On the Genetic and Environmental Relationship Between Suicide Attempt and Death by Suicide

Alexis C. Edwards, Ph.D., Henrik Ohlsson, Ph.D., Eve Mościcki, Sc.D., M.P.H., Casey Crump, M.D., Ph.D., Jan Sundquist, M.D., Ph.D., Paul Lichtenstein, Ph.D., Kenneth S. Kendler, M.D., Kristina Sundquist, M.D., Ph.D.

Objective: The authors examined the extent to which the genetic and environmental etiology of suicide attempt and suicide death is shared or unique.

Methods: The authors used Swedish national registry data for a large cohort of twins, full siblings, and half siblings (N=1,314,990) born between 1960 and 1990 and followed through 2015. They conducted twin-family modeling of suicide attempt and suicide death to estimate heritability for each outcome, along with genetic and environmental correlations between them. They further assessed the relationship between suicide attempt by young people compared with adults.

Results: In bivariate models, suicide attempt and death were moderately heritable among both women (attempt: additive genetic variance component [A]=0.52, 95% CI=0.44, 0.56; death: A=0.45, 95% CI=0.39, 0.59) and men (attempt: A=0.41, 95% CI=0.38, 0.49; death: A=0.44, 95% CI=0.43, 0.44). The outcomes were substantially, but incompletely, genetically correlated (women: rA=0.67, 95% CI=0.55, 0.67; men: rA=0.74, 95% CI=0.63, 0.87). Environmental correlations were weaker (women: rE=0.36, 95% CI=0.29, 0.45; men: rE=0.21, 95% CI=0.19, 0.27). Heritability of suicide attempt was stronger among people ages 10−24 (A=0.55−0.62) than among those age 25 and older (A=0.36−0.38), and the genetic correlation between attempt during youth and during adulthood was stronger for women (rA=0.79, 95% CI=0.72, 0.79) than for men (rA=0.39, 95% CI=0.26, 0.47).

Conclusions: The genetic and environmental etiologies of suicide attempt and death are partially overlapping, exhibit modest sex differences, and shift across the life course. These differences must be considered when developing prevention efforts and risk prediction algorithms. Where feasible, suicide attempt and death should be considered separately rather than collapsed, including in the context of gene identification efforts.

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Suicidal behavior, which includes nonfatal suicide attempts and death by suicide, is a significant public health concern. Suicide accounts for approximately 800,000 deaths per year worldwide (1), and nonfatal attempts are estimated to be up to 30 times more common than suicide deaths (2). A prior attempt is one of the most prominent predictors of future death by suicide (3, 4), and 4%−7% of individuals with a history of self-harm die by suicide in the ensuing 5–9 years (5, 6). While suicide death is more common among men, women attempt more often (7). Furthermore, while attempts and suicide death share many predictors (8), there is some evidence that certain predictors are differentially associated with these two outcomes (9). For example, suicide attempts are more common among women and youths, while deaths are more common among men and adults (10). In addition, social isolation and anxiety disorders are associated more strongly with suicide attempts than with death (10). Clarification of common versus distinct contributions to etiology may improve the ability to assess risk and thereby inform prevention and intervention efforts.

Previous studies have revealed familial clustering and a modest to moderate heritable component to suicidal behavior (11–16), including recent efforts to identify specific genetic variants associated with risk (17–19). While many such studies have limited their analyses to one outcome (e.g., suicide death), others have collapsed manifestations of suicidality (e.g., ideation, attempt, death) into one variable using inconsistent approaches (20–23). Results from such studies may be driven by only one contributing measure (e.g., ideation), potentially obscuring important differences in the genetic underpinnings of different suicidal outcomes. Twin-family studies with a single outcome of interest have reported heritability estimates of 0.17–0.55 for suicide attempt (24–26) and 0.43 for suicide death (27), although, as noted previously (28), limited sample sizes contribute to widely varying heritability estimates. Some analyses have been further complicated by sample selection, precluding generalization to the overall population—for example, where participants are ascertained on the basis of a prior personal or family history of suicidal behavior (21, 29) or a specific psychiatric disorder (17, 23, 30). Notably, Erlangsen et al. (31) found that adjusting for psychiatric comorbidity reduced the single-nucleotide polymorphism (SNP) heritability (h^2_{SNP}) of suicide attempt from 0.05 to 0.02. Based on findings from a recent study of suicide attempt within psychiatric disorders, h^2_{SNP} also varies as a function of the disorder in question—for example, from 0.03 within major depressive disorder to 0.10 within schizophrenia (17). Recent support for classifying suicidal behavior as a distinct mental disorder (32) suggests that viewing suicidal behavior primarily through the lens of psychiatric illness has important limitations.

Efforts to directly compare the etiology of suicide attempt and death are difficult where longitudinal data on both outcomes are not available for a large, representative sample, such as when samples are selected as described above. Furthermore, the relatively low prevalence of suicide attempts and, in particular, suicide deaths has impeded efforts to obtain reliable heritability estimates for these outcomes because of inadequate statistical power. In the near term, these constraints mean that molecular genetic studies are unlikely to be able to elucidate shared versus outcome-specific aspects of etiology. Accordingly, it is necessary to employ other methodologic approaches to this important area of research.

In this study, we leveraged Swedish national registry data, including the recent addition of primary care data, to evaluate the genetic relationship between suicide attempts and death by suicide. While previous reports have employed substantial sample sizes to study familial aggregation of suicidal behavior (11–13), the present study is, to our knowledge, the largest to date that applies formal twin-family modeling, particularly with the goal of estimating genetic and environmental correlations between suicide attempt and death. We previously demonstrated (33) that these outcomes should be treated independently: A liability threshold model, in which attempt and death lie on the same continuum of risk and differ only as a function of severity, does not fit the data well.

We expand on those efforts here by conducting an extended twin-family model of liability to suicide attempt and death. Our use of nationwide registry data, with a high degree of completeness due to universal health care, yields a representative and statistically powerful sample. Given previous evidence of sex differences in the heritability of psychiatric and substance use outcomes (34–36), we also benefit from this large sample by modeling sources of variance separately by sex. The longitudinal nature of the data further enables us to test whether genetic and environmental influences on suicide attempt are stable or dynamic from youth (here, ages 10–24) into adulthood (age 25 and older), which may be relevant given shifts in the heritability of both internalizing and externalizing symptoms across the life course (37).

METHODS

Sample

We collected information on individuals from Swedish population-based mortality, inpatient, and outpatient registers (38) with national coverage linking each person's unique personal identification number, which Statistics Sweden replaced with a serial number to preserve confidentiality. We secured ethical approval from the Regional Ethical Review Board of Lund University (no. 2008/409, 2012/795, and 2016/679). We double-entered all same-sex twin pairs with known zygosity and birth years between 1960 and 1990 from the Swedish Twin Registry, and all Swedish-born same-sex full and half sibling pairs born between 1960 and 1990, and within 5 years of each other, from the Swedish Multi-Generation Register. This cohort was selected to optimize data coverage across time and sample size. An individual could be included several times if he or she had several siblings or different types of siblings; note that this could result in narrowed confidence intervals, but it did not substantively affect variance component estimates. Zygosity was assigned using standard self-report items, which, when validated against DNA markers, were 95%–99% accurate.

Using the Swedish national census and population registers, we assessed cohabitation status for full and half sibling pairs as the proportion of possible years they lived in the same household until the oldest turned 16. Among monozygotic and dizygotic twins and full siblings, we included only pairs who were reared together for ≥80% of their possible years. Half siblings who resided together for ≥80% of the possible years were classified as having been reared together. Those who resided together for ≤20% of the possible years were classified as having been reared apart. See below for implications within the twin-family model.

Phenotypes

The following ICD codes were used to identify suicide attempts and deaths of both known and undetermined intent: ICD-8 codes E950–E959 and E980–987; ICD-9 codes E950–E959 and E980–987; and ICD-10 codes X60–X84 and Y10–Y34. Distinctions between suicide death and nonfatal attempts, where necessary, were determined using the Cause of Death Register. Previous studies have provided support for the inclusion of events of undetermined intent (39, 40), with one reporting that excluding these cases would result in approximately 25% of true suicide attempts being misclassified (40). Suicide attempt and suicide death were treated as binary, and the registration for either outcome (i.e., the date that the ICD code was entered into the medical registry) could occur at any time during the follow-up period, which began when individuals turned 10 and ended in December 2015. Note that an individual could be registered for both suicide attempt and suicide death.

Statistical Analysis

We used classical bivariate twin/sibling modeling, which assumes three sources of liability to nonfatal suicide attempts and death by suicide: additive genetic (A), shared environment (C), and unique environment (E). The model assumes that monozygotic twins share 100% of their genes; dizygotic twins and full siblings share, on average, 50% of their genes; and 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 monozygotic twins, dizygotic twins, and full siblings, while for half siblings, C is equal to 1 for pairs reared together and 0 for pairs reared apart. Finally, the unique environment reflects experiences not shared by siblings, random developmental effects, and random measurement error.

The model is based on the idea of an unobserved distribution of liability underlying each of the two binary outcomes, nonfatal suicide attempt and death by suicide. The correlation within each twin or sibling pair corresponds to the proportion of variance explained by the genes (A) and environment (C) they share. The bivariate model was built using the Cholesky decomposition, where the first factor loads on both suicide attempts and death by suicide, and the second loads only on the latter. Based on results from the univariate ACE models of suicide attempts and death by suicide, we restricted the bivariate model by setting the two C paths to death by suicide to 0. All analyses were separated by sex. The OpenMx software package (41, 42) was used to fit the models.

We conducted a sensitivity analysis in which events of undetermined intent were excluded to account for the possibility that they affected estimates in the primary analysis. ICD-8 and ICD-9 codes corresponding to events of undetermined intent are E980–E987; for ICD-10, the codes are Y10–Y34. A total of 18,436 suicide attempts and 1,063 suicide deaths were excluded in these analyses, corresponding to 42.4% and 25.6% of all attempts and deaths, respectively.

In a secondary analysis, we estimated the genetic and environmental correlations between suicide attempt during youth and adulthood, using the World Health Organization's age range for "young people"—ages 10–24 (43). We selected this age range to capture neurodevelopment of the prefrontal cortex, which persists into the early 20s (44, 45) and may be particularly relevant to impulsive behavior (46, 47), including suicidality (48). We imposed a restriction on the data to avoid misclassifying persistent suicidal behavior toward the end of the earlier developmental period as "adult": Those with a suicide attempt at age 24 were censored for 1 year, such that additional attempts occurring during that year (into age 25) were not counted. Beyond that yearlong censoring period, subsequent attempt registrations were classified as adult attempts. We identified 916 individuals with attempt at age 24 and within the subsequent year; of these, 443 had an additional attempt at a later time and were coded as attempting as a young person and as an adult, while the remaining 473 were classified as attempting only as a young person. We lacked sufficient statistical power to conduct a corresponding analysis of suicide death.

RESULTS

Table 1 provides details on the number of pairs for each relative group (monozygotic or dizygotic twins, full siblings, and half siblings) that contributed to the analyses and corresponding descriptive statistics. The total sample size was 1,314,990. A total of 21,664 women and 21,854 men attempted suicide, and 1,048 women and 3,109 men died by suicide. Suicide attempts were more common among women ($p<0.0001$), while death by suicide was more common among men ($p<0.0001$). Individuals with half siblings exhibited higher rates of both suicide attempts and deaths compared with twins or full siblings.

Among individuals with a prior suicide attempt, 2.1% (N=457) of women and 3.9% (N=846) of men died by suicide during the observation period. Among individuals who died by suicide, 56.0% (N=581) of women and 72.6% (N=2,250) of men had no known prior attempt. The median interval between first attempt and suicide death was 4 years (quartile 1=1, quartile 3=10) for women and 3 years (quartile 1=1, quartile 3=8) for men.

Tetrachoric correlations (used for binary data such as diagnostic status) within and across outcomes, both within individuals and across members of the sibling pairs, are reported in Table 1. In general, correlations were higher for full siblings (including monozygotic and dizygotic twin pairs) than for half siblings, although estimates were imprecise for some correlations. The low prevalence of suicide death prevented us from estimating sibling correlations for some groups. The correlation patterns suggest that genetic factors contribute to resemblance across siblings.

Univariate Twin and Family Models

We first fitted standard ACE models for suicide attempt and suicide death separately, stratified by sex. Variance component estimates are presented in Table 2. Heritability estimates (A) were moderate for both outcomes. We observed low but significant contributions from shared environmental factors for suicide attempt but not death, although the latter could be a false negative finding in light of a relatively limited number of suicide deaths. We therefore elected to specify an ACE structure for attempt and an AE structure for suicide death in subsequent models.

Bivariate Twin and Family Models

Final parameter estimates from the bivariate model of suicide attempt and death by suicide are presented in Figure 1, and variance components are presented in Table 2. We tested whether thresholds for both outcomes for each sibling group, plus genetic and shared environment path estimates, could be equated across men and women, and they could not ($\Delta\chi^2=4973.8$, $\Delta df=15$, $p<0.0001$). The genetic correlation (rA) between suicide attempt and death was 0.67 (95% CI=0.55, 0.67) for women and 0.74 (95% CI=0.63, 0.87) for men. The environmental correlation (rE), attributable to environmental experiences not shared by siblings, was 0.36 (95%

TABLE 1. Descriptive statistics for sibling pairs born in Sweden between 1960 and 1990 in a study of suicide attempt and suicide death[a]

Measure	Monozygotic Twins			Dizygotic Twins			Full Siblings			Half Siblings Reared Together			Half Siblings Reared Apart		
Women															
	Pairs (N)	Suicide attempt (%)	Suicide death (%)	Pairs (N)	Suicide attempt (%)	Suicide death (%)	Pairs (N)	Suicide attempt (%)	Suicide death (%)	Pairs (N)	Suicide attempt (%)	Suicide death (%)	Pairs (N)	Suicide attempt (%)	Suicide death (%)
	3,186	3.2	0.2	2,570	3.5	0.2	275,668	3.7	0.2	9,828	6.5	0.4	19,166	7.1	0.4
	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Age at suicidal event (years)															
Suicide attempt	24	19	32	26	20	35	23	18	31	22	17	30	22	17	32
Suicide death	39	35	42	26.5	20	33.5	30	23	39	27	23	34.5	28	23	38
	r_{tet}	95% CI		r_{tet}	95% CI		r_{tet}	95% CI		r_{tet}	95% CI		r_{tet}	95% CI	
Tetrachoric correlations															
Suicide attempt between siblings	0.57	0.49, 0.65		0.25	0.13, 0.27		0.28	0.27, 0.29		0.17	0.12, 0.21		0.12	0.09, 0.15	
Suicide death between siblings	n/a	n/a		n/a	n/a		0.25	0.18, 0.32		n/a	n/a		0.17	−0.03, 0.37	
Within-sibling suicide attempt and suicide death	0.50	0.28, 0.73		0.47	0.21, 0.73		0.52	0.50, 0.54		0.45	0.36, 0.54		0.43	0.37, 0.50	
Between-sibling suicide attempt and suicide death	0.33	0.04, 0.61		0.21	−0.15, 0.57		0.16	0.12, 0.19		0.15	0.02, 0.27		0.01	−0.09, 0.11	
Men															
	Pairs (N)	Suicide attempt (%)	Suicide death (%)	Pairs (N)	Suicide attempt (%)	Suicide death (%)	Pairs (N)	Suicide attempt (%)	Suicide death (%)	Pairs (N)	Suicide attempt (%)	Suicide death (%)	Pairs (N)	Suicide attempt (%)	Suicide death (%)
	2,646	3.2	0.3	2,294	3.0	0.4	310,569	3.4	0.5	10,138	6.5	0.9	21,430	6.3	0.9
	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Age at suicidal event (years)															
Suicide attempt	28	22	35	28.5	23	35	26	20	34	26	20	33	26	20	35
Suicide death	31	26	36	29.5	26	39	29	23	37	29	24	38	29	23	37
	r_{tet}	95% CI		r_{tet}	95% CI		r_{tet}	95% CI		r_{tet}	95% CI		r_{tet}	95% CI	
Tetrachoric correlations															
Suicide attempt between siblings	0.41	0.30, 0.52		0.29	0.16, 0.43		0.30	0.29, 0.31		0.19	0.15, 0.24		0.12	0.09, 0.16	
Suicide death between siblings	0.83	0.69, 0.96		n/a	n/a		0.20	0.17, 0.24		0.14	−0.02, 0.30		0.12	0.01, 0.23	
Within-sibling suicide attempt and suicide death	0.45	0.25, 0.66		0.60	0.43, 0.76		0.44	0.42, 0.45		0.36	0.29, 0.43		0.38	0.33, 0.43	
Between-sibling suicide attempt and suicide death	0.23	−0.04, 0.50		0.23	−0.04, 0.51		0.15	0.13, 0.18		0.13	0.04, 0.22		0.09	0.02, 0.15	

[a] Individuals may belong to more than one sibling pair. Q1 and Q3=first and third quartiles; r_{tet}=tetrachoric correlation; n/a=not applicable because of sample size.

CI=0.29, 0.45) for women and 0.21 (95% CI=0.19, 0.27) for men.

Sensitivity Analysis

To determine whether parameter estimates were heavily influenced by attempts and deaths of undetermined intent, we conducted a sensitivity analysis excluding those registrations (18,436 suicide attempts and 1,063 suicide deaths). Among women, 15.0% of attempts and 12.5% of deaths were excluded; for men, 30.8% of attempts and 12.6% of deaths were excluded. Variance component estimates changed little for women, and confidence intervals overlapped those in the primary analysis (Table 3). Similarly, rA and rE were comparable to the respective estimates from the primary analysis (sensitivity analysis results: rA=0.71, 95% CI=0.71, 0.87; rE=0.36, 95% CI=0.34, 0.46). For men, exclusion of these events resulted in a lower heritability estimate for suicide attempt, and confidence intervals did not overlap those from the primary analysis. Estimates for suicide death were less affected by the exclusion of these events. The genetic

TABLE 2. Variance components from univariate and bivariate twin-family modeling results in a study of suicide attempt and suicide death[a]

	Univariate Analyses				Bivariate Analyses			
	Women		Men		Women		Men	
Measure	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Suicide attempt								
A	0.50	0.42, 0.54	0.41	0.32, 0.49	0.52	0.44, 0.56	0.41	0.38, 0.49
C	0.03	0.01, 0.03	0.09	0.06, 0.12	0.02	0.00, 0.06	0.09	0.09, 0.12
E	0.47	0.43, 0.51	0.50	0.45, 0.55	0.46	0.44, 0.46	0.50	0.50, 0.50
Suicide death								
A	0.47	0.36, 0.61	0.45	0.32, 0.53	0.45	0.39, 0.59	0.44	0.43, 0.44
C	0.01	0.00, 0.27	0.00	0.00, 0.06	—	—	—	—
E	0.52	0.39, 0.80	0.55	0.47, 0.63	0.55	0.42, 0.67	0.56	0.50, 0.57

[a] A=additive genetic variance component (heritability); C=common/shared environment variance component; E=unshared environment variance component.

and environmental correlations across attempts and suicide death were modestly increased but with overlapping confidence intervals (rA=0.86, 95% CI=0.86, 1.00; rE=0.25, 95% CI=0.2, −0.26). Parameter estimates could not be equated across sex ($\Delta\chi^2$=9667.8, Δdf=15, p<0.0001).

Secondary Analysis of Suicide Attempt as Young Person and/or Adult

We identified 20,893 individuals with an attempt between ages 10 and 24, and 22,625 individuals with an attempt after age 24. A total of 2,752 individuals had attempts during both periods, of whom 58% were women and 42% were men. Results of bivariate twin-family models are presented in Table 4. Heritability estimates were higher for attempt as a young person than as an adult for both sexes. The genetic correlation (rA) between nonfatal attempt as a young person and as an adult was higher among women than among men, and the Olkin-Pratt test for homogeneity of rA across sexes was significant (Q=28.2, df=1, p<0.0001). The shared environmental correlation (rC) between young and adult attempt was in opposite directions across sexes; however, C accounted for very little of the total variance, making substantive interpretation of these disparate estimates difficult.

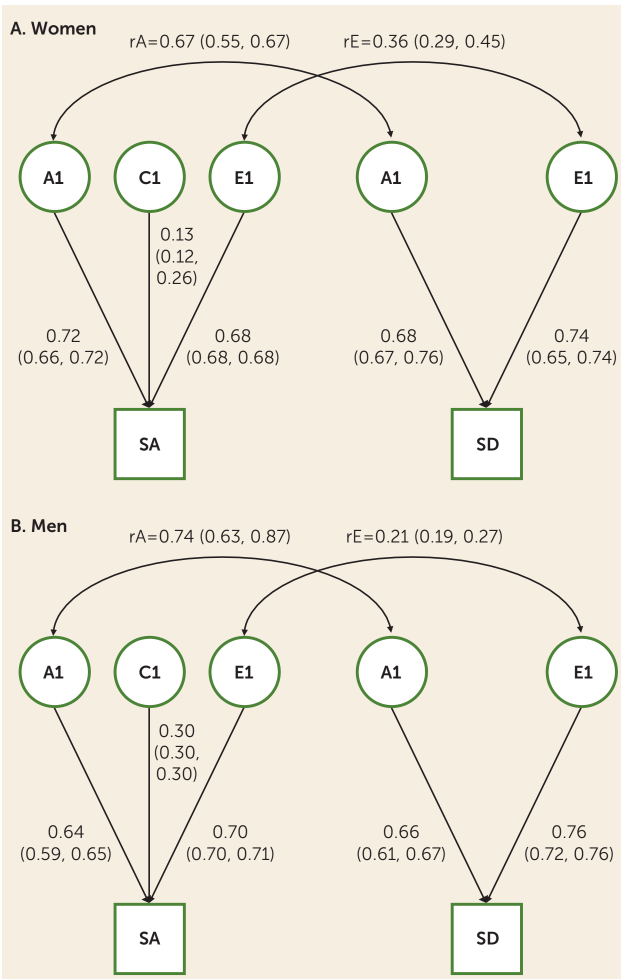
DISCUSSION

Our primary research aim in this study was to quantify the genetic relationship between suicide attempts and death by suicide using a representative national Swedish cohort. We found that attempts and suicide death were moderately heritable, with estimates from our twin-family approach (A=0.41–0.52) considerably higher than those from molecular genetic studies (h^2_{SNP}=0.03 for suicide attempt [17]; h^2_{SNP}=0.16 for suicide death [19]), as is common across these different methodological approaches in part because of limited sample sizes and the inclusion of only common variants in the latter (49, 50). These outcomes are substantially genetically correlated (rA=0.67 for women and rA=0.74 for men), while the unique environmental correlation was more modest (rE=0.36 for women and rE=0.21 for men). Our findings support previous evidence that the etiologies of suicide attempt and suicide death are incompletely overlapping and may thus present distinct opportunities for prevention. In a secondary analysis, we found that the genetic factors contributing to risk of suicide attempt are potentially dynamic across the life course, underscoring the complex roles of biology and development in suicidality.

In conjunction with our previous study (33), which found that the genetic distinction between suicide attempt and death was not merely one of severity of liability, our results have implications for studies aimed at the identification of genetic risk variants for suicidal behavior. Genome-wide association studies (GWASs) that collapse attempt and death are unable to distinguish whether implicated variants or genes have outcome-specific effects or contribute to liability to both. This prevents dissection of differences in the biological etiologies of attempt and death, which may hinder prevention efforts. These complications could be extended to apply to suicidal ideation and nonsuicidal self-injury: Previous evidence suggests that these outcomes are at least partially etiologically distinct from suicide attempts and/or death (51–55), although a recent study revealed strong genetic and unique environmental correlations (rA=0.94 and rE=0.80) in a sample of British twins (56). These outcomes have also been conceptualized as lying on a continuum of self-harm (20). Recent analytic advances that decompose genetic variance into that which is common across outcomes and that which is outcome specific (57–59) may avoid these shortfalls once genotyped samples of sufficient size are available.

In addition, our findings underscore the relevance of evaluating family history of suicidal behaviors. Stigma about suicidal behavior persists even among family members and medical personnel (60, 61), which may lead individuals to feel uncomfortable disclosing their own or their family members' history. This is turn may prevent health care providers from fully appreciating patients' risk, particularly if suicide attempts, which are more readily concealed from family members, are not disclosed. Clinicians should also be aware of both continuity of risk across the life course and the relevance of life stage–specific influences; that is, the impact of environmental

FIGURE 1. Parameter and correlation estimates from the bivariate twin-family model of nonfatal suicide attempt and suicide death for women and men[a]



[a] SA=nonfatal suicide attempt; SD=suicide death; 95% confidence intervals are indicated in parentheses. The sources of variance are additive genetic factors (A), common environmental factors (C; attempt only), and unique environmental factors (E).

exposures experienced during adolescence may persist and be augmented by exposures experienced during adulthood.

We previously reported, in an extended adoption design in Sweden, evidence for substantial environmental transmission of suicide attempt liability from parents to offspring (33), whereas the present study found only a small contribution from the shared environment. These seemingly disparate findings are likely due in part to the different questions posed by these studies—parent-offspring "vertical" transmission of risk versus "horizontal" transmission between siblings close in age. Different, but potentially overlapping, aspects of the environment are captured across these methods. For example, the "shared environment" of the present study includes school and neighborhood-level exposures outside the home, while the "environment" of our previous study includes parenting behaviors that may differ across offspring (e.g., discipline, warmth). We have shown elsewhere (62), using empirical estimates of twin-twin and parent-child correlations for major dimensions of parenting, that the correlation in liability among twins for typical psychiatric phenotypes due to shared parenting would range from 2% to 4%, consistent with the findings of the present study.

The modest environmental correlations between suicide attempt and death, which reflect exposures not shared by family members, indicate that extrinsic factors differentially affect risk for these outcomes. One study found that most environmental factors examined, including low income and exposure to stressful legal, interpersonal, and work-related events, increased risk for both attempts and death (10). However, other factors had outcome-specific effects: A poor parental relationship during childhood was associated with suicide but not with serious attempts, while social isolation was associated with attempt and not death. Another study found that gun availability—that is, access to a high-lethality method—was related to suicide death but not attempt (9); gun ownership may also be a proxy for other risk factors, such as adult antisocial behavior and exposure to violent crime (63). The dearth of studies that examine risk factors for both suicide attempt and death within the same sample—thereby enabling direct comparisons—precludes a nuanced interpretation of the modest environmental correlations we observed. This is a critical deficit in our understanding of the etiology of these outcomes, as it affects risk prediction and prevention. Environmental exposures, in contrast to genetic variants, are potentially modifiable risk factors, but our findings reveal that environmental factors affecting risk for both suicide attempt and death represent an incomplete portrait of prevention targets.

Our secondary analysis examining suicide attempt across young people and adults addresses research questions that have not, to our knowledge, been tested previously: To what extent do genetic factors differentially contribute to risk of suicide attempt across the life course, and is there incomplete overlap of genetic factors across time? We observed that the heritability of suicide attempt was considerably higher among young people, particularly for women (confidence intervals overlapped for men across time). This raises the possibility that temperament and/or psychopathology—that is, intrinsic factors of considerable heritability—may play a more prominent role among young people than adults. In contrast, the variance in liability accounted for by unique environmental factors during adulthood suggests that adverse life experiences are more potent risk factors for suicide attempt among adults. The shared environmental correlation (rC) estimates differed markedly across sexes. These factors accounted for little of the total variance in risk (C=0.01–0.1) and the rC estimate was imprecise among women; substantive interpretation of the rC estimates is therefore not feasible.

Another key finding from the secondary analysis is the considerable sex difference in the genetic correlation between attempts among young people compared with adults (women:

TABLE 3. Variance components from bivariate twin-family modeling results where events of undetermined intent were excluded from the analysis, in a study of suicide attempt and suicide death[a]

Measure	Women		Men	
	Estimate	95% CI	Estimate	95% CI
Suicide attempt				
A	0.55	0.55, 0.56	0.35	0.30, 0.35
C	0.00	0.00, 0.00	0.06	0.06, 0.06
E	0.44	0.42, 0.47	0.59	0.59, 0.62
Suicide death				
A	0.46	0.32, 0.61	0.44	0.44, 0.52
C	—	—	—	—
E	0.54	0.40, 0.68	0.56	0.48, 0.61

[a] A=additive genetic variance component (heritability); C=common/shared environment variance component; E=unshared environment variance component.

rA=0.79, 95% CI=0.72, 0.79; men; rA=0.39, 95% CI=0.26, 0.47). This indicates that, among women, continuity of risk across the life course is due largely to genetic factors whose impact persists across time. In contrast, for men, liability toward suicide attempt in adulthood is more strongly influenced by a qualitatively different facet of genetic influences than were relevant earlier in life. Similar to our findings on the genetic correlation between suicide attempt and death, the results of our secondary analysis have implications for gene identification studies. The higher heritability of attempts among young people may facilitate GWASs (64) relative to studies in adults; however, restricting a GWAS study to only young people is not an ideal solution given the advantages of maximizing sample size. Instead, age at attempt could be included as a covariate along with an interaction term between age and genetic variant.

There are several limitations to these analyses. First, we were reliant on ICD codes for suicide attempts and were therefore unable to detect attempts that did not require medical attention or were not otherwise reported to a health care provider, of which there may be a considerable number (7). Accordingly, our data likely capture more severe suicide attempts, which may be more closely related to suicide deaths than attempts overall. We were also reliant on the quality and consistency of the coding process (65, 66). We were able to identify only one study that obtained self-reports of self-harm in a sample for which institutional records (medical registrations) were also available (67), which found incomplete overlap between sources; however, the small sample precludes generalization to other studies. Previous evidence indicates that individuals hospitalized for self-harm may be less likely to complete a self-report survey (67), and the rate of refusal to participate is higher for nonanonymous surveys (68). These factors would likely lead to underestimation of suicide attempt prevalence as assessed via self-report. Such estimates vary widely—for example, from 2.7% to 14% (68–70). The limitations of our use of registry records may therefore be offset by the reliability of these records.

Although these findings are representative of the Swedish population, they may not be generalizable to populations in other countries. Until relatively recently, Sweden's annual suicide rate was consistently higher than that of the United States, and it became comparable at approximately 12 per 100,000 in the period 2007–2009. Since 2010, the U.S. rate has increased while Sweden's rate has remained stable (71). Our secondary analyses expose potentially important shifts in the etiology of suicide attempt across the life course, including those related to environmental exposures, which may differ markedly across countries and cultures. We also note that our selection of cohort, which maximized available registry data, did not include elderly individuals.

Consistent with other studies (40, 72), we included events of

TABLE 4. Variance components from bivariate twin-family modeling results of suicide attempt among young people ages 10–24 and adults age 25 and older[a]

Measure	Women		Men	
	Estimate	95% CI	Estimate	95% CI
Young people				
A	0.62	0.59, 0.65	0.55	0.44, 0.65
C	0.01	0.00, 0.02	0.07	0.05, 0.07
E	0.37	0.35, 0.41	0.38	0.37, 0.42
Adults				
A	0.36	0.30, 0.42	0.38	0.37, 0.44
C	0.09	0.09, 0.09	0.10	0.10, 0.10
E	0.55	0.52, 0.55	0.52	0.49, 0.55
Correlations between young people and adults	Correlation	95% CI	Correlation	95% CI
rA	0.79	0.72, 0.79	0.39	0.26, 0.47
rC	−0.88	−1.00, 0.00	0.99	0.95, 1.00
rE	0.17	0.17, 0.17	0.22	0.16, 0.26

[a] A=additive genetic variance component (heritability); C=common/shared environment variance component; E=unshared environment variance component; rA=genetic correlation; rC=common/shared environmental correlation; rE=unshared environmental correlation.

undetermined intent in our primary analyses. Our sensitivity analysis excluding those events resulted in shifts in estimates, particularly for suicide attempt among men. While some previous evidence suggests that events of undetermined intent include suicides that would otherwise be undetected (73, 74), the conservative approach is to regard the variance component and correlation estimates from our primary and sensitivity analyses as the bounds within which the "true" estimates fall.

Our models do not account for psychiatric disorders, which are genetically related to suicidal behavior (17). This limitation is offset by the insight provided by the present approach to the genetic and environmental influences on suicidal behavior in the general population. Indeed, the majority of those with registrations for suicide attempt (70.7%) or death (51.3%) did not have a prior registration for a major psychiatric disorder.

Although we demonstrated shifts in suicide attempt heritability, and a genetic correlation <1, across development, our analyses did not otherwise account for the potential effect of age. Given previous evidence of age, period, and cohort effects on suicidal behavior (75–77), additional research is warranted.

CONCLUSIONS

Suicide attempt and death are moderately heritable and are substantially—but not completely—genetically correlated. In conjunction with modest environmental correlations, our findings speak to partially distinct etiologies, raising the likelihood of incompletely overlapping opportunities for prevention and risk prediction. Furthermore, as demonstrated by our analysis of suicide attempt across young people and adults, both genetic and environmental influences on risk are temporally dynamic, particularly among men. Efforts to reduce risk of suicidal behavior must therefore consider sex differences and shifts across the life course, and gene identification efforts would benefit from distinguishing between suicide attempts and suicide deaths.

AUTHOR AND ARTICLE INFORMATION

Department of Psychiatry, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University School of Medicine, Richmond (Edwards, Kendler); Center for Primary Health Care Research, Lund University, Malmö, Sweden (Ohlsson, J. Sundquist, K. Sundquist); Department of Family Medicine and Community Health and Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York (Crump, J. Sundquist, K. Sundquist); Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm (Lichtenstein); independent researcher (Mościcki).

Send correspondence to Dr. Edwards (alexis.edwards@vcuhealth.org).

Dr. Kendler and Dr. K. Sundquist are joint senior authors.

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