

# Prevalence, Heritability, and Prospective Risk Factors for Anorexia Nervosa

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**Context:** Anorexia nervosa (AN) is a serious mental illness with marked morbidity and mortality.

**Objective:** To explore the prevalence, heritability, and prospectively assessed risk factors for AN in a large population-based cohort of Swedish twins.

**Design:** During a 4-year period ending in 2002, all living, contactable, interviewable, and consenting twins in the Swedish Twin Registry (N=31 406) born between January 1, 1935, and December 31, 1958, underwent screening for a range of disorders, including AN. Information collected systematically in 1972 to 1973, before the onset of AN, was used to examine prospective risk factors for AN.

**Setting:** Population-based sample of twins in Sweden.

**Participants:** Cases of AN were identified as those individuals who met full DSM-IV criteria by means of clinical interview of the Swedish Twin Registry, who had a hospital discharge diagnosis of AN, or who had a cause-of-death certificate including an AN diagnosis.

**Results:** The overall prevalence of AN was 1.20% and 0.29% for female and male participants, respectively. The

prevalence of AN in both sexes was greater among those born after 1945. Individuals with lifetime AN reported lower body mass index, greater physical activity, and better health satisfaction than those without lifetime AN. Anorexia nervosa was inversely associated with the development of overweight (odds ratio, 0.29; 95% confidence interval [CI], 0.16-0.54 [ $P < .001$ ]). The heritability of narrowly defined DSM-IV AN (additive genetic effects) was estimated to be  $a^2 = 0.56$  (95% CI, 0.00-0.87), with the remaining variance attributable to shared environment ( $c^2 = 0.05$ ; 95% CI, 0.00-0.64) and unique environment ( $e^2 = 0.38$ ; 95% CI, 0.13-0.84). Neuroticism measured about 3 decades before the diagnostic assessment was significantly associated with the development of later AN (odds ratio, 1.62; 95% CI, 1.27-2.05 [ $P < .001$ ]).

**Conclusions:** The prevalence of AN was higher in both male and female participants born after 1945. Individuals who survive AN and who no longer have body mass indexes in the AN range appear to be at lower risk for the development of overweight. Prospectively assessed neuroticism was associated with the subsequent development of AN, the liability to which is under considerable genetic influence.

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**A**NOREXIA NERVOSA (AN) IS a perplexing psychiatric illness that primarily strikes female patients and is associated with the highest mortality rate of any mental disorder.<sup>1,2</sup> Hoek and van Hoeken<sup>3</sup> report the average prevalence of AN to be 0.3%, with the prevalence of subthreshold variants ranging from 0.37% to 1.3%.<sup>4,5</sup> The data on temporal incidence trends are conflicting, with some studies suggesting that the incidence is increasing<sup>6-12</sup> and others reporting stable rates.<sup>13-17</sup> Hoek and van Hoeken<sup>3</sup> indicate that the incidence of AN increased during the past century, reaching a plateau in the 1970s. The peak age of onset is 15 to 19 years.<sup>18</sup>

Anorexia nervosa is familial, with significantly elevated relative risks for AN, bulimia nervosa, and eating disorders not otherwise specified in family members.<sup>19,20</sup> The relative risk of AN in family members of males with AN is even higher (>20).<sup>21</sup> Given the relative rarity of the condition, twin studies have used various strategies to enhance statistical power, including reporting the heritability of AN in the context of a bivariate twin analysis with AN and major depression ( $a^2 = 58\%$ ; 95% confidence interval [CI], 0.33-0.84)<sup>22</sup>; basing analysis on a simple question of "Have you ever had anorexia nervosa?" ( $a^2 = 48\%$ ; 95% CI, 0.27-0.65)<sup>23</sup>; and using a broad definition of AN syndrome ( $a^2 = 76\%$ ; 95% CI, 0.35-0.95).<sup>24</sup> In each case, shared en-

vironment was negligible ( $c^2$ ), and the remaining variance was primarily attributable to unique environmental factors ( $e^2$ ). Although important contributions, each of these approaches is suboptimal, and no heritability estimates of narrowly defined threshold *DSM-IV* AN currently exist.

Despite the seriousness of the disorder, we know little about risk factors for the development of AN. Risk factor studies for AN have been challenged by the relative rarity of AN in that longitudinal observational studies often identify only a small number of cases.<sup>4,25</sup> Case-control comparisons have highlighted perfectionism and negative self-evaluation as associated with AN and bulimia nervosa.<sup>26</sup> Comprehensive reviews of risk factors for AN exist.<sup>27,28</sup> Jacobi et al<sup>27</sup> reported several general risk factors for eating disorders, including sex, race/ethnicity, early childhood eating and gastrointestinal tract problems, elevated shape and weight concerns, negative self-evaluation, sexual abuse and other adverse experiences, and general psychiatric morbidity, although none was specific for AN. In terms of factors specifically predictive of AN, only pregnancy- and birth-related complications have been reported from a Swedish population-based study.<sup>29</sup> Many of the other identified predictors could simply be prodromal symptoms of the disorder.

The present study had the following goals: (1) to report the prevalence of AN in a large cohort of female and male Swedish twins born between January 1, 1935, and December 31, 1958; (2) using a prospective longitudinal design, to identify variables measured in 1972 to 1973 that were associated with the subsequent onset of AN; and (3) to provide estimates of the genetic and environmental contributions to liability to AN.

## METHODS

### SWEDISH TWIN REGISTRY

The Swedish Twin Registry (STR) ([http://www.mep.ki.se/twinreg/index\\_en.html](http://www.mep.ki.se/twinreg/index_en.html)) is the largest population-based registry of twin births in the world.<sup>30,31</sup> For this study, we focused on the STR subset of twin births in Sweden between January 1, 1935, and December 31, 1958, with both twins alive and who were participants in the Screening Across the Lifespan of Twins cohort (SALT). The SALT interviews included questions on eating habits, smoking habits, and medical illnesses. For the entire STR, data on current vital status, marital status, address, and place of birth are available for more than 99% of the 160 000 registered individuals.

### INTERVIEW PROCEDURES AND DATA SOURCES

During a 4-year period ending in 2002, all living, contactable, interviewable, and consenting twins in the STR underwent screening for a range of disorders, including AN. The interview procedure had the following steps. Each month, we matched the master twin register to national records to update vital status and current address information; we randomly selected approximately 1000 pairs for interviews and sent introductory letters describing the study; and we then attempted to complete a telephone interview about 2 weeks later. This process was repeated during the 4 years of the study. In the SALT

interviews, lifetime history of AN was assessed via an interview based on the Structured Clinical Interview for *DSM-IV* Axis I Disorders.<sup>32</sup> All interviews were conducted by trained interviewers with adequate medical background using a computer-based data collection system. Detailed procedural information about the SALT interviews can be found in Lichtenstein et al<sup>30</sup> and Pedersen et al.<sup>31</sup>

### HOSPITAL DISCHARGE REGISTRY IDENTIFICATION OF CASES

The Swedish Hospital Discharge Register covers all public, inpatient hospitalizations in Sweden and is maintained by the Centre for Epidemiology at the National Board of Health and Welfare (<http://www.sos.se/epc/english/ParEng.htm>). For psychiatric diagnoses, the register is complete from 1973. Each record contains the admission and discharge dates, the main discharge diagnosis, and as many as 8 secondary diagnosis codes from the *International Classification of Diseases, Eighth Revision (ICD-8)*,<sup>33</sup> *International Classification of Diseases, Ninth Revision (ICD-9)*,<sup>34</sup> or *International Statistical Classification of Diseases, 10th Revision (ICD-10)*.<sup>35</sup> These diagnoses are based on the clinical diagnosis made by the attending physician. The psychiatric discharge registry contains data from the 3.8 million hospitalizations of 960 000 people. We searched this registry for discharge diagnoses corresponding to AN (codes 306.50 [*ICD-8*], 307B [*ICD-9*], and F50.0 [*ICD-10*]).

### CAUSE-OF-DEATH REGISTER

The national cause-of-death registry contains information on all deaths in Sweden since 1961.<sup>36</sup> The diagnoses and causes of death are coded according to the *International Classification of Disease* revisions.<sup>33-35</sup> To define cases of AN, we used codes 306.50, 307B, and F50.0. Exploration of other codes that might overlap with AN did not reveal additional cases consistent with the presence of AN.

### DEFINITIONS OF AN

Given that we had multiple sources of information (the SALT interview, hospital discharge registry, and cause-of-death registry) that could inform us of eating disorder status, we studied 3 definitions of AN. The first definition, all-source AN, includes individuals who met full *DSM-IV* criteria by means of the SALT interview ( $n=121$ ), any registry discharge diagnosis of AN ( $n=143$ ), or a death certificate that included an AN diagnosis ( $n=2$ ). The second definition, narrow *DSM-IV* AN, includes individuals who met full *DSM-IV* criteria by means of the SALT interview (excluding amenorrhea for male participants). The third definition, broad *DSM-IV* AN, includes individuals who met all *DSM-IV* criteria for AN with the exception of amenorrhea, as amenorrhea has been shown to be an unreliable diagnostic criterion for AN.<sup>37-40</sup>

### ASSESSMENT OF ADDITIONAL CONDITIONS

In the SALT interview, lifetime *DSM-III-R* major depression<sup>41</sup> and generalized anxiety disorder were assessed during the SALT telephone interview via an adaptation of the Composite International Diagnostic Interview.<sup>42</sup> We also report on 4 dichotomously scored general health variables. Affirmative responses to the general health item reflect those individuals who rated their current health as excellent or good. Positive responses to the change in health item reflect those individuals who state that their current health is better than or the same as their health 5 years earlier. Health limitation variables include the "health

limits activities" item with a positive score being no limitation and "days health limited activities" item with a positive score being limitations of fewer than 7 days in the past year.

## PROSPECTIVE RISK FACTOR QUESTIONNAIRE

A questionnaire was sent in 1972 and 1973 to twins of like-sexed pairs and assessed demographics (height and weight), physical illnesses (including gastric problems), physical activity level, personality, stress, and work exposures. Neuroticism and extraversion were measured using a short form of the Eysenck Personality Inventory<sup>43</sup> that has been widely used in previous Scandinavian twin studies.<sup>44-46</sup> Each scale score is based on the sum of no (0) or yes (1) responses to 9 items. We used mean imputation if 1 item for a particular scale was missing. Individuals having more than 1 missing item for a particular scale were excluded. Raw scale scores were standardized by using regression to adjust for the effects of age. Stress score was based on the question "Do you experience your daily existence as being very 'stress-filled?'"

## ZYGOSITY DETERMINATION

Zygoty information for like-sexed pairs was obtained at the time of registry compilation on the basis of questions about childhood resemblance and updated during the most recent screening for those with previously uncertain diagnoses. Four separate validation studies using serology and/or genotyping have shown that these items correctly classify the zygoty of 98% of twin pairs.<sup>30</sup>

## STATISTICAL ANALYSES

Descriptive statistics and basic analyses were conducted using SAS software, version 9.<sup>47</sup> Asymmetric, exact CIs were obtained using PROC FREQ.<sup>47</sup> We used linear and logistic regression with generalized estimating equations<sup>48-51</sup> to investigate the associations with demographic and prospective risk factors.

Most biometrical twin analyses of complex disorders are based on the liability-threshold model.<sup>52,53</sup> This model postulates the existence of an unobserved (or latent) liability to an illness that results from numerous components. These components act additively and may be genetic and/or environmental in origin. The existence of a liability threshold is postulated that defines the observed affection status: individuals whose liability is above this threshold are affected; those whose liability is below are unaffected. We assume that the observed similarity of members of a twin pair results from variance in 3 types of causes. Additive genetic effects ( $a^2$ , the cumulative impact of multiple genes individually of small effect) contribute twice as much to the monozygoty as to the dizygoty twin correlation under the assumptions that monozygoty twins are genetically identical, whereas dizygoty twins share half their genes identical by descent (this assumption is clearly not precisely correct but may serve as a first approximation). Shared environmental effects ( $c^2$ , environmental effects to which both members of a twin pair are exposed) contribute equally to the correlation in monozygoty and dizygoty twins. Individual-specific environmental effects ( $e^2$ ) reflect environmental experiences that are not shared by the members of a twin pair and tend to make them different in liability to illness. The sum of  $a^2$ ,  $c^2$ , and  $e^2$  is constrained to unity.

The goal of univariate twin analysis is to decompose the variance in liability to the disorder in the population studied into that due to  $a^2$ ,  $c^2$ , and  $e^2$ . We were able to fit models that estimated these parameters in female participants only, as the prevalence of AN was too low in males to allow biometrical modeling. Thresholds were estimated from the data. By tradition, twin modelers

have come to use a parsimony index to determine the best-fitting submodel determined by eliminating effects due to  $a^2$  and/or  $c^2$ . However, we have shown that this is ill-advised, because simulations indicated that this practice frequently yielded the incorrect model and sharply and misleadingly biased parameter estimates.<sup>54</sup> Therefore, we present the full ACE model ( $a^2$ ,  $c^2$ , and  $e^2$ ), including parameter estimates and CIs, together with the  $\chi^2$  goodness-of-fit statistic. We used Mx for all analyses<sup>55</sup> with a script from the GenomEUtwin library (<http://www.psy.vu.nl/mxbib>) to analyze contingency tables and with CI calculation.<sup>56</sup>

## RESULTS

### SAMPLE DESCRIPTION

Of all eligible twins (N=41 499), 31 406 individual twins responded, giving an individual response rate of 75.68%. Data were obtained from both members of 12 407 pairs and from 1 member of 6592 pairs. Of the complete pairs, 3269 pairs were monozygoty, 9010 pairs were dizygoty, and 128 pairs were of unknown zygoty.

The median age of the sample was 54.6 years (interquartile range, 49.0-57.6 years). The sex distribution had a slight female predominance (50.6%). Participants had completed a median of 11.0 years of education (interquartile range, 9-14 years). The 2 cohorts consisted of twins born between 1935 and 1944 and those born between 1945 and 1958.

### RELIABILITY AND PREDICTORS OF PARTICIPATION

To establish test-retest reliability, 105 individual twins who completed the telephone screening were selected at random and reinterviewed within 2 weeks. We assessed short-term reliability for 2 key variables associated with eating disorders—low weight and dieting behavior. The Cohen  $\kappa$ <sup>57</sup> was 0.63 for AN criterion A ("Did you ever weigh less than other people thought you should weigh?") and 0.48 for the broader variable querying dieting history. These  $\kappa$  values suggest moderate to substantial test-retest reliability.<sup>58</sup>

We had access to data on all eligible twins independent of participation and were thus able to examine the predictors of participation. Significant predictors of participation in a multivariate logistic regression model included being a monozygoty twin (odds ratio [OR], 1.68 [ $P<.001$ ]), having a co-twin who was also eligible for the present study (OR, 1.44 [ $P<.001$ ]), female sex (OR, 1.39 [ $P<.001$ ]), fewer total hospitalizations (dichotomized at the 75th percentile of 4 hospitalizations; OR, 1.18 [ $P<.001$ ]), and age (OR, 1.01 [ $P<.001$ ]), but not registration in the Swedish Cancer Registry (OR, 1.01 [ $P=.85$ ]). Having a hospital discharge diagnosis of AN was not a significant predictor of participation in the SALT interview (OR, 0.79; 95% CI, 0.56-1.11). A hospital discharge diagnosis of AN was associated with increased mortality according to the death registry (OR, 2.18; 95% CI, 1.33-3.58).

### ZYGOSITY BIAS

There was no association between zygoty and any anorexia-related variable in same-sex female twins ( $P\geq.19$  for all com-

**Table 1. Prevalence by Sex, Cohort, and Diagnostic Definition\***

Diagnostic Definition of AN	No. of Participants (Prevalence, %) (95% CI)						
	Overall	Female	Female (1935-1944)	Female (1945-1958)	Male	Male (1935-1944)	Male (1945-1958)
All-source	331 (0.72) (0.64-0.80)	253 (1.20) (1.06-1.36)	54 (0.65) (0.49-0.85)	199 (1.56) (1.4-1.8)	59 (0.29) (0.22-0.37)	22 (0.29) (0.18-0.44)	37 (0.29) (0.20-0.40)
Narrow <i>DSM-IV</i>	112 (0.36) (0.29-1.43)	102 (0.62) (0.50-0.74)	14 (0.22) (0.12-0.36)	88 (0.88) (0.71-1.08)	10 (0.07) (0.03-0.12)	0	10 (0.11) (0.15-0.20)
Broad <i>DSM-IV</i>	201 (0.64) (0.55-0.73)	191 (1.16) (1.00-1.33)	31 (0.48) (0.32-0.68)	160 (1.60) (1.36-1.87)	10 (0.07) (0.03-0.12)	0	10 (0.11) (0.05-0.20)

Abbreviations: AN, anorexia nervosa; CI, confidence interval.

\*Definitions are explained in "Definitions of AN" subsection of the "Methods" section.

parisons). The absence of statistically significant association between zygosity and the traits under study suggests that zygosity bias did not have an impact on the results.

### PREVALENCE

**Table 1** presents the prevalence of the 3 diagnostic definitions of AN by sex and cohort. The prevalence of AN for all 3 definitions of illness was significantly greater in the younger cohort of twins (all-source AN,  $\chi^2=5.73$  [ $P<.001$ ]; narrow *DSM-IV* AN,  $\chi^2=4.91$  [ $P<.001$ ]; broad *DSM-IV* AN,  $\chi^2=6.19$  [ $P<.001$ ]). There were no cases of broad or narrow *DSM-IV* AN identified in male participants in the older cohort of SALT twins.

### SAMPLE CHARACTERISTICS

**Table 2** presents the demographic and clinical characteristics obtained from SALT interviews of individuals with narrow *DSM-IV* AN and broad *DSM-IV* AN compared with those without AN. Individuals with narrow *DSM-IV* AN were significantly younger and had significantly more education than those without AN. In addition, after controlling for age, they had significantly lower current body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters), but there were no differences in lifetime maximum BMI. Their age at maximum lifetime BMI was significantly lower than those without AN. As expected, individuals with narrow *DSM-IV* AN reported significantly greater behavioral features of eating disorders, including dieting, purging, laxative use, vomiting, and excessive exercise, than those without AN. They also reported significantly higher prevalences of lifetime major depressive disorder and generalized anxiety disorder. Notably, a significantly greater proportion of individuals with AN reported themselves to be in good or excellent health. The pattern of results for broad *DSM-IV* AN was identical, with the exception of there being no significant difference in self-rated current general health.

### IMPACT OF AN ON LATER OVERWEIGHT

To determine the extent to which lifetime AN is protective against the development of later overweight (BMI,  $\geq 25$ ) (<http://www.cdc.gov/nccdphp/dnpa/obesity/defining>

.htm), we used logistic regression with generalized estimating equation corrections, with overweight status at the time of the SALT interview as the outcome variable. We focused on individuals with lifetime narrow *DSM-IV* AN who did not have a BMI at the time of the SALT interview of 17.5 or lower (the BMI cutoff for *ICD-10* AN, which was used as a proxy for current illness to exclude individuals from the analysis who may still have had symptomatic AN at the time of the SALT interview). Results indicated that 36.5% of individuals without AN and 12.5% of individuals with a history of AN were overweight (OR, 0.29; 95% CI, 0.16-0.54 [ $P<.001$ ]), suggesting that a lifetime history of AN is protective against the later development of overweight.

### PROSPECTIVE RISK FACTORS

**Table 3** presents the results of logistic regressions using generalized estimating equation corrections predicting all-source AN status from prospective data collected in 1973 for female participants only. We chose to use the all-source AN variable as the outcome to minimize the possibility of including individuals who were cases of AN in the control sample. We restricted the analyses to female participants because there were few males with AN. Using this definition, we excluded 48 individuals who had all-source AN but who reported their onset of AN to be before 1973 (using a 5-year grace period to account for the duration of the 1973 assessment and inaccuracies of recall). Seventy-six individuals met criteria for all-source AN and reported their onset of AN to be after 1973. These 76 women constitute the sample for this analysis in comparison with 12 999 women who did not meet the criteria for AN. Based on the literature and available data, we chose the following 7 self-reported potential predictors assessed in 1973: BMI, gastric problems, excessive exercise (defined as much or very much physical activity vs little or almost no physical activity), perceived excessive life stress, neuroticism, and extraversion. Of these variables, only higher neuroticism in 1973 was strongly predictive of all-source AN ( $P<.001$ ).

### TETRACHORIC CORRELATIONS

For twin modeling, we focused on twin data from the SALT interview and therefore present results for narrow

**Table 2. Sample Description of Female Participants Controlling for Age\***

Variable	Narrow <i>DSM-IV</i> AN					Broad <i>DSM-IV</i> AN				
	AN (n = 102)	No AN (n = 16 295)	OR (95% CI)	$\chi^2$ Test	P Value	AN (n = 191)	No AN (n = 16 206)	OR (95% CI)	$\chi^2$ Test	P Value
Age, mean (SD), y	49.5 (5.2)	53.8 (5.8)	1.15 (1.11-1.19)	7.19	<.001	50.3 (5.1)	53.8 (5.8)	1.12 (1.09-1.14)	8.64	<.001
Education, mean (SD), y	12.7 (2.9)	11.2 (3.1)	0.91 (0.84-0.97)	-2.85	.004	12.3 (2.9)	11.2 (3.1)	0.93 (0.89-0.98)	-2.76	.006
BMI at interview, mean (SD)	22.1 (3.9)	24.4 (3.7)	1.23 (1.10-1.37)	3.78	<.001	22.8 (3.9)	24.4 (3.7)	1.13 (1.21-3.88)	3.88	<.001
BMI maximum, mean (SD)	25.0 (4.2)	25.8 (4.2)	1.03 (0.97-1.10)	1.08	.28	25.2 (4.3)	25.8 (4.2)	1.02 (0.98-1.06)	1.02	.31
Age at maximum weight, mean (SD), y	32.2 (13.7)	45.8 (12.3)	1.07 (1.05-1.09)	8.24	<.001	35.8 (14.0)	45.8 (12.3)	1.05 (1.04-1.06)	8.42	<.001
Dieting for weight loss Use of compensatory behaviors	51 (50.0)	733 (4.5)	19.03 (12.69-28.53)	14.26	<.001	93 (48.7)	691 (4.3)	19.66 (14.59-26.49)	19.58	<.001
Laxatives	18 (17.6)	41 (0.3)	91.91 (49.26-171.51)	14.20	<.001	26 (13.6)	33 (0.2)	82.89 (47.86-143.57)	15.76	<.001
Vomiting	24 (23.5)	114 (0.7)	32.37 (19.49-53.75)	13.43	<.001	43 (22.5)	95 (0.6)	39.65 (26.55-59.20)	17.99	<.001
Excessive exercise	56 (54.9)	212 (1.3)	74.22 (48.72-112.97)	20.10	<.001	82 (42.9)	186 (1.1)	54.53 (39.32-75.62)	23.97	<.001
Any form (including dieting)	78 (76.5)	896 (5.5)	49.02 (30.86-77.86)	16.49	<.001	136 (71.2)	838 (5.2)	41.18 (29.84-56.83)	22.63	<.001
General health	64 (62.7)	8863 (54.5)	1.51 (1.01-2.27)	1.99	.046	109 (57.1)	8818 (54.6)	1.18 (0.88-1.58)	1.10	.27
Change in health	78 (76.5)	12 192 (75.1)	1.01 (0.64-1.59)	0.04	.97	147 (77.0)	12 123 (75.0)	1.05 (0.75-1.44)	0.29	.77
Health limits activities	75 (73.5)	11 479 (70.6)	0.86 (0.51-1.44)	-0.59	.55	128 (67.4)	11 426 (70.7)	0.75 (0.55-1.02)	-1.82	.07
Days health limits activities, mean (SD)	85 (83.3)	13 948 (85.6)	0.99 (0.63-1.51)	-0.07	.95	159 (83.2)	13 874 (85.7)	0.86 (0.59-1.26)	-0.79	.43
Lifetime MDD	60 (59.4)	4660 (29.1)	3.32 (2.24-4.94)	5.93	<.001	107 (57.2)	4613 (29.0)	3.10 (2.31-4.15)	7.58	<.001
Lifetime GAD	19 (18.8)	925 (5.7)	3.47 (2.12-5.67)	4.96	<.001	38 (20.1)	906 (5.7)	3.90 (2.72-5.58)	7.43	<.001

Abbreviations: AN, anorexia nervosa; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; GAD, generalized anxiety disorder; MDD, major depression; OR, odds ratio.

\*Unless otherwise indicated, variables are expressed as number (percentage) of participants. Because of missing data, percentages may vary. Narrow and broad *DSM-IV* definitions of AN are described in the "Definitions of AN" subsection of the "Methods" section. Statistics are Wald  $\chi^2$  from logistic regressions with generalized estimating equations for correlated samples.

**Table 3. 1972-1973—Measured Variables Predicting All-Source AN in Female Participants of All Ages, Covarying Age at 1973**

Predictor Variable in 1973	AN (n = 76)	No AN (n = 12 999)	OR (95% CI)	$\chi^2$ Test	P Value
BMI, mean (SD)	19.92 (2.74)	20.66 (2.53)	0.99 (0.87-1.14)	-0.11	.91
Neuroticism, mean (SD), z score	0.46 (1.06)	-0.02 (0.99)	1.62 (1.27-2.05)	-3.91	<.001
Extraversion, mean (SD), z score	0.06 (1.11)	0.00 (1.00)	1.07 (1.23-1.43)	-0.51	.61
Gastric problems, %	23	19	1.18 (0.61-2.30)	0.49	.62
Excessive exercise, %	6	4	0.42 (0.13-1.34)	-1.47	.14
Perceived life stress, %	13	18	1.42 (0.76-2.64)	1.1	.27

Abbreviations: AN, anorexia nervosa; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; OR, odds ratio.

and broad *DSM-IV* AN. **Table 4** presents descriptive data for the twins used in this report. The tetrachoric correlations and contingency table data for narrow and broad *DSM-IV* AN are shown for the different types of twin pairs (monozygotic male, dizygotic male-male, monozygotic female, dizygotic female-female, and dizygotic male-female and female-male twin pairs).

First, as can be seen in the rightmost columns of Table 4, the rarity of AN in male participants and the infrequency of concordant pairs rendered it impossible to calculate tetrachoric correlations for male twins for either definition of illness. Second, for both definitions of illness in female participants, the tetrachoric correlations for monozygotic twin pairs were substantially larger than

those for dizygotic pairs. Third, for opposite-sex dizygotic twin pairs, tetrachoric correlations were negative, reflecting the absence of concordant male-female pairs for either definition of illness and the disproportionate female-male ratio of AN.

#### TWIN MODELING

We conducted twin analyses only for female-female twin pairs, given the rarity of AN in male participants. **Table 5** depicts the results of structural equation modeling for the narrow and broad *DSM-IV* definitions of AN from SALT. For both definitions of illness, the structural equation models provided an adequate fit to the data. We sug-

gest a predominant focus on the 95% CIs rather than the point estimates because these contain information not only about the estimate but also about the precision with which the estimate is known.<sup>54</sup> The heritability of narrow *DSM-IV* AN was estimated to be  $a^2=0.56$  (95% CI, 0.00-0.87) with the remaining variance attributable to shared environment ( $c^2=0.05$ ; 95% CI, 0.00-0.64) and unique environment ( $e^2=0.38$ ; 95% CI, 0.13-0.84). Estimates for broad *DSM-IV* AN are presented in Table 5.

## COMMENT

This study represents, to our knowledge, the largest twin study conducted to date of individuals with rigorously diagnosed AN. Our results confirm and extend the findings of previous studies on prevalence, risk factors, and heritability.

Consistent with several studies, the lifetime prevalence of AN identified by all sources was 1.20% in female participants and 0.29% in male participants, reflecting the typically observed disproportionate sex ratio. Similarly, our data show a clear increase in prevalence of *DSM-IV* AN (broadly and narrowly defined) with historical time in Swedish twins. The increase was apparent for both sexes. Hoek and van Hoeken<sup>3</sup> also reported

a consistent increase in prevalence, with a leveling out of the trajectory around the 1970s. Future studies in younger STR participants will allow verification of this observation.

Several observed differences between individuals with and without AN were expected, ie, more frequent endorsement of symptoms of eating disorders. Other differences are noteworthy. Consistent with previous observations, individuals with lifetime AN reported lower BMIs at the time of interview than did individuals with no history of AN. Although this could be partially accounted for by the presence of currently symptomatic individuals in the sample, our results remained unchanged when we excluded individuals likely to have current AN (ie, current BMI,  $\leq 17.5$ ). Previous studies have shown that, even after recovery, individuals with a history of AN have a low BMI.<sup>59</sup> Although perhaps obvious, a history of AN appears to offer protection against becoming overweight. The protective effect also holds for obesity (BMI,  $\geq 30$ ), although there were too few individuals in the sample with histories of AN who had become obese for meaningful analyses. Despite the obvious nature of this observation, the mechanism whereby protection against overweight is afforded is not immediately clear. Those with a history of AN reported greater current exercise and a perception of being in better physical health. One possible interpretation of this pattern of findings is that individuals with a history of AN continue to display subthreshold symptoms of AN (ie, excessive exercise and caloric restriction) that contribute to their low BMIs. Alternatively, symptoms that were pathologic during acute phases of AN, such as excessive exercise and decreased caloric intake, may resolve over time into healthy behaviors, such as consistent exercise patterns and a healthful diet, that result in better weight control and self-rated health.

Regardless of which of these hypotheses is true, another intriguing difference is that individuals with lifetime AN report a lower age at highest BMI, although the magnitude of the highest lifetime BMI does not differ in those with and without a history of AN. Those with AN report their highest lifetime BMIs early in their fourth decade of life on average, whereas those without AN report their highest BMIs in the middle of their fifth decade of life (close to the age at interview). On a population level, adults tend to gain on average 2.25 kg (5 lb) per decade until reaching their eighth decade of life.<sup>60</sup> Although more detailed data are necessary to make definitive statements about different weight trajectories, our results suggest not only that individuals with AN may maintain low BMIs but also that they may not follow the typical adult weight gain trajec-

**Table 4. Descriptive Twin Data for Univariate Analyses of AN Definitions\***

Phenotype, Zygosity	Tetrachoric Correlation	ASE	No. of Twin Pairs		
			T1-No/ T2-No	T1-Yes/ T2-No	T1-Yes/ T2-Yes
<b>Narrow <i>DSM-IV</i> AN</b>					
MZ-F	0.563	0.205	1802	14	1
DZ-F	0.355	0.199	2375	33	1
MZ-M	†	†	1425	2	0
DZ-M	†	†	2023	1	0
DZ-FM	-0.741	0.000	2230	20	0
DZ-MF	0.726	0.000	2212	16	0
<b>Broad <i>DSM-IV</i> AN</b>					
MZ-F	0.303	0.203	1782	34	1
DZ-F	0.151	1.184	2347	52	1
MZ-M	†	†	1425	2	0
DZ-M	†	†	2023	1	0
DZ-FM	-0.999	0.000	2218	32	0
DZ-MF	-0.891	0.000	2201	27	0

Abbreviations: AN, anorexia nervosa; ASE, asymptotic standard error; DZ, dizygotic; F, female; M, male; MZ, monozygotic; no, AN absent; T1, twin 1; T2, twin 2; yes, AN present.

\*Narrow and broad *DSM-IV* definitions of AN are described in the "Definitions of AN" subsection of the "Methods" section.

†Indicates not calculable.

**Table 5. Parameter Estimates of Univariate Analyses of Anorexia Definitions in Female Participants\***

Phenotype	Goodness of Fit, $\chi^2$	$a^2$ (95% CI)	$c^2$ (95% CI)	$e^2$ (95% CI)
Narrow <i>DSM-IV</i> AN	2.38†	0.56 (0.00-0.87)	0.05 (0.00-0.64)	0.38 (0.13-0.84)
Broad <i>DSM-IV</i> AN	5.12†	0.31 (0.00-0.62)	0.00 (0.00-0.44)	0.68 (0.37-1.00)

Abbreviations:  $a^2$ , proportion of variance due to additive genetic effects; AN, anorexia nervosa;  $c^2$ , proportion of variance due to common or shared environmental effects; CI, confidence interval;  $e^2$ , proportion of variance due to environmental effects specific to an individual.

\*Narrow and broad *DSM-IV* definitions of AN are described in the "Definitions of AN" subsection of the "Methods" section.

†Differences were not significant.

tories. These data are particularly intriguing in light of recent reports of AN being associated with reduced risk of certain cancers<sup>61,62</sup> and protective against mortality due to diseases of the circulatory system.<sup>63,64</sup> Energy intake is closely related to fat intake and obesity, both of which have also been related to cancer development<sup>65,66</sup> and both of which are reduced in AN. Further detailed studies of the weight trajectories and health of individuals with histories of AN are required to explicate the nature and magnitude of these intriguing findings.

Of the variables assessed in 1972 to 1973, neuroticism emerged as the only significant prospective predictor of AN. This is notable because there have been few truly prospective risk factor studies of AN. This finding is intriguing and entirely consistent with studies reporting increased antecedent anxiety disorders in individuals in whom AN later developed.<sup>67,68</sup> Individuals with high neuroticism scores are characterized by emotional instability, low self-esteem, and feelings of anxiety, depression, and guilt.<sup>69</sup> The construct of neuroticism is extraordinarily robust<sup>70</sup>: neuroticism or a very similar construct can be found in essentially every major theory of personality.<sup>71-73</sup> Our results suggest that the early existence of this trait may predispose to AN. However, neuroticism is known to covary with depression,<sup>74,75</sup> and in the absence of data on depression in the 1972-1973 assessment, we were unable to determine the extent to which high neuroticism reflected current mood state. Nonetheless, these findings, coupled with the elevated rates of generalized anxiety disorder and major depression in individuals with AN observed in this sample, are in line with an increasingly large body of clinical literature suggesting that anxiety proneness may represent a risk pathway to AN.<sup>76</sup> What remains unknown is whether neuroticism is a non-specific predictor of the development of psychopathology in general or whether it is specifically predictive of the emergence of AN. Finally and somewhat surprisingly, BMI and exercise levels did not predict AN onset.

Although the strengths of this study include the sample size and prospective risk factor data, several limitations must be considered. First, our sample represents individuals born between 1935 and 1958, before widespread recognition of eating disorders. Although our diagnostic interviews were lifetime retrospective interviews, many individuals in this cohort may never have been detected or labeled as having had AN. Moreover, the likelihood of detection may have increased in the latter birth years, meaning that the observed increase in prevalence, rather than being a true secular trend, may merely be a reflection of increased detection. Second, as is often the case in large population-based investigations, one is forced to make trade-offs between the size of a population and the comprehensiveness of an evaluation. Thus, we are hampered by somewhat cursory evaluations of some of our variables such as exercise, health, and personality.

Owing to the relative rarity of the condition, we have not had reliable estimates of the contribution of genes and environment to liability to AN. To our knowledge, ours represents the first twin study of both narrowly and broadly defined AN characterized by structured diagnostic interviews. As such, these results suggest a substantial contribution of genetic factors to liability to AN, with heritability estimates of 0.56 and 0.31 for narrow

and broad DSM-IV AN, respectively. Despite the size of the study, our estimates remain imprecise, as reflected in the broad CIs. Comparing the biometrical models for narrow and broad DSM-IV AN, the narrow DSM-IV AN model fit the data better and yielded a higher heritability estimate. The more narrowly defined disorder may represent a more homogeneous phenotype that yields higher heritability estimates. Indeed, molecular genetic research has found that restricting the clinical definition of AN to the narrow phenotype of restricting AN enabled the detection of linkage, whereas broader phenotypes failed to yield significant linkage signals.<sup>77</sup>

In conclusion, the prevalence of AN increased in both sexes between 1935 and 1958, while consistently afflicting females disproportionately. Individuals with a history of AN appear to be protected from the development of overweight later in life. Anorexia nervosa is a moderately heritable psychiatric disorder that may be predicted by the presence of early neuroticism.

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### Correction

**Errors in Table.** In the Original Article by Cynthia M. Bulik, PhD, et al, titled "Prevalence, Heritability, and Prospective Risk Factors for Anorexia Nervosa," published in the March 2006 issue of the *Archives* (2006;63[3]:305-312), errors of presentation occurred in **Table 4** on page 310. These were errors of presentation only and have no effect on the findings of the study. The corrected table is reproduced here in its entirety.

**Table 4. Descriptive Twin Data for Univariate Analyses of AN Definitions\***

Phenotype	Zygosity	Tetrachoric Correlation	ASE	No. of Twin Pairs			
				T1-No/T2-No	T1-Yes/T2-No	T1-No/T2-Yes	T1-Yes/T2-Yes
Narrow DSM-IV AN	MZ-M	†	†	1425	0	2	0
	DZ-M	†	†	2023	0	1	0
	MZ-F	0.563	0.205	1802	7	7	1
	DZ-F	0.355	0.199	2375	12	21	1
	DZ-FM	-0.741	0.000	2230	18	2	0
	DZ-MF	-0.726	0.000	2212	3	13	0
Broad DSM-IV AN	MZ-M	†	†	1425	0	2	0
	DZ-M	†	†	2023	0	1	0
	MZ-F	0.303	0.203	1782	15	19	1
	DZ-F	0.151	1.184	2347	20	32	1
	DZ-FM	-0.999	0.000	2218	30	2	0
	DZ-MF	-0.891	0.000	2201	3	24	0

Abbreviations: AN, anorexia nervosa; ASE, asymptotic standard error; DZ, dizygotic; F, female; M, male; MZ, monozygotic; no, AN absent; T1, twin 1 (number refers to birth order); T2, twin 2; yes, AN present.

\*Phenotypes are described in the "Definitions of AN" subsection of the "Methods" section.

†Indicates not calculable.

*For editorial comment, see page 994. See also page 1052.*