Anorexia Nervosa, Major Depression, and Suicide Attempts: Shared Genetic Factors

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Abstract

We evaluated the extent to which genetic and environmental factors influenced anorexia nervosa (AN), major depressive disorder (MDD), and suicide attempts (SA). Participants were 6,899 women from the Swedish Twin study of Adults Genes and Environment. A Cholesky decomposition assessed independent and overlapping genetic and environmental contributions to AN, MDD, and SA. Genetic factors accounted for a substantial amount of liability to all three traits; unique environmental factors accounted for most of the remaining liability. Shared genetic factors may underlie the co-expression of these traits. Results underscore the importance of assessing for signs of suicide among individuals with AN.

Keywords

anorexia nervosa; major depressive disorder; suicide; twins; comorbidity

INTRODUCTION

Suicide is a global problem. In 2012, suicide was the second leading cause of death among 15–29 year olds (World Health Organization, 2015) and the leading cause of death among 15–19 year old females (Patton et al., 2009). The World Health Organization estimates that 800,000 people worldwide end their lives by suicide each year. Around 90% of individuals who commit suicide are believed to suffer from psychiatric disorders (Hawton & van Heeringen, 2009), with anorexia nervosa (AN) and major depressive disorder (MDD) among the disorders with the highest risk (Chesney, Goodwin, & Fazel, 2014). In this paper, we explore the connections among AN, MDD, and suicide attempts (SA) with the aim of clarifying the role that genetic and environmental factors play on these phenotypes.

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Mortality in AN is amongst the highest of all psychiatric disorders (Hoang, Goldacre, & James, 2014), with suicide being one of the leading causes of death and implicated in about 20% of deaths (Arcelus et al., 2011). According to a recent meta-analysis, individuals with AN have an 18.1 [95% confidence interval (CI): 11.5, 28.7] times higher risk of dying from suicide than the general population of females aged 15–34 years (Keshaviah et al., 2014). Although the suicide rate in those with AN may be declining in recent decades (Preti et al., 2011), it remains substantially elevated compared with the general population (Pisetsky et al., 2013). Additionally, the lifetime prevalence of SA in patients ranges from 3.0%–29.7% (Bulik et al., 2008; Forcano et al., 2011; Franko & Keel, 2006; Runfola et al., 2014). According to the Interpersonal Theory of Suicide, an individual has to have both an increased fearlessness about death and an increased tolerance to pain in order to be capable of attempting suicide (Ribeiro et al., 2014). The repeated exposure to pain via restriction (Selby et al., 2010) coupled with decreased pain sensitivity (whether acquired or inborn) (Papezová, Yamamotová, & Uher, 2005), may contribute to the increased prevalence of SA in this population.

The association between MDD and suicide is well known. Psychological autopsy studies have found that 30%–90% of individuals who die from suicide suffered from MDD (Isometsa, 2001). MDD is common in individuals with AN: 50–75% of individuals with AN experience lifetime MDD (Calugi et al., 2014; Fernandez-Aranda et al., 2007; Mischoulon et al., 2011; Rastam, Gillberg, & Gillberg, 1995; Wade et al., 2000), which may be a risk factor for suicide in AN (Preti et al., 2011). Individuals with an eating disorder who attempt suicide are more likely to have a lifetime history of MDD than individuals with an eating disorder who do not attempt suicide (Anderson et al., 2002; Bulik et al., 2008; Corcos et al., 2002; Favaro & Santonastaso, 1997). In fact, over 80% of individuals with AN who attempted suicide reported that their worst attempt occurred during an episode of MDD (Bulik et al., 2008).

Behavioral genetic methods can explicate the nature of the relationship among AN, MDD, and suicide. Genetic factors contribute to the liability to AN, MDD, and suicide (Bulik et al., 2010; Hawton, Saunder, & O'Connor, 2012; Kendler et al., 2006) and, by using a genetically informative twin sample, we can evaluate the extent to which these phenotypes share genetic or environmental factors. A recent study by Wade et al. (Wade et al., 2015) gave a glimpse into the relation among broadly defined eating disorders (including AN, bulimia nervosa, binge eating disorder, and purging disorder), MDD, and broadly defined suicidality (ranging from transitory thoughts to suicide attempts). Their model revealed a common genetic influence on eating disorders and suicidality (but not MDD), and no appreciable influence of common environmental factors.

Here, we refine and extend the results of Wade et al. (Wade et al., 2015) by focusing on AN, which has the highest rates of suicidality (Franko & Keel, 2006), rather than incorporating multiple eating disorders simultaneously, and only including health care detected suicide attempts and death by suicide. We applied multivariate twin models to data from women to determine whether shared genetic and environmental factors contributed to liability to AN, MDD, and SA.

METHOD

Participants

Participants were women from monozygotic (MZ) and same-sex dizygotic (DZ) twin pairs who participated in the Swedish Twin study of Adults Genes and Environment (STAGE). STAGE, a population-based prospective study of Swedish twins born 1959–1985, assessed more than 30 different health and demographic topics (Furberg et al., 2008; Lichtenstein et al., 2006). Data were collected on-line in 2005; twins were between 20 and 47 years old. The Regional Ethics Committee of Karolinska Institutet and the University of North Carolina's Biomedical Institutional Review Board approved this study.

Zygosity

Zygosity was assigned based on responses from two questions: (Q1) During childhood, were you and your twin partner as alike as 'two peas in a pod' or no more alike than siblings in general? and (Q2) How often did strangers have difficulty distinguishing between you and your twin partner when you were children? Twins were classified as MZ if both twins within a pair responded 'alike as two peas in a pod' for Q1 and 'almost always' or 'often' for Q2. Twins were classified as DZ if both twins responded 'not alike' for Q1 and 'seldom,' 'almost never', or 'never' for Q2. All other twins were classified as 'not determined.' This algorithm was validated using 47 single nucleotide polymorphisms in 198 randomly selected twin pairs (Lichtenstein et al., 2002). Ninety-five percent were correctly classified; ten pairs (8 MZ and 2 DZ) were misclassified.

Measures

Anorexia Nervosa—A lifetime history of AN was assessed in STAGE using an expanded, on-line Structured Clinical Interview for DSM-IV (SCID)-based instrument (First et al., 1997). AN was considered present if the following criteria were met: 1) having a period of time when the respondent weighed much less than people thought she should weigh and had a BMI < 18.55; 2) being slightly, somewhat, very, or extremely afraid of gaining weight or becoming fat; and 3) feeling slightly, somewhat, very, or extremely fat when at low weight. Amenorrhea, Criterion D, was not required (Dellava et al., 2011) and is consistent with DSM-5.

Depression—In STAGE, lifetime history of DSM-IV-TR (American Psychiatric Association, 2000) MDD was considered present if, during the same two week period, 1) the participant indicated the presence of at least five of the following: depressed mood, loss of interest or pleasure, significant weight change or appetite change, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feeling worthless or full of guilt, problems concentrating, and suicidal ideation, with either depressed mood or loss of interest in nearly all activities most of the day endorsed; and 2) the participant indicated that the symptoms caused significant impairment or distress.

Suicide Attempts—Information regarding SA was obtained from the National Patient Register [years 1973–2009; (National Board of Health and Welfare, 2012)]. Information regarding death by suicide was obtained from the Cause of Death Register [years 2005–2008

for this study; (National Board of Health and Welfare, 2010)]. The National Patient Register, established in 1964, records all hospital admissions in Sweden. As of 1987 and 2001, all inpatient and outpatient admissions, respectively, are reported and maintained in the database. For each admission, the primary discharge diagnosis and as many as eight secondary diagnoses are listed using codes from the *International Classification of Diseases, Eighth Revision* [ICD-8; 1973–1986 (World Health Organization, 1967)], *International Classification of Diseases, Ninth Revision* [ICD-9; 1987–1996 (World Health Organization, 1978)] or *International Classification of Diseases, Tenth Revision* [ICD-10; 1997-present (World Health Organization, 1992)]. Similarly, primary and secondary causes of death, as reported on death certificates, are listed in the Cause of Death Register. Since 1961, >99% of all deaths both in Sweden and abroad are reported. In both registers, definite SA and causes of death by suicide are coded using ICD codes: ICD-8 (World Health Organization, 1967) and ICD-9 (World Health Organization, 1978): E950–E958; ICD-10 (World Health Organization, 1992): X60–X64. Since 4 women died by suicide after participation in STAGE in 2005 (Pisetsky et al., 2013), one suicide variable was created. Any person identified as having attempted and or died by suicide was classified as having a SA.

Information from STAGE, the National Patient Register, and the Cause of Death Register was merged using a personal identification number that is assigned to all individuals born in Sweden or residing in Sweden for at least one year (Ludvigsson et al., 2009).

Statistical Analyses

Biometrical twin modeling was used to assess the relative contributions of genetic and environmental factors that influence liability to AN, MDD, and SA, and to estimate whether genetic and environmental factors are shared across traits. Additive genetic effects (A) are those genetic factors which influence a trait. Common environmental effects (C) are environmental influences which both members of a twin pair experience that increase similarity between twins. Unique environmental factors (E) make twins less similar; this term also includes measurement error. By comparing the intrapair correlation for MZ twins to the intrapair correlation for DZ twins, classic twin modeling assesses the contribution of: (1) additive genetic effects (i.e., heritability, a^2); (2) common environmental effects (c^2); and (3) unique environmental effects (e^2) to the liability of a phenotype. The sum these effects, $a^2 + c^2 + e^2$, accounts for 100% of the underlying variance of the phenotype.

A Cholesky decomposition was applied with Mx (M. C. Neale et al., 1999) using raw ordinal data that allowed for missing data within a twin and when no cotwin information was available. This approach decomposes the variance of the individual phenotypes, i.e., AN, MDD, and SA, and the covariance among these phenotypes to estimate: 1) the contribution of additive genetic, common environmental, and unique environmental factors; and 2) the genetic, common environmental, and unique environmental correlations (r_a, r_c, and r_e, respectively). These correlations indicate the extent to which the traits share the respective factors. When no cotwin data are available, the twin's information is still useful because it contributes to the variance, but not correlations, of the phenotypes.

The full model (Model I), in which all parameter estimates (a^2, c^2, and e^2) for AN, MDD, and SA, as well as the parameter correlations (r_a, r_c, and r_e) for each pair of disorders, was

applied to the data. We then applied five nested models: Model II, all common environmental correlations were set to zero; Model III, all common environmental variance parameters and all common environmental correlations were set to zero; Model IV, the common environmental variance parameters and correlations were set to zero and the genetic correlations were set to zero; Model V, the common environmental variance parameters and correlations and the unique environmental correlations were set to zero; and Model VI, the common environmental variance parameters and correlations were set to zero and the genetic variance parameters and correlations were set to zero. The fit of each nested model was compared with the full model. If the difference in χ^2 values between the nested model and the full model (Neale & Cardon, 1992), where degrees of freedom (df) is equal to the difference between the df of the nested model and the full model, was not significant, indicating no decrement in fit, the nested model was retained because it was the more parsimonious model. The model with the lowest Akaike's Information Criteria [AIC; (Akaike, 1987)], the best-fitting model with regard to precision and complexity, was then selected as the overall best-fitting model. Results from the full and best-fitting models are presented.

RESULTS

Sample Characteristics

Our final sample for modeling included 6,899 women from MZ and same-sex DZ twin pairs. There were 1,651 MZ and 1,109 DZ pairs with complete data, 256 MZ and 245 DZ pairs with incomplete data, and 222 MZ and 155 DZ individuals with no cotwin information. The mean (sd) age of the sample was 33.0 (7.6) years.

The prevalence of each disorder was: AN = 3.6% (n = 245), MDD = 26.2% (n = 1,659), and SA (including suicide completions) = 1.9% (n = 128). A total of 226 women (3.3%) met criteria for both AN and MDD, 17 (0.2%) had AN and SA, and 90 (1.3%) had MDD and SA. Fifteen women had a lifetime history of all three phenotypes. No differences in prevalence between MZ and DZ twins were observed for AN ($\chi^2 = 1.31$, $p < .26$), MDD ($\chi^2 = 0.11$, $p < .74$), or SA ($\chi^2 = 0.32$, $p < .58$). The phenotypic correlations were .34 (95% CI: .27, .41), .30 (95% CI: .18, .42), and .50 (95% CI: .42, .57) for AN-MDD, AN-SA, and MDD-SA, respectively.

Twin Models

Table 1 lists the results from fitting the full model (Model I) and the five nested models. Based on the χ^2 difference tests, Models IV and VI fit significantly worse than the full model. Model III was considered to be the best-fitting model because it had the lowest AIC value.

Table 2 presents the results for the full (Model I) and best-fitting (Model III) models. Results from the full model show that genetic factors account for 38% (95% CI: 8%, 53%) of the liability to AN, 44% (95% CI: 24%, 50%) of the liability to MDD, and 58% (95% CI: 8%, 78%) of the liability to SA. Unique environmental factors account for most of the remaining liability. The genetic correlations suggest some sharing of genetic risk factors: r_a=.49 for AN

with MDD, r_a=.52 for AN with SA, and r_a=.77 for MDD with SA. All correlations in the full model have wide confidence intervals, indicating a lack of power to obtain precise estimates. Genetic and unique environmental parameter estimates for the best-fitting model were similar to those obtained from the full model.

DISCUSSION

This study sheds light on factors that underlie the commonly observed phenomenon of comorbid AN, MDD, and SA and points to mechanisms that implicate shared genetic factors in their co-occurrence. In contrast, the 95% CIs for unique environmental correlations for AN and SA, as well as MDD and SA, included zero, suggesting that unique environmental effects contributing to each of these phenotypes might not overlap but, rather, be trait specific.

The lifetime prevalence of AN in our sample was somewhat higher than the prevalence reported among female Australian (Wade et al., 2006) and Finnish (Keski-Rahkonen et al., 2007) twins (3.6% versus 1.9% and 2.2%, respectively), but well in line with estimates that AN affects between 1%–4% of the population (Hudson et al., 2007; Smink, van Hoeken, & Hoek, 2012). This increased prevalence could be due to the use of a broader AN definition in our study. The prevalence of SA was lower than that reported in a large nationally representative US sample [4.6%; (Kessler, Borges, & Walters, 1999)]; however, it should be noted that SA in the present study only reflected attempts resulting in clinical care and thus less serious attempts that did not warrant medical attention would not have been detected, yielding a conservative estimate of SA. Although the lifetime prevalence of MDD in our sample was higher (26.6%) than in the US sample [16.6%; (Kessler et al., 2005)], which could reflect true differences or variable estimates due to different assessment strategies (i.e., self-report versus interview), it was similar (25.1% in women) to that reported in another Swedish twin sample (Kendler et al., 2006).

Previous studies have consistently documented that both AN and MDD are associated with a higher risk of SA [e.g., (Bolton et al., 2008; Bulik et al., 2008; Chesney et al., 2014; Forcano et al., 2011; Pisetsky et al., 2013)]. Furthermore, genetic factors are known to play a role in all three phenotypes [e.g., (Bulik et al., 2010; Hawton et al., 2012; Roy, Segal, & Sarchiapone, 1995)]. However, the heritability estimate for AN in this study was lower than that observed in prior reports; this is likely due to the broader AN definition used here (Dellava et al., 2011). Our observations that the comorbidity of AN and SA and of MDD and SA can be largely attributed to shared genetic factors are similar to those reported by Wade et al. (Wade et al., 2015) in a general population sample of twins. The authors found that eating disorders are associated with increased risk for suicidality and the comorbid pattern appeared to be almost entirely explained by shared genetic factors.

Although results from our multivariate twin modeling show that genetic factors account for a large part of the liability of the three traits, unique environmental factors (including measurement error) account for essentially all the remaining liability. Common environmental factors play a negligible role in liability to any of the three traits.

The main finding in the current study is an indication of shared biological underpinnings across AN, MDD, and SA. Genetic epidemiological studies reveal the proportion of genetic variance in liability to a trait attributable to additive genetic factors, and trivariate designs such as that employed here allow us to estimate the extent to which genetic and environmental factors are shared among phenotypes. Importantly, they do not directly measure genetic or environmental risk factors. Thus, to further our knowledge, genetic epidemiological studies have to be enriched with measured genotypes and environmental exposures. The calculation of genetic and environmental risk scores will allow us to estimate risk on an individual level and promote understanding of the structure, function, and processes of genetic and environmental risk factors. Ultimately, this will pave the way for the development of more precise diagnostics that in turn will improve both prevention and treatment.

Limitations

The results of this study should be evaluated within the context of the limitations. First, the data used came from adult women from Sweden; results might not be generalizable to men or to different ancestry and age groups. Second, STAGE data were collected via computer-administered assessments. Although computer-administered self-report assessments might be less precise than interview-based assessment methods, participants might be more forthcoming with sensitive information (Lind et al., 2013). Third, SA were only captured if the result of the attempt required clinical care. Thus, results may only apply to more serious attempts. Fourth, causal conclusions regarding which specific genetic and/or unique environmental factors that may be involved in the associations between the three disorders cannot be determined. Fifth, there is likely some confounding between MDD and both AN and SA since the symptom list for MDD includes appetite, weight changes, and suicidal ideation.

Conclusions and Clinical Implications

Our results help us understand processes that underlie the common clinical observation of MDD and suicide in individuals with AN. They show that the comorbidity of AN and SA that require clinical care is largely due to genetic factors. This is in contrast to AN and MDD, where the unique environmental correlation is substantial. Second, our results are meaningful for clinical practice. Although caution must be engaged when transferring knowledge from the population to individuals, our results encourage clinicians to consider that shared biology could underlie the frequency with which suicide attempts occur in individuals with AN. As such, clinicians should screen for a family history of SA in individuals with AN, regardless of lifetime MDD status. These findings further underscore the seriousness of AN and alert clinicians to be vigilant for signs of suicide. Third, quantifying the contribution of genetic and environmental factors to AN, MDD, and SA lends evidence to explanatory models that account for their co-occurrence. Our models provide valuable insight into the association among these traits and to factors that contribute to the lethality of AN.

Acknowledgements

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Table 1

Model fit statistics

Model No.	Model	−2lnL	df	χ^2 diff (df)	AIC
I	Saturated ACE Cholesky ACE, r_a, r_c, r_e	10255.9	20113	---	−29970.1
II	ACE, r_a, r_e ($r_c = 0$)	10261.4	20116	5.51 (3)	−29970.6
III	**AE, r_a, r_e (C = 0; $r_c = 0$)**	**10255.9**	**20119**	**0.039 (6)**	**−29982.1**
IV	AE, r_e (C = 0; $r_a = 0$; $r_c = 0$)	10326.0	20122	70.18 (9)[*]	−29918.0
V	AE, r_a (C = 0; $r_c = 0$; $r_e = 0$)	10267.8	20122	11.89 (9)	−29976.2
VI	E, r_e (A = 0; C = 0; $r_a = 0$; $r_c = 0$)	10453.7	20125	197.83 (12)[*]	−29796.3

Note. AIC = Akiake's Information Criterion (Akaike, 1987); −2lnL = −2 log likelihood; df = degrees of freedom; ACE = additive genetic, common environment, and unique environmental effects model; AE = additive genetic and unique environmental effects model; E = unique environmental effects model; r_a = genetic correlations; r_c = common environmental correlations; r_e = unique environmental correlations

[*] Significantly worse fit than the full model.

Table 2

Parameter and correlation estimates (95% confidence interval) for anorexia nervosa (AN), major depressive disorder (MDD), and suicide attempts (SA) for the full and best-fit models

Model Number	Parameter	AN	MDD	SA	Correlation	AN with MDD	AN with SA	MDD with SA
I Full Model	A	.38 (.08, .53)	.44 (.24, .50)	.58 (.08, .78)	r_a	.49 (.18, 1.00)	.52 (−.14, 1.00)	.77 (.45, 1.00)
	C	.00 (.00, .24)	.01 (.00, .17)	.05 (.00, .53)	r_c	1.00 (−1.00, 1.00)	1.00 (−1.00, 1.00)	1.00 (−1.00, 1.00)
	E	.62 (.47, .79)	.56 (.49, .63)	.37 (.22, .54)	r_e	.25 (.08, .38)	.12 (−.22, .45)	.20 (−.04, .43)
III Best Fit	A	.38 (.21, .53)	.45 (.38, .51)	.64 (.46, .78)	r_a	.48 (.27, .73)	.49 (.17, .83)	.77 (.58, .98)
	E	.62 (.47, .79)	.55 (.49, .63)	.36 (.22, .54)	r_e	.25 (.08, .40)	.13 (−.22, .45)	.20 (−.04, .43)

Note. ACE = additive genetic, common environment, and unique environmental effects model; AE = additive genetic and unique environmental effects model; r_a = genetic correlations; r_c = common environmental correlations; r_e = unique environmental correlations