Familial Liability for Eating Disorders and Suicide Attempts: Evidence From a Population Registry in Sweden.

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Abstract

Importance: Suicide attempts are common in individuals with eating disorders. More precise understanding of the mechanisms underlying their co-occurrence is needed.

Objective: To examine the association between eating disorders and suicide attempts and whether familial risk factors contribute to the association.

Design: A cohort design following a Swedish birth cohort 1979-2001 from age 6 until 31/12/2009.

Setting: Information was acquired from Swedish national registers.

Participants: Individuals born 1979-2001 and living in Sweden before age 6 (N= 2,268,786) were eligible for the study. Each individual was linked to his/her biological full-siblings, maternal half-siblings, paternal half-siblings, full-cousins, and half-cousins.

Eating disorders were captured by three variables: any eating disorder, anorexia nervosa (AN), and bulimia nervosa (BN), identified by any lifetime diagnoses recorded in the registers.

Suicide attempts were defined as any suicide attempts, including death by suicide, recorded in the registers. We examined the association between eating disorders and death by suicide separately, but were underpowered to explore familial liability for this association.

Results: Individuals with any eating disorder had increased risk of suicide attempts (OR=5.28, 95%CI [5.04, 5.54]) and death by suicide (OR=5.39, 95%CI [4.00, 7.25]). The risks attenuated but remained significant after adjusting for comorbid major depressive disorder, anxiety disorders, and substance use disorder. Similar results were found for AN and BN, except

that adjusted OR of death by suicide in BN became insignificant, possibly due to insufficient power. Individuals (index) who had a full-sibling with any eating disorder had increased risk of suicide attempts (OR=1.41, 95%CI [1.29, 1.53]). The risk attenuated for any eating disorder in more distant relatives (maternal half-siblings, OR=1.10, 95%CI [0.90, 1.34]; paternal half-siblings, OR=1.21, 95%CI [0.98, 1.49]; full-cousins, OR=1.11, 95%CI [1.06, 1.18]; half-cousins, OR=0.90, 95%CI [0.78, 1.03]). This familial pattern remained stable after adjusting for the index individuals' eating disorders. Similar patterns were found for AN and BN.

Conclusions and Relevance: Our results suggest increased risk of suicide attempts in individuals with lifetime eating disorders and their relatives. The pattern of familial co-aggregation suggests familial liability for the association between eating disorders and suicide. Psychiatric comorbidities partially explain this association, suggesting particularly high-risk presentations.

Introduction

Eating disorders, including anorexia nervosa (AN) and bulimia nervosa (BN), are severe psychiatric disorders with peak onset during adolescence and early adulthood.[1] They are associated with high premature mortality,[2] including elevated risk of suicide.[3-5] Based on meta-analyses, roughly 1 out of 5 premature deaths in AN patients was due to suicide;[2] suicide-specific standardized mortality ratios in AN and BN were estimated to be 18.1[4] and 7.5 respectively.[3] However, studies included in the meta-analyses reported considerably varied estimates, possibly due to differences in follow-up time, source, sample size, and representativeness of the samples.[2,3,6] Large population based studies are essential to provide more reliable estimates of the risk of suicide in individuals with eating disorders.

The mechanism underlying the association between eating disorders and suicide attempts remains unclear. Few studies have been adequately powered to explore the influence of psychiatric comorbidities on the association,[2] although major depressive disorder (MDD), anxiety disorders (ANX), and substance use disorder (SUD) have been associated with both eating disorders and suicide attempts.[7-10] Evaluating the influence of psychiatric comorbidities on the elevated suicide risk in eating disorders can elucidate the etiology of suicide attempts in individuals with eating disorders and inform clinical decision-making in suicide prevention.

Both eating disorders and suicide attempts aggregate in families;[11,12] however, their co-aggregation in families has not been thoroughly explored, with the exception of investigations of the effect of family history of a range of psychiatric disorders on suicide.[13,14] Genetically informative designs, such as comparison of the co-aggregation of disorders across relatives with different degrees of relatedness, can shed light on the extent to which familial risk factors influence the association between eating disorders and suicide attempts.[15,16]

Using a genetically informative design and population data from Swedish national registers we 1) estimated the association between eating disorders and suicide attempts, before and after accounting for the effect of psychiatric comorbidities, and 2) investigated the extent to which familial risk factors contributed to the association.

Method

The study was approved by the regional ethical review board in Stockholm, Sweden (DNR 2009/939-31/5 and 2010/1258-31/5).

Study population and Swedish national registers

The study population included individuals born between 1979 and 2001 and living in Sweden before age 6 who had both biological parents identifiable in the population registers; adopted individuals were excluded (yielding 2,268,786 individuals, 51.4% males). We followed up the study population until 31/12/2009, when the youngest individuals were 8 years old and the oldest individuals were 30 years old. Using unique personal identification numbers, we linked several Swedish registers.[17] We obtained birth year and sex from the Total Population Register (Statistics Sweden). We linked individuals to their biological parents using the Multi-Generation Register.[18] Immigration and emigration were obtained from the Migration Register (Statistics Sweden). From the National Patient Register (NPR; National Board of Health and Welfare) we obtained records of psychiatric inpatient (since 1973) and outpatient (since 2001) contacts from across Sweden. Discharge diagnoses were recorded according to the Swedish versions of the *International Classification of Diseases, Eighth Revision* (ICD-8; 1973-1986), *Ninth Revision* (ICD-9; 1987-1996), and *Tenth Revision* (ICD-10; 1997-present).[19] From the Swedish National

Quality Assurances Register for Specialized Eating Disorder Treatment (RIKSÄT, since 1999) and the Internet-based quality assurance system for eating disorders (Stepwise, since 2005) we obtained eating disorder diagnoses from across Sweden.[20,21] The coverage of the quality registers (RIKSÄT and Stepwise) increased over time.[22] Diagnoses in both quality registers were coded based on the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV),[23] and individuals were registered once intent to treat was established. We acquired causes of death coded according to ICD 8-10 from the Cause of Death Register (the National Board of Health and Welfare).

Identification of families and relatives

Using the Multi-Generation Register, we identified five cohorts of biological relatives representing decreasing levels of shared genetic and environmental relatedness: full-siblings, maternal half-siblings, paternal half-siblings, full-cousins, and half-cousins (offspring whose parents are half-siblings). Family identification numbers linked the relatives together and were used to statistically control for non-independence within the data.

Eating disorders

Based on lifetime diagnoses of eating disorders in NPR and the quality registers, we defined three analytic sets which were not mutually exclusive: 1) any eating disorder, defined as ICD-9 codes 307B or 307F and ICD-10 codes F50.0, F50.1, F50.2, F50.3, or F50.9 in NPR, or meeting DSM-IV criteria for eating disorders (AN, atypical AN, BN, atypical BN, or eating disorders not otherwise specified) in the quality registers; 2) AN, defined as any diagnosis of AN or atypical AN, identified with ICD-9 code 307B and ICD-10 codes F50.0 or F50.1 in NPR, or meeting DSM-IV criteria for AN or atypical AN in the quality registers (other lifetime eating disorders could be presented); and 3) BN, defined as any diagnosis of BN or atypical BN,

identified with ICD-10 codes F50.2 or F50.3 in NPR, or meeting DSM-IV criteria for BN or atypical BN in the quality registers (other lifetime eating disorders could be presented). The period of BN diagnosis was shorter than that of any eating disorders and AN because BN was not an independent eating disorder category in the Swedish versions of ICD before ICD-10.[24]

Suicide attempts

Suicide attempts were defined as any suicide attempt reported in NPR or death by suicide reported in the Cause of Death Register, based on ICD-9 codes E950-E959, E980-E989 and ICD-10 codes X60-X84, or Y10-Y34.[16] We examined the association between eating disorders and death by suicide separately, but were underpowered to explore familial liability for this association.

Comorbid psychiatric disorders

Psychiatric comorbidities were identified from NPR and included MDD (ICD-9: 296.3, 300.4, or 311; ICD-10: F32-F39, except F34.0), ANX (ICD-9: 300, 300.09, or 300.29; ICD-10: F40-F41), and SUD (ICD-9: 303-304, 305.0, or 305.9; ICD-10: F10-F16, or F18-F19).[25]

Statistical analyses

1. The association between eating disorders and suicide attempts

We applied a cohort design to evaluate the association between eating disorders and suicide attempts; results are presented as odds ratios (ORs). We first fitted logistic regressions to the total population (adjusted for sex), and to females and males separately, to obtain crude ORs. We then adjusted the models for psychiatric comorbidities to obtain adjusted ORs. In all models we adjusted for birth year, and used a robust (sandwich) estimator of standard errors to account

for non-independence due to familial clustering.[26] We analyzed death by suicide as a separate outcome.

2. Familial liability for the association

To explore the extent to which familial risk factors contribute to the association between eating disorders and suicide attempts, we fitted a logistic model in each of the five relative cohorts to estimate the ORs of suicide attempts in individuals who had at least one relative in the cohort with an eating disorder compared to individuals whose relative(s) in the cohort did not have the eating disorder. A significantly increased OR (i.e., an increased risk of suicide attempts in people who had at least one relative with an eating disorder compared to those whose relatives did not) suggests that familial risk factors shared among relatives contribute to the association between eating disorders and suicide attempts. Further, a higher OR in full-siblings than in maternal half-siblings suggests that genetic factors are operative because the two types of siblings are assumed to share similar family environment, whereas full-siblings are more genetically similar than maternal half-siblings. A higher OR in maternal half-siblings than in paternal half-siblings suggests that family environmental factors are operative because the two types of half-siblings have equivalent genetic sharing, whereas maternal half-siblings are assumed to share more family environment than paternal half-siblings because children are more often reared with their mothers after parental divorce.[15,16,27] In each model we adjusted for birth year, sex, and number of relatives in the specific cohort, and used a robust (sandwich) estimator of standard errors to account for non-independence due to familial clustering.

Sensitivity analysis

In each of the five relative cohorts, we repeated the analyses adjusting for eating disorders in the index individual (the individual from whom we acquired information on suicide attempts and relatives' eating disorders). If the ORs remained significant after adjustment, the contribution of common familial risk factors to eating disorders and suicide attempts would be further supported (explained in a directed acyclic graph, eFigure 1).[28] We also adjusted for MDD, ANX, and SUD in index individuals and in relatives to further test if the comorbidities relate to the familial liability.

Data management was performed using SAS 9.3; analyses were performed using Stata 13.0.

Results

Descriptive statistics

More females than males presented with a lifetime history of eating disorders (Table 1). Specifically, 15,457 females (1.40% of all females) and 991 males (0.09% of all males) had any eating disorder; 7,680 females (0.70%) and 453 males (0.04%) had AN; and 3,349 females (0.30%) and 61 males (0.01%) had BN. In both sexes, the prevalence of suicide attempts and psychiatric comorbidities were higher in individuals with eating disorders than in those without eating disorders.

Table 1 about here

The association between eating disorders and suicide attempts

Individuals with any eating disorder had increased risk of suicide attempts (OR=5.28, 95% confidence interval (95%CI) [5.04, 5.54]) and death by suicide (OR=5.39, 95%CI [4.00, 7.25]) (Table 2). The associations remained significant even after adjusting for comorbid MDD, ANX, and SUD (OR=1.82, 95%CI [1.72, 1.93] for suicide attempts; OR=2.04, 95%CI [1.49, 2.80] for death by suicide). Although risk of suicide attempts remained elevated after adjustment, adjustment for each comorbid disorder decreased the magnitude of the effect, with the greatest reduction associated with MDD followed by ANX and SUD (eTable 1). Similar patterns were found for AN and BN in both sexes, except that the adjusted OR of death by suicide in BN became insignificant, possibly due to power. BN presented stronger crude associations with suicide attempts than AN; AN presented slightly stronger crude associations with death by suicide than BN.

Table 2 about here

We did not find support for sex difference in the association between eating disorders and suicide. Results of tests of interaction between sex and eating disorders are shown in eTable 2.

Familial liability for the association

As we did not find support for sex difference in the association between eating disorders and suicide attempts (eTable 2), we collapsed (and adjusted for) sex to increase power in analyses addressing familial liability for the association (Table 3). The risk of suicide attempts was significantly increased in individuals with any full-sibling with any eating disorder compared to those without full-siblings with any eating disorder in the full-sibling cohort (OR=1.41, 95%CI [1.29, 1.53]). The risk was also increased in individuals with any full-cousin with any eating disorder compared to those without full-cousins with any eating disorder in the full-cousin cohort

(OR=1.11, 95%CI [1.06, 1.18]). These results suggest that familial risk factors underlie the association between eating disorders and suicide attempts. The OR in full-siblings was higher than that in full-cousins, further supporting the importance of familial risk factors in accounting for the association. We did not detect significant ORs in half-siblings. Similar patterns were observed for individuals with relatives with AN (full-siblings, OR=1.21, 95%CI [1.06, 1.37]; full-cousins, OR=1.13, 95%CI [1.04, 1.22]) and individuals with relatives with BN (full-siblings, OR=1.56, 95%CI [1.31, 1.86]; full-cousins, OR=1.20, 95%CI [1.07, 1.34]) (Table 3). For any eating disorder, the OR in full-siblings was slightly higher than the OR in maternal half-siblings (p=.024), suggesting that some common familial risk factors for any eating disorder and suicide attempts may be genetic in origin. We did not detect significant difference between the OR in maternal and paternal half-siblings. For AN or BN, the ORs did not differ significantly between full-siblings and maternal half-siblings or between half-siblings.

Table 3 about here

Sensitivity analysis

The ORs of suicide attempts in individuals (index) with any full-sibling or full-cousin with an eating disorder remained statistically significant even after adjusting for the index individuals' eating disorders (eTable 3), further supporting familial liability for eating disorders and suicide attempts. Controlling for MDD, but not other comorbidities, in the index individuals and in relatives reduced familial liability for any eating disorder, AN, and BN and suicide attempts (eTables 4.1-4.2).

Discussion

Using nationwide register data, we thoroughly explored the association between eating disorders and suicide attempts and revealed a familial liability for the association.

In line with previous research,[2] we found strong associations between any eating disorder, AN, and BN and suicide attempts. We extended previous studies by adjusting for comorbid psychiatric disorders. The associations remained significant, suggesting the elevated risks of suicide attempts in eating disorders are not entirely accounted for by psychiatric comorbidity. We did not observe sex difference in the association between eating disorders and suicide attempts.

Although previous research has suggested familial influences on both eating disorders and suicide separately,[29,30] whether they have common familial risk was unclear. We addressed this uncertainty by demonstrating elevated risk of suicide attempts in individuals with any full-sibling/full-cousin with any eating disorder, AN, and BN, compared to individuals without any full-sibling/full-cousin with the eating disorders (Table 3), even after controlling for the index individuals' eating disorders (eTable 3). This finding reveals that the association between eating disorders and suicide is influenced by familial risk factors. By comparing the ORs across different types of relatives, our design allowed deeper exploration of the origin of the familial liability. If the familial liability was genetic in origin, higher OR would be expected in full-siblings than in maternal half-siblings, because these relatives share similar family environment, but full-siblings share more genetic factors than maternal half-siblings.[15,16] We observed a slightly higher OR in full-siblings than in maternal half-siblings for any eating disorder (p=.024), suggesting genetic influence on the association between any eating disorder and suicide attempts. If the familial liability originated from family environment, higher ORs would be expected in maternal half-siblings than in paternal half-siblings, because these relatives have equivalent genetic sharing, but maternal half-siblings share greater family environment.[15,16] We did not

observe this pattern, which could be due to 1) the absence of family environmental effects, consistent with twin studies reporting minimal family environmental effects on either eating disorders or suicide,[29-32] or 2) inadequate statistical power, or that 3) changes in custody arrangements have led to fewer differences in shared family environment between maternal and paternal half-siblings than expected.[33] Our pattern of results reflects a recent twin study reporting common genetic, but not family environmental, influence on both eating disorders and suicide.[34] These results suggest that heritable and common risk factors for both eating disorders and suicide attempts may exist and may be a candidate for risk identification.

In addition to the main findings, our study has two important contributions. First, we confirmed and further quantified the effect of comorbid MDD, ANX, and SUD on suicide risk in individuals with eating disorders. This is in line with previous studies reporting associations between the comorbidities and both eating disorders and suicide attempts[9,10,35] and studies showing elevated suicide risk in individuals with eating disorders with greater comorbid psychiatric burden.[36,37] Additionally, the decreased familial risk when adjusting for MDD in family members suggests that the familial liability may partly relate to MDD (eTables 4.1-4.2). However, whether the relation is genetic and/or environmental in origin requires further study.

Second, we found that BN presented higher crude OR of suicide attempts, and lower, yet comparable, crude OR of death by suicide than AN (Table 2). This observation differs from results in a meta-analysis showing lower suicide risk in BN than in AN,[3] but is in line with a Danish study reporting higher hazard ratio of suicide attempts in BN than in AN,[38] and an outpatient-based mortality study reporting comparable suicide-specific standardized mortality ratios for AN and BN.[39] In aggregate these findings encourage vigilance for suicidality in both AN and BN.

Our findings should be contextualized by considering limitations to our design. First, the lifetime prevalence of eating disorders we observed in the register data was lower than survey-based lifetime prevalence in other studies,[1] including one based on Swedish adult twins.[31] This could be due to: 1) register data capturing only treatment-seeking cases (and treatment-seeking can differ across eating disorders), 2) the coverage of the eating disorder quality registers increasing over time,[22] and, 3) for BN particularly, the diagnosis being unavailable in the Swedish ICD-9.[24] Such under-detection might dilute the association if the under-detection were non-differential between people with and without suicide attempts. The effect should be minor however, as eating disorders were relatively rare. Nevertheless, the association might be overestimated if suicide attempts were overrepresented in treatment-seeking cases compared with eating disorder cases who did not seek treatment, or if the diagnosis of eating disorders facilitated the discovery of suicide attempts and vice versa. Additionally, the generalizability of our findings might be limited as the registers captured only treatment-seeking cases. Similar limitations could be attributed to possible misclassification in the diagnosis of suicide attempts.[40] Second, it is possible that there remain confounding effects after adjusting for comorbidities and that the adjustment may over-correct the association or may introduce bias due to the complexity of the correlations between psychiatric disorders. The adjusted OR should therefore not be over-interpreted. Nevertheless, it suggests particularly high-risk groups in eating disorders. Importantly, potential problems related to over-adjustment do not influence our main conclusion about familial liability between eating disorders and suicide attempts. Third, despite the large sample size and long follow-up period, we remained under-powered to clearly distinguish genetic from family environmental effects. This is illustrated by the wide confidence intervals for ORs in half-siblings. Even larger studies are needed to distinguish genetic from family environmental

factors with greater certainty. Additionally, the inference of the origin of familial liability by comparing different types of siblings was based on an assumption that full-siblings shared equal family environment with maternal but not paternal half-siblings.[15,16] The assumption was supported by the fact that most (91%) children live with their mother after parental divorce.[27] However, it is important to notice that more children spend equal amount of time with both parents after parental divorce nowadays than before.[33] Nevertheless, this trend was less likely to influence the older individuals in the study population. Lastly, the identification of the comorbid conditions might be incomplete as only diagnoses captured via healthcare contacts were included in the register.

This is one of the largest studies investigating the association between eating disorders and suicide attempts and their co-aggregation in families. Using data from the total Swedish population guaranteed the representativeness and improved the precision of the estimates. The use of the national registers eliminated potential recall bias. Furthermore, the genetically informative design allowed us to examine the familial liability for eating disorders and suicide attempts. The study represents an important step towards understanding the mechanism underlying the association between eating disorders and suicide, and encourages future studies to distinguish between genetic and environmental risk factors, and their interaction.

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Tables:

Table 1. Distribution of suicide attempts stratified by sex and eating disorder diagnosis

	Any eating disorder		**Anorexia nervosa**		**Bulimia nervosa**	
	Yes	No	Yes	No	Yes	No
Eating disorders						
N	16448	2252338	8133	2260653	3410	2265376
Female	15457	1088136	7680	1095913	3349	1100244
Male	991	1164202	453	1164740	61	1165132
Prevalence, %	0.72	-	0.36	-	0.15	-
Female	1.40	-	0.70	-	0.30	-
Male	0.09	-	0.04	-	0.01	-
Age at first diagnosis, mean (S.D.)	18.4 (4.0)	-	17.4 (3.6)	-	21.0 (3.4)	-
Female	18.5 (4.0)	-	17.4 (3.6)	-	21.0 (3.4)	-
Male	16.1 (4.5)	-	15.9 (3.6)	-	21.0 (4.0)	-
Suicide attempts						
Any suicide attempts, N (%)	2148 (13.1)	44293 (2.0)	923 (11.3)	45518 (2.0)	595 (17.4)	45846 (2.0)
Female	2077 (13.4)	23491 (2.2)	895 (11.6)	24673 (2.3)	581 (17.3)	24987 (2.3)
Male	71 (7.2)	20802 (1.8)	28 (6.2)	20845 (1.8)	14 (23.0)	20859 (1.8)
Age at first suicide attempts, mean (S.D.)	18.9 (3.5)	18.0 (4.8)	18.7 (3.4)	18.0 (4.8)	19.6 (3.3)	18.0 (4.8)
Female	18.8 (3.5)	17.6 (4.4)	18.7 (3.4)	17.7 (4.4)	19.6 (3.3)	17.7 (4.4)
Male	19.3 (3.8)	18.4 (5.2)	18.8 (3.8)	18.4 (5.2)	20.3 (3.1)	18.4 (5.2)
Death by suicide, N (%)	48 (0.29)	1467 (0.07)	27 (0.33)	1488 (0.07)	11 (0.32)	1504 (0.07)
Female	43 (0.28)	400 (0.04)	23 (0.30)	420 (0.04)	10 (0.30)	433 (0.04)
Male	5 (0.50)	1067 (0.09)	4 (0.88)	1068 (0.09)	1 (1.6)	1071 (0.09)
Age at death by suicide, mean (S.D.)	20.8 (3.5)	21.2 (3.9)	20.3 (3.2)	21.2 (3.9)	22.0 (3.0)	21.2 (3.9)
Female	20.8 (3.5)	20.3 (3.9)	20.2 (3.1)	20.3 (3.9)	22.1 (3.1)	20.3 (3.9)
Male	20.4 (3.5)	21.5 (3.8)	20.3 (4.0)	21.5 (3.8)	21.0 (-)	21.5 (3.8)
Psychiatric comorbidities						
Major depression, N (%)	5247 (31.9)	49255 (2.2)	2320 (28.5)	52182 (2.3)	1349 (39.6)	53153 (2.3)
Female	5011 (32.4)	30358 (2.8)	2217 (28.9)	33152 (3.0)	1323 (39.5)	34046 (3.1)
Male	236 (23.8)	18897 (1.6)	103 (22.7)	19030 (1.6)	26 (42.6)	19107 (1.6)
Anxiety disorder, N (%)	3742 (22.8)	45684 (2.0)	1506 (18.5)	47920 (2.1)	958 (28.1)	48468 (2.1)

Female	3544 (22.9)	28602 (2.6)	1439 (18.7)	30707 (2.8)	934 (27.9)	31212 (2.8)
Male	198 (20.0)	17082 (1.5)	67 (14.8)	17213 (1.5)	24 (39.3)	17256 (1.5)
Substance use disorder, N (%)	1731 (10.5)	52897 (2.4)	741 (9.1)	53887 (2.4)	507 (14.9)	54121 (2.4)
Female	1655 (10.7)	23813 (2.2)	709 (9.2)	24759 (2.3)	494 (14.8)	24974 (2.3)
Male	76 (7.7)	29084 (2.5)	32 (7.1)	29128 (2.5)	13 (21.3)	29147 (2.5)

Note: The diagnostic period for bulimia nervosa (BN) differed from any eating disorders and anorexia nervosa (AN). Any eating disorder and AN were identified based on the Swedish ICD-9 (1987-1996) and ICD-10 (1997-2009) diagnoses in NPR and DSM-IV diagnoses in the quality registers, i.e., RIKSÄT (1998-2009) and Stepwise (2005-2009); whereas BN was identified based on only ICD-10 diagnoses in NPR and DSM-IV diagnoses in the quality registers.

Table 2. Odds ratio of suicide attempts and death by suicide in individuals with eating disorders

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	# Obs. used in analyses
	Suicide attempts				
Total population					2,268,786
Any eating disorder	**5.28 (5.04, 5.54)**	<.001	**1.82 (1.72, 1.93)**	<.001	
Anorexia nervosa	**4.42 (4.12, 4.74)**	<.001	**1.70 (1.56, 1.85)**	<.001	
Bulimia nervosa	**6.26 (5.73, 6.85)**	<.001	**1.88 (1.68, 2.10)**	<.001	
Female					1,103,593
Any eating disorder	**5.29 (5.04, 5.56)**	<.001	**1.66 (1.56, 1.77)**	<.001	
Anorexia nervosa	**4.40 (4.10, 4.72)**	<.001	**1.55 (1.42, 1.70)**	<.001	
Bulimia nervosa	**6.19 (5.65, 6.78)**	<.001	**1.68 (1.50, 1.89)**	<.001	
Male					1,165,193
Any eating disorder	**3.86 (3.03, 4.91)**	<.001	**1.57 (1.19, 2.06)**	.001	
Anorexia nervosa	**3.29 (2.25, 4.82)**	<.001	**1.49 (0.97, 2.27)**	.07	
Bulimia nervosa	**11.24 (6.22, 20.32)**	<.001	**2.88 (1.40, 5.93)**	.004	
	Death by suicide				
Total population					1,919,114
Any eating disorder	**5.39 (4.00, 7.25)**	<.001	**2.04 (1.49, 2.80)**	<.001	
Anorexia nervosa	**6.46 (4.38, 9.54)**	<.001	**2.67 (1.78, 4.01)**	<.001	
Bulimia nervosa	**4.45 (2.44, 8.11)**	<.001	1.48 (0.81, 2.72)	.20	
Female					891,434
Any eating disorder	**5.36 (3.91, 7.36)**	<.001	**1.81 (1.28, 2.56)**	.001	
Anorexia nervosa	**5.93 (3.89, 9.03)**	<.001	**2.18 (1.39, 3.42)**	.001	
Bulimia nervosa	**4.39 (2.34, 8.23)**	<.001	1.29 (0.68, 2.45)	.44	
Male					938,205
Any eating disorder	**5.36 (2.21, 12.97)**	<.001	2.27 (0.90, 5.72)	.08	
Anorexia nervosa	**9.96 (3.69, 26.89)**	<.001	**4.62 (1.59, 13.40)**	.005	
Bulimia nervosa	**9.56 (1.30, 70.65)**	.03	2.44 (0.32, 18.71)	.39	

Note: OR: Odds Ratio; CI: Confidence Interval. When estimating crude ORs, we adjusted for birth year, sex (for total population), and used a robust (sandwich) estimator of standard errors to account for non-independence due to familial clustering. When estimating adjusted ORs, we additionally adjusted for psychiatric comorbidities including MDD, ANX, and SUD. Individuals with any eating disorder, AN, and BN had significantly increased risk of both suicide attempts and death by suicide. Most of the association remained significant even after adjusting for psychiatric comorbidities, except a few, possibly due to limited power resulted from the rarity of the eating disorder and death by suicide in the corresponding population. Individuals in some birth year strata were excluded from analyses for death by suicide (females born in 1997-2001 and males born in 1996 and 1998-2001), because there were no death by suicide in these years. This resulted in a smaller number of observations used in analyses for death by suicide than that in analyses for suicide attempts where no individual was excluded.

Table 3. Odds ratio of suicide attempts in individuals with at least one relative with eating disorders

	Any eating disorder		Anorexia nervosa		Bulimia nervosa		
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	# Obs. Used in analyses
Full-sibling	**1.41 (1.29, 1.53)**	<.001	**1.21 (1.06, 1.37)**	.004	**1.56 (1.31, 1.86)**	<.001	1,680,658
Maternal half-sibling	1.10 (0.90, 1.34)	.36	1.09 (0.81, 1.47)	.56	1.13 (0.74, 1.73)	.57	253,172
Paternal half-sibling	1.21 (0.98, 1.49)	.08	1.25 (0.91, 1.72)	.17	1.36 (0.89, 2.06)	.15	248,939
Full-cousin	**1.11 (1.06, 1.18)**	<.001	**1.13 (1.04, 1.22)**	.003	**1.20 (1.07, 1.34)**	.001	1,753,065
Half-cousin	0.90 (0.78, 1.03)	.14	0.82 (0.67, 1.00)	.54	1.01 (0.77, 1.33)	.92	384,222

Note: OR: Odds Ratio; CI: Confidence Interval. Outcome was defined as suicide attempts (any suicidal attempts or death by suicide). The models estimated the risk of suicide attempts in people with at least one relative with an eating disorder. We controlled for birth year, sex, number of the type of relatives in the models, and used a robust (sandwich) estimator of standard errors to account for non-independence due to familial clustering. Significantly elevated risk of suicide attempts was found in individuals with any full-sibling with any eating disorder, AN, and BN, and in individuals with any full-cousin with any eating disorder, AN, and BN.