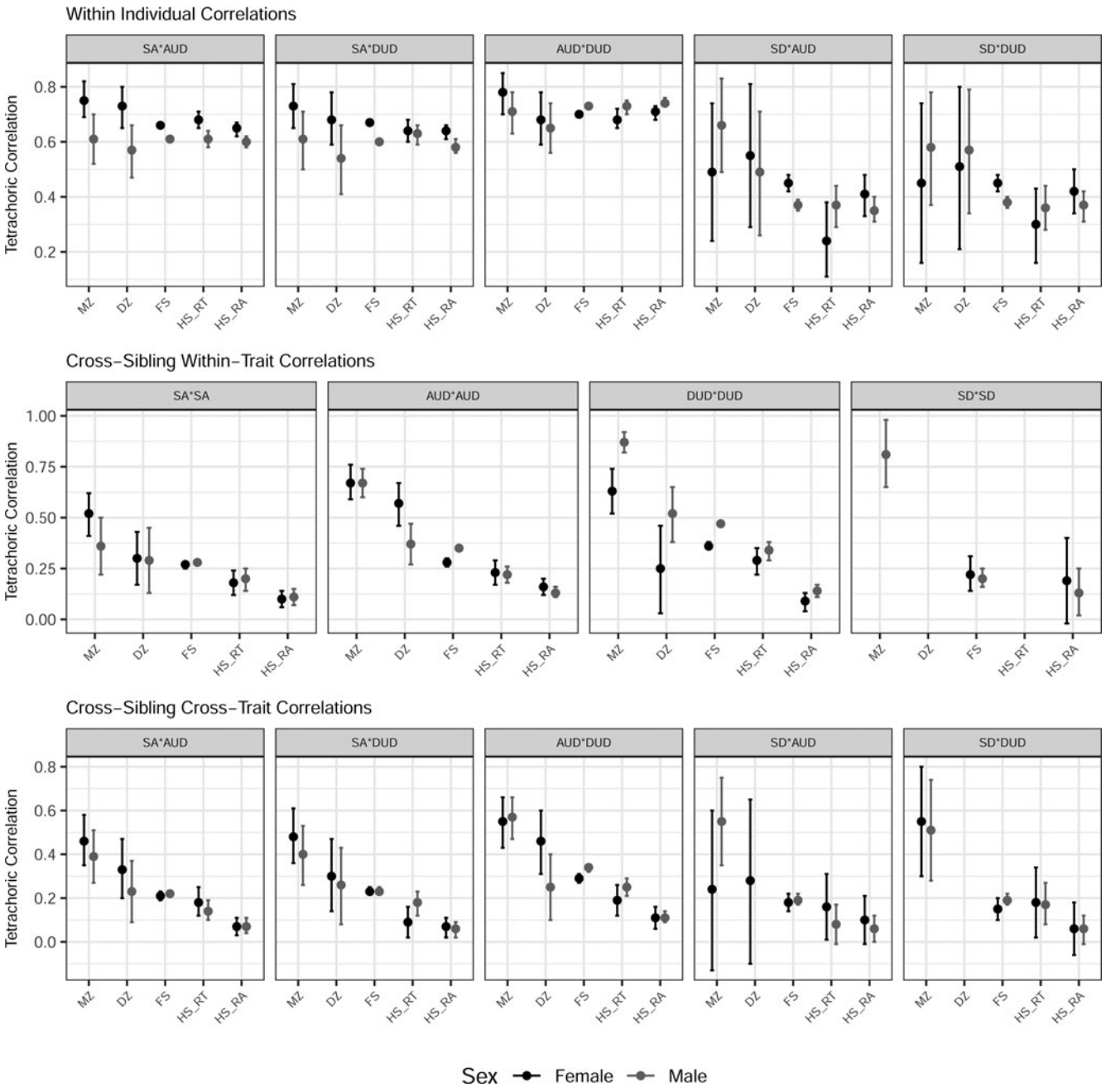

Fig. 1. Tetrachoric phenotypic correlations and 95% confidence intervals, by sex. The top panel illustrates cross-trait correlations within individuals, for each sibling pair group. The center panel illustrates correlations across siblings, within each phenotype. The bottom panel illustrates cross-sibling, cross-trait correlations. Females are depicted in black lines and males in grey lines. For suicide death, data were too sparse to calculate all correlations. Complete correlation results are available in online Supplementary Table S1. SA, suicide attempt; AUD, alcohol use disorder; DUD, drug use disorder; SD, suicide death; MZ, monozygotic twins; DZ, dizygotic twins; FS, full siblings; HS_RT, half siblings reared together; HS_RA, half siblings reared apart.

almost without exception, phenotypic correlations across sibling pairs declined with decreasing degrees of genetic relatedness, suggesting a genetic component to liability for SA, SD, AUD, and DUD.

Univariate twin models

We initially fit univariate models of each outcome in order to derive starting values for trivariate models. Complete results are presented in online Supplementary Table S2 and Figure. Each outcome exhibited modest to moderate heritability for both sexes (A = 0.39–0.59 for women and A = 0.36–0.65 for men). Shared environmental influences were low to modest (C = 0–0.17 for women and C = 0.00–0.15 for men), and the balance was accounted for by unique environmental factors (E = 0.41–0.57 for women and E = 0.20–0.56 for men).

Trivariate twin models

We focus here on trivariate models including SA; see below for parallel analyses where SD replaces SA. We observed slight shifts in some variance component estimates relative to the univariate

https://doi.org/10.1017/S0033291721004256 Published online by Cambridge University Press

Table 2. Variance component and 95% confidence interval estimates from trivariate models

	Females		Males	
	Estimate	95% Confidence intervals	Estimate	95% Confidence intervals
Suicide attempt				
A	0.48	0.40–0.61	0.40	0.38–0.50
C	0.04	0.00–0.23	0.11	0.04–0.15
E	0.48	0.45–0.53	0.49	0.43–0.52
Alcohol use disorder				
A	0.50	0.42–0.53	0.57	0.50–0.62
C	0.03	0.00–0.07	0.06	0.03–0.09
E	0.46	0.44–0.52	0.37	0.34–0.40
Drug use disorder				
A	0.51	0.15–0.59	0.67	0.61–0.72
C	0.09	0.00–0.10	0.16	0.03–0.18
E	0.40	0.19–0.44	0.17	0.17–0.18
Suicide death				
A	0.38	0.09–0.52	0.41	0.23–0.48
C	0.01	0.00–0.12	0.01	0.00–0.08
E	0.62	0.51–0.79	0.58	0.52–0.69

models, likely due to the increased power of the multivariate models. Complete estimates for each variance component are provided in Table 2. Some estimates, particularly those related to suicidal behavior, were imprecise. We elected to avoid subsequent model fitting (i.e. testing whether a specific path could be dropped from the model without a substantial decrement in fit) because we may lack sufficient power to accurately detect important changes. Thus, results from the full model are presented.

Genetic and environmental correlations between outcomes are depicted in Fig. 2 and provided in online Supplementary Table S3. Among women, SA was substantially genetically correlated with both AUD (rA = 0.72) and DUD (rA = 0.88). The corresponding estimates were more moderate among men (rA = 0.60 and rA = 0.62, respectively), though confidence intervals overlapped across sexes for AUD. Shared environmental correlations were moderate to high (rC = 0.42–0.89) and were more pronounced for attempt and AUD than for attempt and DUD among both women and men. However, these influences accounted for little of the total variance for all four outcomes (C = 0.03–0.16) (Table 2). Unique environmental correlations were moderate and were higher between attempt and AUD (rE = 0.56–0.57) than between attempt and DUD (rE = 0.42–0.47).

We performed a parallel analysis replacing SA with SD, as previous studies have found that these outcomes are not completely genetically correlated (Kendler et al., 2020; Mullins et al., 2021) and other etiologic differences may exist (Beautrais, 2001). Potentially notable differences relative to analyses including SA were: (i) a lower rA with DUD among women (rA = 0.59); (ii) among men, a slightly higher rA with AUD (rA = 0.72) and a lower rA with DUD (rA = 0.48); and (iii) within both sexes, a markedly lower rE with both AUD and DUD (rE = −0.01 to 0.31). However, due to the low prevalence of SD (0.2–1.1%), estimates from these analyses lack precision and should be considered with caution. Complete results are available in Fig. 3, Table 2, and online Supplementary Table S3. Online Supplementary Table S4 provides bivariate decomposition estimates.

Discussion

In this population-based study of suicidal behavior and SUD, we found that SA was substantially genetically correlated with both AUD and DUD in both sexes. Environmental factors shared by siblings also jointly influenced liability to SUD and SA, though overall these factors contributed little to total risk. Finally, unique environmental factors – those that do not contribute to sibling similarity – were moderately correlated across SA and SUD. Findings were similar, though with some notable differences, for analyses of SD instead of SA, where data were more sparse and statistical power was reduced. These findings provide critical insight to the etiology of comorbidity between SUD and suicidal behavior.

While SUD have consistently been associated with an increased risk of suicidal behavior (Barak-Corren et al., 2020; Conner & Bagge, 2019; Darvishi, Farhadi, Haghtalab, & Poorolajal, 2015; Edwards et al., 2020; Lynch et al., 2020), discerning the nature of this association has proved challenging. We have previously used co-relative models to examine the association between AUD and SD (Edwards et al., 2020) or SA (Edwards et al., 2021*a*, 2021b), reporting in both cases that familial confounding factors contributed to the association alongside a potentially causal path from AUD to suicidal outcomes. DUD, while not the focus of those studies, were included as covariates and exhibited similar associations. Further evidence of a potentially causal association has been observed using Mendelian randomization: Orri et al. (2020) reported that lifetime cannabis use, but not drinks per week or tobacco use, was causally associated with the risk for SA. The subclinical nature of these predictors may account for differences relative to SUD.

The current findings have potential clinical implications. The first pertains to consideration of family history of psychiatric and SUD. Family history of suicidal behavior is widely recognized among clinicians to be an indicator of risk for one's own suicidal behavior (McDowell, Lineberry, & Bostwick, 2011). The current results suggest that family history may also be informative *across* outcomes – i.e. a family history of suicidal behavior should be considered a risk indicator for SUD, even if the patient themselves has not yet manifested suicidal behavior. We note, however, that family history screening is not without limitations in clinical settings (Khoury, Feero, & Valdez, 2010; Valdez, Yoon, Qureshi, Green, & Khoury, 2010). Second, given the non-trivial environmental correlations between SUD and SA, clinicians treating patients for one outcome should continue to be vigilant about the risk for the other (McDowell et al., 2011). For example, an individual's first SUD registration may represent a key opportunity in the therapeutic process, where environmental stressors that contributed to SUD onset may be evaluated for their potential impact on SA risk.

Comparison to molecular genetic studies

The current study expands on prior research by providing evidence of non-causal associations between SUD and suicidal

https://doi.org/10.1017/S0033291721004256 Published online by Cambridge University Press

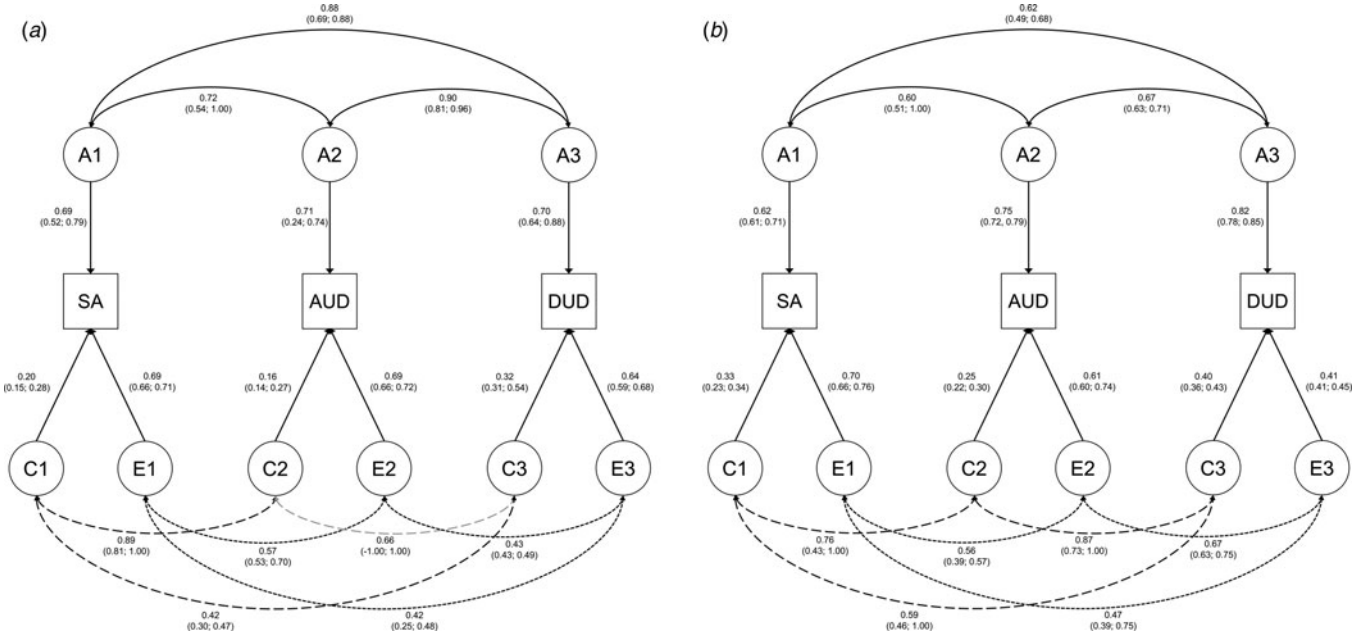

Fig. 2. Parameter estimates (95% confidence intervals) from the correlated factors models of suicide attempt (SA), alcohol use disorder (AUD), and drug use disorder (DUD) in women (panel A) and men (panel B). The sources of variance are additive genetics (A), shared environment (C), and unique environment (E). To facilitate distinction between shared and unique environmental correlation paths, we used dashed lines for the former and dotted lines for the latter. Paths or correlations whose confidence intervals overlap 0 are depicted in grey.

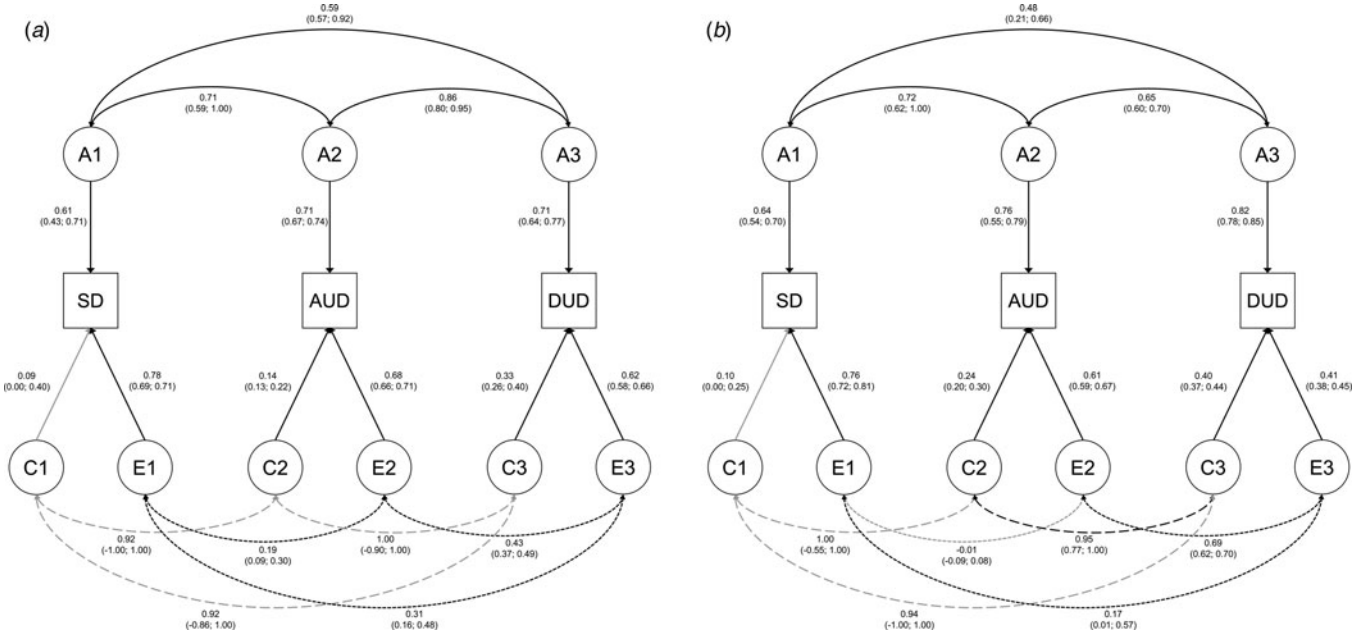

Fig. 3. Parameter estimates (95% confidence intervals) from the correlated factors models of suicide death (SD), alcohol use disorder (AUD), and drug use disorder (DUD) in women (panel A) and men (panel B). The sources of variance are additive genetics (A), shared environment (C), and unique environment (E). To facilitate distinction between shared and unique environmental correlation paths, we used dashed lines for the former and dotted lines for the latter. Paths or correlations whose confidence intervals overlap 0 are depicted in grey.

behavior using biometrical analyses in a large, representative Swedish cohort. Importantly, there is now convergent evidence across methods for a moderate to substantial genetic correlation between SA and AUD: Mullins et al. (2021), using genomewide association study summary statistics, reported a remarkably similar genetic correlation (rA = 0.52–0.63). Colbert et al. (2021) also reported a comparable rA between problematic alcohol use and SA (rA = 0.52), but a considerably lower genetic correlation with SD (rA = 0.34). The discrepancy with the current study's findings for SD (rA = 0.71–0.72) could be due to the

https://doi.org/10.1017/S0033291721004256 Published online by Cambridge University Press

heterogeneity of the phenotypes included in the problematic alcohol use discovery GWAS [i.e. 27.9% of the sample was assessed using the AUDIT-P, which was incompletely genetically correlated with AUD (rA = 0.71)] (Zhou et al., 2020), sample differences (e.g. the Million Veterans Project accounted for >60% of the discovery sample), or other factors.

With respect to DUD, Colbert et al. (2021), also using GWAS summary statistics, reported that the genetic correlations between SA and cannabis use disorder and opioid use disorder were rA~0.6, similar to the male-specific genetic correlation in the current study. As in the Swedish cohort, rA was modestly lower for these two SUD and SD, ranging from 0.33 to 0.53. A SUD common factor, which loaded onto cannabis use disorder, problematic alcohol use, nicotine dependence, and opioid use disorder, was moderately correlated with SA and SD (rA = 0.31–0.46). While sex-specific rA estimates are not available in the above studies (Colbert et al., 2021; Mullins et al., 2021), and rE estimates are not possible using that approach, the overall similarities in genetic findings across methods are encouraging. The current study therefore expands our understanding of sex differences and environmental contributions to risk, yet our findings should be considered tentative until they are replicated in an independent sample.

Comparison of findings across suicide attempt and suicide death

Our primary analyses focused on SA, with additional analyses on SD, where data were sparse. Several differences emerged with respect to the genetic and environmental correlations between SUD and attempt *v.* death. First, while the genetic correlation with AUD was similar for SA and SD for women (rA = 0.71 and 0.72, respectively), rA was modestly higher for SD among men (0.72 *v.* 0.60), though the upper confidence intervals overlapped. DUD was more strongly genetically correlated with SA than SD for both women (rA = 0.88 *v.* 0.59) and men (rA = 0.62 *v.* 0.48). Nevertheless, these estimates indicate that shared genetic liability substantially contributes to comorbidity between suicidal behavior and SUD.

Differences across SA and SD were more pronounced for environmental correlations with SUD. For both AUD and DUD, in both sexes, rE with SA ranged from 0.42 to 0.57 – lower than rA in all cases, yet nontrivial. In contrast, rE with SD ranged from −0.01 to 0.31: For men, the AUD-death rE did not differ from 0. One implication of these findings is that, while specific environmental exposures, such as divorce (Edwards et al., 2018; Fjeldsted et al., 2017; Roskar et al., 2011), unemployment (Henkel, 2011; Nordt et al., 2015), and trauma (Conner et al., 2014; Hughes, McCabe, Wilsnack, West, & Boyd, 2010), have been previously associated with increased risk for both SUD and SD, they may contribute relatively little to comorbidity; alternatively, observed phenotypic associations may involve causal pathways (e.g. divorce→SUD→SD). This is less applicable to SUD and SA, suggesting that some environmental stressors may serve as useful targets for prevention or intervention across SUD and attempt.

Comparison of findings across sexes

We observed both similarities and potentially important differences across women and men, though wide confidence intervals for many correlation estimates suggest that we lack sufficient power to formally test for quantitative sex differences. The following observations should therefore be considered preliminary, warranting further study in other samples. First, the genetic correlation between DUD and SA was substantially higher among women than men (rA = 0.88 *v.* 0.62, respectively; confidence intervals did not overlap). As we did not assess qualitative sex differences, we cannot determine whether these disparate estimates are attributable to the joint impact of different genetic variants across sex (i.e. different variants contribute to comorbidity between DUD and SA in males *v.* females), or whether they reflect cross-trait differences in effect size between the sexes (i.e. a variant has a similar effect on DUD and SA in women but only impacts one of these behaviors in men). Second, the environmental correlation between AUD and SD for women, while somewhat low, was considerably higher than for men (rE = 0.19 *v.* −0.01; confidence intervals did not overlap). As noted above, this has implications for joint prevention and intervention of AUD and SD, which could differ in efficacy across sex. While sex differences in the prevalence of suicidal thoughts and behaviors are well-established (Beautrais, 2001; Nock et al., 2008; Schrijvers, Bollen, & Sabbe, 2012), evidence of sex differences in the association between substance misuse and suicidal behavior, i.e. a modifying effect of sex, is inconsistent (Kittel, Bishop, & Ashrafioun, 2019; Kotila, & Lonnqvist,1988; Oquendo et al., 2007). Our observation that genetic and unique environmental correlations are modestly higher among women suggests that stronger associations might be expected for women than men. However, most confidence intervals overlapped. The extent to which shared genetic liability between SUD and suicidal outcomes contributes to phenotypic sex differences warrants further study, ideally within the context of biopsychosocial models of risk.

Limitations

The current analyses are not without limitations. First, SUD encompass a wide range of drugs (e.g. opioids, stimulants, cannabis), and while we distinguished between AUD and DUD, we did not pursue other substance-specific analyses. Previous research indicates that, while a substantial component of genetic risk for illicit substance use and abuse is attributable to a common factor, substance-specific genetic factors also play a role (Kendler, Jacobson, Prescott, & Neale, 2003) and that genetic correlations with suicidal behavior might vary across substances (Colbert et al., 2021). Second, our use of national registry data results in prevalences of AUD, DUD, and SA that are lower than typically observed in studies utilizing self-reports. We are likely to be identifying more severe cases of SUD and primarily medically serious SA. It is possible that this impacts variance component and correlation estimates; ideally, these models should be replicated in a sample assessed via self-report. This concern is somewhat offset by the likelihood that our findings apply to a group of SUD cases who may interface more with health care providers due to the severity of their disorder, thereby presenting opportunities for suicide risk assessment and intervention. Third, SUD and suicidal behaviors are influenced by a constellation of factors that impact other psychiatric outcomes (e.g. depression). The current analyses do not explicitly incorporate these other outcomes, which could result in attenuated estimates of genetic and environmental correlations that are specific to SUD and suicidal behavior. Finally, while parameter estimates and 95% confidence intervals are suggestive of sex differences, technical features of our analysis, including the use of likelihood-based confidence intervals, make formal tests difficult. However, in a multi-group modeling context, constraining parameters to be equal across the sexes resulted in a

https://doi.org/10.1017/S0033291721004256 Published online by Cambridge University Press

detriment to model fit (LRT = 66 096, df = 30, $p < 0.0001$ for the SA-AUD-DUD model; LRT = 51 390, df = 30, $p < 0.0001$ for the SD-AUD-DUD model), providing support for stratification by sex as presented above.

Conclusions

The current study provides empirical evidence of modest to substantial genetic and environmental correlations between SUD and suicidal behavior using a representative Swedish national cohort. In conjunction with prior research, these findings indicate that phenotypic associations among these outcomes are due to a combination of shared liability and causal relationships. Differences in the genetic and environmental correlations across AUD and DUD with SA *v.* SD, and across sexes, underscore the complexities of shared etiology. Awareness of the substantial common genetic liability may be clinically useful, for example, by encouraging health care providers to provide educational materials about the risk of suicidal behavior to individuals seeking care for SUD or those with a family history of SUD; however, given the highly polygenic nature of both suicidal behaviors and SUD, opportunities for personalized genomics are not feasible. In addition, interventions predicated on perceived shared environmental risks, such as divorce, may be more effective for SA and SUD than SD and SUD.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721004256.

Financial support. The current study was supported by NIH grants AA027522, AA023534, and DA030005; and by Swedish Research Council and ALF funding from Region Skåne, Sweden. We acknowledge The Swedish Twin Registry for access to data. The Swedish Twin Registry is managed by Karolinska Institutet, Stockholm, Sweden.

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.

References

Agrawal, A., Tillman, R., Grucza, R. A., Nelson, E. C., McCutcheon, V. V., Few, L., … Bucholz, K. K. (2017). Reciprocal relationships between substance use and disorders and suicidal ideation and suicide attempts in the collaborative study of the genetics of alcoholism. *Journal of Affective Disorders*, *213*, 96–104. doi: 10.1016/j.jad.2016.12.060

Ballard, E. D., Cui, L., Vandeleur, C., Castelao, E., Zarate, C. A. Jr., Preisig, M., & Merikangas, K. R. (2019). Familial aggregation and coaggregation of suicide attempts and comorbid mental disorders in adults. *JAMA Psychiatry*, *76*(8), 826–833. doi:10.1001/jamapsychiatry.2019.0248

Barak-Corren, Y., Castro, V. M., Javitt, S., Hoffnagle, A. G., Dai, Y., Perlis, R. H., … Reis, B. Y. (2017). Predicting suicidal behavior from longitudinal electronic health records. *American Journal of Psychiatry*, *174*(2), 154–162. doi: 10.1176/appi.ajp.2016.16010077

Barak-Corren, Y., Castro, V. M., Nock, M. K., Mandl, K. D., Madsen, E. M., Seiger, A., … Smoller, J. W. (2020). Validation of an electronic health record-based suicide risk prediction modeling approach across multiple health care systems. *JAMA Network Open*, *3*(3), e201262. doi: 10.1001/jamanetworkopen.2020.1262

Beautrais, A. L. (2001). Suicides and serious suicide attempts: Two populations or one? *Psychological Medicine*, *31*(5), 837–845. doi: 10.1017/s0033291701003889

Birnbaum, H. G., White, A. G., Schiller, M., Waldman, T., Cleveland, J. M., & Roland, C. L. (2011). Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Medicine*, *12*(4), 657–667. doi: 10.1111/j.1526-4637.2011.01075.x

Boker, S., Neale, M., Maes, H., Wilde, M., Spiegel, M., Brick, T., … Niesen, J. (2020). OpenMx 2.18.1 User Guide. In.

Bridge, J. A., Brent, D., Johnson, B. A., & Connolly, J. (1997). Familial aggregation of psychiatric disorders in a community sample of adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(5), 628–636. doi: 10.1097/00004583-199705000-00013

Centers for Disease Control and Prevention. Web-based injury statistics query and reporting system (WISQARS) [online]. www.cdc.gov/injury/wisqars.

Centers for Disease Control and Prevention (2020). Annual average for United States 2011–2015 alcohol-attributable deaths due to excessive alcohol use, all ages (alcohol and public health: alcohol-related disease impact (ARDI), issue. https://nccd.cdc.gov/DPH_ARDI/Default/Default.aspx.

Colbert, S. M. C., Hatoum, A. S., Shabalin, A., Coon, H., Nelson, E. C., Agrawal, A., … Johnson, E. C. (2021). Exploring the genetic overlap of suicide-related behaviors and substance use disorders. medRxiv, 2021.2004.2005.21254944. doi:10.1101/2021.04.05.21254944.

Conner, K. R., & Bagge, C. L. (2019). Suicidal behavior: Links between alcohol use disorder and acute use of alcohol. *Alcohol Research*, *40*(1). doi: 10.35946/arcr.v40.1.02

Conner, K. R., Bossarte, R. M., He, H., Arora, J., Lu, N., Tu, X. M., & Katz, I. R. (2014). Posttraumatic stress disorder and suicide in 5.9 million individuals receiving care in the veterans health administration health system. *Journal of Affective Disorders*, *166*, 1–5. doi: 10.1016/j.jad.2014.04.067

Conner, K. R., Bridge, J. A., Davidson, D. J., Pilcher, C., & Brent, D. A. (2019). Metaanalysis of mood and substance use disorders in proximal risk for suicide deaths. *Suicide and Life-Threatening Behavior*, *49*(1), 278–292. doi: 10.1111/sltb.12422

Conner, K. R., Duberstein, P. R., & Conwell, Y. (1999). Age-related patterns of factors associated with completed suicide in men with alcohol dependence. *American Journal on Addictions*, *8*(4), 312–318. doi: 10.1080/105504999305712

Darvishi, N., Farhadi, M., Haghtalab, T., & Poorolajal, J. (2015). Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: A meta-analysis. *PLoS ONE*, *10*(5), e0126870. doi: 10.1371/journal.pone.0126870

Edwards, A. C., Larsson Lonn, S., Sundquist, J., Kendler, K. S., & Sundquist, K. (2018). Associations between divorce and onset of drug abuse in a Swedish national sample. *American Journal of Epidemiology*, *187*(5), 1010–1018. doi: 10.1093/aje/kwx321

Edwards, A. C., Ohlsson, H., Moscicki, E., Crump, C., Sundquist, J., Kendler, K. S., & Sundquist, K. (2021a). Alcohol use disorder and non-fatal suicide attempt: Findings from a Swedish national cohort study. *Addiction*. doi: 10.1111/add.15621

Edwards, A. C., Ohlsson, H., Moscicki, E. K., Crump, C., Sundquist, J., Lichtenstein, P., … Sundquist, K. (2021b). On the genetic and environmental relationship between suicide attempt and death by suicide. *American Journal of Psychiatry*, *178*(11), 1060–1069. https://doi.org/10.1176/appi.ajp.2020.20121705

Edwards, A. C., Ohlsson, H., Sundquist, J., Sundquist, K., & Kendler, K. S. (2020). Alcohol use disorder and risk of suicide in a Swedish population-based cohort. *American Journal of Psychiatry*, *177*(7), 627–634. doi: 10.1176/appi.ajp.2019.19070673

Fjeldsted, R., Teasdale, T. W., Jensen, M., & Erlangsen, A. (2017). Suicide in relation to the experience of stressful life events: A population-based study. *Archives of Suicide Research*, *21*(4), 544–555. doi: 10.1080/13811118.2016.1259596

Flensborg-Madsen, T., Knop, J., Mortensen, E. L., Becker, U., Sher, L., & Gronbaek, M. (2009). Alcohol use disorders increase the risk of completed suicide – irrespective of other psychiatric disorders. A longitudinal cohort study. *Psychiatry Research*, *167*(1–2), 123–130. doi: 10.1016/j.psychres.2008.01.008

Florence, C. S., Zhou, C., Luo, F., & Xu, L. (2016). The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. *Medical Care*, *54*(10), 901–906. doi: 10.1097/MLR.0000000000000625

Henkel, D. (2011). Unemployment and substance use: A review of the literature (1990–2010). *Current Drug Abuse Reviews*, *4*(1), 4–27. doi: 10.2174/1874473711104010004

Hesse, M., Thylstrup, B., Seid, A. K., & Skogen, J. C. (2020). Suicide among people treated for drug use disorders: A Danish national

record-linkage study. *BMC Public Health*, *20*(1), 146. doi: 10.1186/s12889-020-8261-4

Hughes, T., McCabe, S. E., Wilsnack, S. C., West, B. T., & Boyd, C. J. (2010). Victimization and substance use disorders in a national sample of heterosexual and sexual minority women and men. *Addiction*, *105*(12), 2130–2140. doi: 10.1111/j.1360-0443.2010.03088.x

Kendler, K. S., Jacobson, K. C., Prescott, C. A., & Neale, M. C. (2003). Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *American Journal of Psychiatry*, *160*(4), 687–695. doi: 10.1176/appi.ajp.160.4.687

Kendler, K. S., Lonn, S. L., Maes, H. H., Lichtenstein, P., Sundquist, J., & Sundquist, K. (2016). A Swedish population-based multivariate twin study of externalizing disorders. *Behavior Genetics*, *46*(2), 183–192. doi: 10.1007/s10519-015-9741-7

Kendler, K. S., Lonn, S. L., Salvatore, J., Sundquist, J., & Sundquist, K. (2017). Divorce and the onset of alcohol use disorder: A Swedish population-based longitudinal cohort and co-relative study. *American Journal of Psychiatry*, *174*(5), 451–458. doi: 10.1176/appi.ajp.2016.16050589

Kendler, K. S., Neale, M. C., MacLean, C. J., Heath, A. C., Eaves, L. J., & Kessler, R. C. (1993). Smoking and major depression. A causal analysis. *Archives of General Psychiatry*, *50*(1), 36–43. doi: 10.1001/archpsyc.1993.01820130038007

Kendler, K. S., Ohlsson, H., Sundquist, J., Sundquist, K., & Edwards, A. C. (2020). The sources of parent-child transmission of risk for suicide attempt and deaths by suicide in Swedish national samples. *American Journal of Psychiatry*, *177*(10), 928–935. doi: 10.1176/appi.ajp.2020.20010017

Khoury, M. J., Feero, W. G., & Valdez, R. (2010). Family history and personal genomics as tools for improving health in an era of evidence-based medicine. *American Journal of Preventive Medicine*, *39*(2), 184–188. doi: 10.1016/j.amepre.2010.03.019

Kim, C. D., Seguin, M., Therrien, N., Riopel, G., Chawky, N., Lesage, A. D., & Turecki, G. (2005). Familial aggregation of suicidal behavior: A family study of male suicide completers from the general population. *American Journal of Psychiatry*, *162*(5), 1017–1019. doi: 10.1176/appi.ajp.162.5.1017

Kittel, J. A., Bishop, T. M., & Ashrafioun, L. (2019). Sex differences in binge drinking and suicide attempts in a nationally representative sample. *General Hospital Psychiatry*, *60*, 6–11. https://doi.org/10.1016/j.genhosppsych.2019.06.011

Kotila, L., & Lonnqvist, J. (1988). Adolescent suicide attempts: sex differences predicting suicide. *Acta Psychiatrica Scandinavica*, *77*(3), 264–270. https://doi.org/10.1111/j.1600-0447.1988.tb05119.x

Lynch, F. L., Peterson, E. L., Lu, C. Y., Hu, Y., Rossom, R. C., Waitzfelder, B. E., … Ahmedani, B. K. (2020). Substance use disorders and risk of suicide in a general US population: A case control study. *Addiction Science & Clinical Practice*, *15*(1), 14. doi: 10.1186/s13722-020-0181-1

Lynskey, M. T., Agrawal, A., Henders, A., Nelson, E. C., Madden, P. A., & Martin, N. G. (2012). An Australian twin study of cannabis and other illicit drug use and misuse, and other psychopathology. *Twin Research and Human Genetics*, *15*(5), 631–641. doi: 10.1017/thg.2012.41

McDowell, A. K., Lineberry, T. W., & Bostwick, J. M. (2011). Practical suicide-risk management for the busy primary care physician. *Mayo Clinic Proceedings*, *86*(8), 792–800. doi: 10.4065/mcp.2011.0076

Morin, J., Wiktorsson, S., Marlow, T., Olesen, P. J., Skoog, I., & Waern, M. (2013). Alcohol use disorder in elderly suicide attempters: A comparison study. *American Journal of Geriatric Psychiatry*, *21*(2), 196–203. doi: 10.1016/j.jagp.2012.10.020

Mullins, N., Kang, J., Campos, A. I., Coleman, J. R. I., Edwards, A. C., Galfalvy, H., … Ruderfer, D. M. (2021). Dissecting the shared genetic architecture of suicide attempt, psychiatric disorders and known risk factors. *Biological Psychiatry*. doi: https://doi.org/10.1016/j.biopsych.2021.05.029

National Drug Intelligence Center (2011). National drug threat assessment.

National Institute on Drug Abuse (2020). Overdose death rates. National Institute on Drug Abuse. Retrieved 3/17/2021 from https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates.

National Institutes of Mental Health (2019). Suicide. National Institutes of Mental Health, Office of Science Policy, Planning, and Communications. Retrieved 04/25/2021 from https://www.nimh.nih.gov/health/statistics/suicide.shtml.

Neale, M. C., Hunter, M. D., Pritikin, J. N., Zahery, M., Brick, T. R., Kirkpatrick, R. M., … Boker, S. M. (2016). OpenMx 2.0: Extended structural equation and statistical modeling. *Psychometrika*, *81*(2), 535–549. doi: 10.1007/s11336-014-9435-8

Nock, M. K., Borges, G., Bromet, E. J., Alonso, J., Angermeyer, M., Beautrais, A., … Williams, D. (2008). Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *British Journal of Psychiatry*, *192*(2), 98–105. doi: 10.1192/bjp.bp.107.040113

Nordt, C., Warnke, I., Seifritz, E., & Kawohl, W. (2015). Modelling suicide and unemployment: A longitudinal analysis covering 63 countries, 2000–11. *The Lancet Psychiatry*, *2*(3), 239–245. doi: 10.1016/s2215-0366(14)00118-7

Oquendo, M. A., Bongiovi-Garcia, M. E., Galfalvy, H., Goldberg, P. H., Grunebaum, M. F., Burke, A. K., & Mann, J. J. (2007). Sex differences in clinical predictors of suicidal acts after major depression: a prospective study. *American Journal of Psychiatry*, *164*(1), 134–141. https://doi.org/10.1176/ajp.2007.164.1.134

Orri, M., Seguin, J. R., Castellanos-Ryan, N., Tremblay, R. E., Cote, S. M., Turecki, G., & Geoffroy, M. C. (2020). A genetically informed study on the association of cannabis, alcohol, and tobacco smoking with suicide attempt. *Molecular Psychiatry*. doi: 10.1038/s41380-020-0785-6

Ostergaard, M. L. D., Nordentoft, M., & Hjorthoj, C. (2017). Associations between substance use disorders and suicide or suicide attempts in people with mental illness: A Danish nation-wide, prospective, register-based study of patients diagnosed with schizophrenia, bipolar disorder, unipolar depression or personality disorder. *Addiction*, *112*(7), 1250–1259. doi: 10.1111/add.13788

Polimanti, R., Levey, D. F., Pathak, G. A., Wendt, F. R., Nunez, Y. Z., Ursano, R. J., … Gelernter, J. (2021). Multi-environment gene interactions linked to the interplay between polysubstance dependence and suicidality. *Translational Psychiatry*, *11*(1), 34. doi: 10.1038/s41398-020-01153-1

Roskar, S., Podlesek, A., Kuzmanic, M., Demsar, L. O., Zaletel, M., & Marusic, A. (2011). Suicide risk and its relationship to change in marital status. *Crisis*, *32*(1), 24–30. doi: 10.1027/0227-5910/a000054

Roy, A. (1983). Family history of suicide. *Archives of General Psychiatry*, *40*(9), 971–974. doi: 10.1001/archpsyc.1983.01790080053007

Roy, A. (2000). Relation of family history of suicide to suicide attempts in alcoholics. *American Journal of Psychiatry*, *157*(12), 2050–2051. doi: 10.1176/appi.ajp.157.12.2050

Røysamb, E., & Tambs, K. (2016). The beauty, logic and limitations of twin studies. *Norsk Epidemiologi*, *26*(1–2). doi: 10.5324/nje.v26i1-2.2014

Sacks, J. J., Gonzales, K. R., Bouchery, E. E., Tomedi, L. E., & Brewer, R. D. (2015). 2010 National and state costs of excessive alcohol consumption. *American Journal of Preventive Medicine*, *49*(5), e73–e79. doi: 10.1016/j.amepre.2015.05.031

Schrijvers, D. L., Bollen, J., & Sabbe, B. G. (2012). The gender paradox in suicidal behavior and its impact on the suicidal process. *Journal of Affective Disorders*, *138*(1–2), 19–26. doi: 10.1016/j.jad.2011.03.050

Shepard, D. S., Gurewich, D., Lwin, A. K., Reed, G. A. Jr., & Silverman, M. M. (2016). Suicide and suicidal attempts in the United States: Costs and policy implications. *Suicide and Life-Threatening Behavior*, *46*(3), 352–362. 10.1111/sltb.12225

Valdez, R., Yoon, P. W., Qureshi, N., Green, R. F., & Khoury, M. J. (2010). Family history in public health practice: A genomic tool for disease prevention and health promotion. *Annual Review of Public Health*, *31*(1), 69–87 61 *p* following 87. doi:10.1146/annurev.publhealth.012809.103621

Westman, J., Wahlbeck, K., Laursen, T. M., Gissler, M., Nordentoft, M., Hallgren, J., … Osby, U. (2015). Mortality and life expectancy of people with alcohol use disorder in Denmark, Finland and Sweden. *Acta Psychiatrica Scandinavica*, *131*(4), 297–306. doi: 10.1111/acps.12330

Zhou, H., Sealock, J. M., Sanchez-Roige, S., Clarke, T. K., Levey, D. F., Cheng, Z., … Gelernter, J. (2020). Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. *Nature Neuroscience*, *23*(7), 809–818. doi: 10.1038/s41593-020-0643-5