

# A Controlled Family Study of Anorexia Nervosa and Bulimia Nervosa

## Psychiatric Disorders in First-Degree Relatives and Effects of Proband Comorbidity

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**Background:** We used contemporary family-epidemiological methods to examine patterns of comorbidity and familial aggregation of psychiatric disorders for anorexia and bulimia nervosa.

**Methods:** Direct interviews and blind best-estimate diagnostic procedures were used with diagnostically "pure" groups of probands with eating disorders and a matched control group. Lifetime prevalence rates of eating disorders, mood disorders, substance use disorders, anxiety disorders, and selected personality disorders were determined in female probands with restricting anorexia nervosa (n = 26) or bulimia nervosa (n = 47), control women (n = 44), and first-degree biological relatives (n = 460).

**Results:** Relatives of anorexic and bulimic probands had increased risk of clinically subthreshold forms of an eating disorder, major depressive disorder, and obsessive-compulsive disorder. Familial aggregation of major depressive disorder and obsessive-compulsive disorder was

independent of that of anorexia nervosa and bulimia nervosa. These relatives also had increased risk of other anxiety disorders, but the mode of familial transmission was not clear-cut. The risk of substance dependence was elevated among relatives of bulimic probands compared with relatives of anorexic probands, and familial aggregation was independent of that of bulimia nervosa. The risk of obsessive-compulsive personality disorder was elevated only among relatives of anorexic probands, and there was evidence that these 2 disorders may have shared familial risk factors.

**Conclusions:** There may be a common familial vulnerability for anorexia nervosa and bulimia nervosa. Major depressive disorder, obsessive-compulsive disorder, and substance dependence are not likely to share a common cause with eating disorders. However, obsessional personality traits may be a specific familial risk factor for anorexia nervosa.

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**T**HE PATHOGENESIS of eating disorders (EDs) is poorly understood, although it is well recognized that these conditions are often accompanied by other psychiatric symptoms, in particular depression, anxiety, substance abuse, and obsessive-compulsive symptoms. These comorbid symptoms are substantially exaggerated by malnutrition and pathological eating behaviors, but in some they antedate weight loss or disordered eating or persist after recovery from disordered eating.<sup>1-3</sup> Both the premorbid and continued presence of such symptoms after recovery suggest that they may not simply be sequelae of malnutrition or pathological feeding behavior.

In the absence of high-risk paradigms, unraveling cause and effect in people with EDs is a vexing task. One potential strategy to investigate familial transmissible liabilities and mechanisms that

may underlie susceptibility to EDs is the use of the family study design, in which patterns of familial aggregation of other disorders among first-degree relatives of probands are examined.

The degree to which EDs may share transmitted liabilities with other psychiatric disorders remains uncertain. Whereas the incidence of major mood disorders is often elevated in relatives of probands with EDs,<sup>4-8</sup> several family<sup>4,6</sup> and twin<sup>9</sup> studies show that mood disorders and EDs do not have a shared underlying diathesis. Likewise, several studies<sup>8,10,11</sup> have found increased rates of substance abuse or dependence among the relatives of bulimic women; however, recent evidence<sup>9,12-14</sup> suggests that bulimia nervosa (BN) and substance use disorders are transmitted independently in families. Few data exist regarding the rates, or transmission patterns, of other psychiatric disorders among family members, despite the fact that anxi-

## SUBJECTS AND METHODS

### PROBANDS

Probands included 26 women who fulfilled *DSM-III-R* criteria<sup>24</sup> for AN, 47 women who fulfilled *DSM-III-R* criteria for BN, and 44 control women (CW) with no history of an ED. All probands with EDs were recruited from the inpatient and outpatient ED programs at Western Psychiatric Institute and Clinic, Pittsburgh, Pa, and from advertisements in a campus newspaper. The CW were recruited from a commercial mailing list and were matched by age and ZIP code to the probands with EDs. All probands gave informed consent to participate in this study according to institutional guidelines, and to permit research staff to contact first-degree relatives to solicit participation in this study.

The probands with AN ranged in age from 16 to 39 years (mean  $\pm$  SD, 24.5  $\pm$  5.9 years) and had never engaged in bingeing or vomiting. Since a sizable minority of women with AN eventually develop binge eating,<sup>25</sup> recruitment was limited to women who fulfilled diagnostic criteria for a minimum of 3 years before ascertainment. These criteria were used to ensure that the AN group consisted of "pure restrictors" who would be less likely to later develop bulimic symptoms. Similarly, to obtain a "pure bulimic" group, probands with BN must have had the onset of BN at least 3 years before study entry and have had no history of AN. The probands with BN ranged in age from 17 to 43 years (mean  $\pm$  SD, 25.3  $\pm$  5.9 years).

The CW were selected to have never had a history of any diagnosable ED or ED behavior. This was done to ascertain rates of psychiatric illness in family members when an ED was not present in the proband. These probands ranged in age from 17 to 41 years (mean  $\pm$  SD, 26.1  $\pm$  6.2 years). Potential CW probands were excluded if they had a history of weighing less than 90% or more than 125% of ideal body weight since menarche.<sup>26</sup> Because CW were chosen to otherwise be a representative community sample, they were not screened for a lifetime history of any other psychiatric disorder, aside from an ED, before entering the study. We have no evidence to suggest that our CW were not representative of the general population,<sup>27</sup> with the exception that they had

no history of ED problems. However, they also had a relatively low rate of major depressive disorder (MDD). Because malnutrition has been shown to exaggerate depressive symptoms,<sup>28,29</sup> we used additional criteria requiring substantial impairment in school or occupational functioning independent of an episode of malnutrition to make this diagnosis for all probands and relatives. All other diagnoses were made according to *DSM-III-R* criteria.<sup>24</sup>

### ASSESSMENT OF PROBANDS

All interviews with AN, BN, and CW probands were conducted face to face. Eighty-five percent of AN probands had restored their weight (ie, above 85% of ideal body weight) at the time of interview. Because impaired cognitive functioning at low body weight might have confounded the collection of reliable information, subjects below 85% of ideal body weight were interviewed only after a psychiatrist (W.H.K.) judged them to have reasonably intact cognitive functioning.

### ASSESSMENT OF RELATIVES

Whenever possible, first-degree relatives were interviewed in person; otherwise they were interviewed by telephone. Few relatives of each proband group (8 in the AN group, 17 in the BN group, and 14 in the CW group) refused participation in the study. The mean number of relatives in the study per proband was 3.4 for AN, 3.5 for BN, and 4.3 for CW. The percentage of relatives who were directly interviewed either in person or by telephone was 73% for AN, 64% for BN, and 72% for CW. These rates did not differ significantly across groups ( $\chi^2 = 3.52, P < .17$ ). Among relatives who were directly interviewed, 29% of AN, 31% of BN, and 37% of CW probands' relatives were interviewed in person; the remainder were interviewed by telephone. These rates also did not differ significantly from each other across groups ( $\chi^2 = 1.47, P < .48$ ). Information was obtained on unavailable relatives through family history interviews, with the proband and all other participating family members serving as informants. Thus, every proband, and the majority of relatives, was directly interviewed and also had multiple informants from whom psychiatric

ety disorders and personality disorders commonly occur in probands with EDs.<sup>15-22</sup> Finally, although evidence of the familiarity of EDs exists,<sup>4,10,23</sup> whether EDs "breed true" or share transmitted liabilities with various behavioral phenotypes remains largely unsettled.

The purpose of the study reported herein was to use contemporary family-epidemiological methods to determine rates and patterns of cotransmission of psychiatric disorders in families of probands with EDs. The questions addressed in this study are as follows: (1) Do EDs aggregate in families of probands with EDs? (2) Are rates of other psychiatric disorders elevated in relatives of such probands, and are there differential patterns of familial aggregation in probands with anorexia nervosa (AN) and BN? (3) Is there evidence that EDs share transmissible risk factors in common with other major psychiatric disorders?

## RESULTS

### CHARACTERISTICS OF PROBANDS AND RELATIVES

The 3 groups of probands (**Table 1**) were of similar ages at the time of the study. The AN and BN probands had similar ages at onset of their ED. Predictably, AN probands weighed significantly less at the time of the study and had been at a lower percentage body weight in the past compared with BN and CW probands. In the past, BN probands had weighed significantly more than both other groups, and CW had been at higher weights than AN probands. The 3 groups of relatives were of similar ages at the time of the study, with the exception of a trend for the sisters of AN probands to have a younger average age than the sisters of BN and CW probands

diagnostic information was obtained. Interviewers were kept blind to the identity and diagnosis of the proband whose relative they were assessing. Their report on the proband was obtained last, to keep the interviewer blind as to the identification of the family.

## MEASURES

All interviewers were master's- or doctoral-level psychologists with diagnostic assessment experience. Interviewers underwent extensive training with each assessment instrument. Initial training of the 5 interviewers involved didactic instruction and reviews of taped and live interviews. All scored interviews were reviewed by a senior member of the research team.

All probands and relatives older than 17 years were given the Schedule for Affective Disorders and Schizophrenia–Lifetime Version,<sup>30</sup> as modified by Merikangas and colleagues,<sup>31</sup> to establish lifetime *DSM-III-R* Axis I disorders. The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic Version<sup>32</sup> was used to assess lifetime psychopathological disorders in those subjects who were younger than 18 years. The Eating Disorders Family History Interview, a structured clinical interview (M.S., unpublished data, 1987), was used to gather detailed information on weight and eating history. A modified version of the Eating Disorders Family History Interview was used to make *DSM-III-R* ED diagnoses among probands and relatives, as it provides extensive information about eating-related variables and complements the briefer ED modules of the Schedule for Affective Disorders and Schizophrenia–Lifetime Version and Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic Version. The Family History Research Diagnostic Criteria,<sup>33</sup> updated by Merikangas and colleagues<sup>31</sup> to conform to *DSM-III-R* criteria, was also used to collect psychiatric history data on first-degree relatives. We additionally conducted a preliminary assessment of obsessive-compulsive personality disorder (OCPD) and cluster B personality disorders in probands and relatives. Subjects were asked the 11 questions from the Structured Clinical Interview for *DSM-III-R* Personality Disorders<sup>34</sup> that constitute an OCPD diagnosis, and were also asked questions from

the Personality Disorders Examination<sup>35</sup> that were chosen to assess cluster B disorders.

## BEST-ESTIMATE DIAGNOSTIC PROCEDURES

Final diagnoses were rendered at conferences where the interviewers, reviewers, and the principal investigator were kept blind to the identity of the families. Interviewers presented their diagnoses to the team, and supporting evidence for these diagnoses was discussed. Also included was the interviewer's level of certainty for assigned diagnoses on a 3-point scale indicating extent of confidence in the subject's report. Members of the same family were not presented consecutively, to prevent diagnostic bias that might have resulted from hearing diagnoses of other family members. Probands were presented after all other relatives' diagnoses were completed.

## DATA ANALYSIS

Unadjusted lifetime rates of disorders for probands and relatives were compared by  $\chi^2$  tests with 1 *df* and Yates correction for  $2 \times 2$  tables or Fisher exact tests where appropriate. The same analyses were performed to compare disorder rates between siblings and parents in each group. Alpha was set at  $P < .05$ . Age-corrected lifetime rates among relatives were compared by Cox proportional hazards (PH) model, a semi-parametric multivariate regression model for survival data.<sup>36</sup> The PH procedure yields a ratio of the hazards, or age-specific incidences, of the outcome variable (ie, disorders of interest in relatives) while simultaneously controlling for potentially confounding variables. Three covariates were included in all PH models: the sex, age, and interview status of the relative (ie, whether the relative was directly interviewed or whether information was obtained solely from family history interviews with other relatives). The specificity of transmission of EDs and other disorders was examined by stratification of AN and BN probands by the presence or absence of comorbid disorders in which significant aggregation was observed in the PH models. Rates of illness in the relatives of these stratified groups were then compared with rates among the relatives of CW. All analyses were performed with BMDP statistical software.<sup>37</sup>

**(Table 2).** Similar percentages of relatives from each proband group were directly interviewed.

### LIFETIME RATES OF PSYCHIATRIC DISORDERS IN PROBANDS

The AN and BN probands had similar lifetime rates of MDD, and these rates were significantly greater than rates among CW probands (**Table 3**). The highest rates of obsessive-compulsive disorder (OCD) and OCPD comorbidity were found among AN probands, who differed significantly from both BN and CW probands. The AN probands also had increased rates of generalized anxiety disorder (GAD), as well as social and simple phobias, compared with CW. The BN probands had significantly increased rates of alcohol and drug dependence compared with both AN and CW probands. In addition, BN probands had significantly el-

evated rates of posttraumatic stress disorder, OCD, and cluster B personality disorders compared with CW.

### LIFETIME RATES OF PSYCHIATRIC DISORDERS IN RELATIVES

Unadjusted lifetime rates of disorders among first-degree relatives are shown in **Table 4**. Relatives of AN and BN probands had similar lifetime rates of ED not otherwise specified and any ED, and these rates were significantly greater than rates among relatives of CW probands. Relatives of BN probands had significantly higher rates, and relatives of AN probands had a trend ( $P < .06$ ) toward higher rates, of MDD than relatives of CW probands. Relatives of both AN and BN probands demonstrated increased rates of GAD and panic disorder compared with relatives of CW. Relatives of AN probands had significantly increased rates of social phobia and

**Table 1. Characteristics of Probands\***

	AN (n = 26)†	BN (n = 47)†	CW (n = 44)†	Test	P
Age at study, y	24.5 ± 5.9	25.3 ± 5.9	26.1 ± 6.2	F <sub>2,114</sub> = 0.57	.57
Age at eating disorder onset, y	16.3 ± 4.3	16.9 ± 3.2	..‡	F <sub>1,71</sub> = 1.24	.27
% IBW at study entry	90.4 ± 14.8 <sub>a</sub>	106.6 ± 13.0 <sub>b</sub>	107.9 ± 9.7 <sub>b</sub>	F <sub>2,114</sub> = 18.98	<.001
Lowest % IBW	62.6 ± 11.4 <sub>a</sub>	91.4 ± 8.6 <sub>b</sub>	95.1 ± 9.6 <sub>b</sub>	F <sub>2,114</sub> = 103.04	<.001
Highest % IBW	102.3 ± 11.1 <sub>a</sub>	118.6 ± 12.5 <sub>b</sub>	109.4 ± 9.1 <sub>c</sub>	F <sub>2,114</sub> = 19.51	<.001

\*AN indicates anorexic probands; BN, bulimic probands; CW, control women; and IBW, ideal body weight.<sup>26</sup> Each row represents a separate analysis of variance and pairwise comparison. For IBW variables, values with different subscript letters differ at P<.01.

†Data are given as mean ± SD.

‡Ellipses indicate data not applicable.

**Table 2. Characteristics of Relatives\***

	AN	BN	CW	Test	P
All relatives, No. (age, y)	93 (40.1 ± 15.3)	177 (41.9 ± 15.6)	190 (40.2 ± 14.8)	F <sub>2,457</sub> = 0.33	.72
Females, No.	46	89	100		
Mothers, No. (age, y)	26 (51.7 ± 7.4)	47 (50.7 ± 9.5)	44 (52.5 ± 8.6)	F <sub>2,114</sub> = 0.50	.61
Sisters, No. (age, y)	20 (24.4 ± 6.9)	42 (30.0 ± 11.9)	56 (29.6 ± 7.7)	F <sub>2,115</sub> = 2.74	.07
Males, No.	47	88	90		
Fathers, No. (age, y)	25 (52.9 ± 6.9)	47 (54.9 ± 11.1)	44 (54.9 ± 8.7)	F <sub>2,113</sub> = 0.42	.66
Brothers, No. (age, y)	22 (26.7 ± 8.5)	41 (30.1 ± 10.0)	46 (27.9 ± 7.0)	F <sub>2,106</sub> = 1.34	.27
% of all relatives directly interviewed	73	64	72	χ <sup>2</sup> = 3.52	.17†

\*AN indicates relatives of anorexic probands; BN, relatives of bulimic probands; and CW, relatives of control women. Ages are given as mean ± SD. All results are from 1-way analyses of variance and pairwise comparisons unless otherwise noted.

†Results of a χ<sup>2</sup> test with 2 df.

OCD compared with relatives of CW probands. They also had significantly increased rates of OCPD compared with relatives of both BN and CW probands. Relatives of BN probands had significantly increased rates of posttraumatic stress disorder and cluster B personality disorders compared with relatives of CW probands.

When siblings and parents were analyzed separately, several patterns emerged. First, siblings had higher rates of substance use disorders than parents. Specifically, siblings of BN probands had higher rates of alcohol abuse (χ<sup>2</sup> = 4.88, P<.03), drug abuse (χ<sup>2</sup> = 7.86, P<.01), and drug dependence (χ<sup>2</sup> = 10.83, P<.001) than parents of BN probands. Siblings of CW probands also had higher rates of drug dependence (χ<sup>2</sup> = 5.02, P<.03) than parents of CW probands. Second, siblings of BN probands demonstrated a trend toward higher rates of ED not otherwise specified diagnoses (χ<sup>2</sup> = 3.55, P<.06) compared with their parents. In contrast, there were several disorders where parents had higher rates than siblings. Parents of CW probands had significantly higher rates of simple phobia (χ<sup>2</sup> = 4.68, P<.04) than siblings. There were also significantly higher rates of OCPD among parents of AN probands (χ<sup>2</sup> = 5.96, P<.02) and BN probands (χ<sup>2</sup> = 4.39, P<.04) than siblings of these proband groups.

**Table 5** describes the risk ratios obtained from the PH regression models for selected disorders that occurred at sufficient frequencies in relatives to allow for such comparisons. The risk ratios are adjusted for effects of potentially influential covariates, specifically, sex, age, and interview status of the relative in the model. The major findings are as follows. First, MDD, ED not otherwise specified, GAD, and OCD occurred with significantly greater fre-

quency among relatives of both groups of ED probands, as compared with relatives of CW probands, with risk ratios ranging from 2.3 to 30.7. Importantly, relatives of AN and BN probands had roughly similar relative risk ratios of these disorders in comparison with relatives of CW probands. Panic disorder also appeared to occur at similarly elevated rates among relatives of both ED proband groups, but rates were too low to include in the PH analyses. Second, the risk of social phobia was twice as high among relatives of AN probands than relatives of CW probands. Third, the risk of OCPD was more than 3 times as high among relatives of AN probands than relatives of BN and CW probands. By contrast, the risk of alcohol and/or drug dependence was half as much among relatives of AN probands as among relatives of BN probands.

#### EFFECTS OF PROBAND COMORBIDITY ON OBSERVED FAMILIAL AGGREGATION

To determine if proband comorbidity accounted for the familial aggregation of the disorders described in Table 5, AN and BN probands were stratified by the presence or absence of each comorbid disorder. Unadjusted rates of disorders in relatives of stratified AN and BN probands compared with relatives of CW probands are presented in **Table 6**. Adjusted risk ratios compare the relative risk of disorders among relatives of these stratified AN and BN proband groups with that among relatives of CW (**Table 7**).

After stratification by proband comorbidity status, there were elevated adjusted risk ratios for MDD only among relatives of AN and BN probands who themselves had MDD, suggesting independent familial trans-

**Table 3. Lifetime Rates of Psychiatric Disorders Among Probands With Eating Disorders and Control Probands\***

Diagnosis in Probands	AN (n = 26)	BN (n = 47)	CW (n = 44)	$\chi^2$	P
Mood disorders					
Major depressive disorder	46 <sub>a</sub>	55 <sub>a</sub>	2 <sub>b</sub>	31.25	<.001
Substance disorders					
Alcohol abuse	8	19	9	2.50	.29
Alcohol dependence	4 <sub>a</sub>	32 <sub>b</sub>	5 <sub>a</sub>	15.25	.001
Drug abuse	4	9	2	1.70	.43
Drug dependence	0 <sub>a</sub>	26 <sub>b</sub>	2 <sub>a</sub>	15.23	.001
Anxiety disorders					
Generalized anxiety disorder	31 <sub>a</sub>	13	2 <sub>b</sub>	11.30	.01
Social phobia	31 <sub>a</sub>	15	5 <sub>b</sub>	8.69	.02
Simple phobia	27 <sub>a</sub>	19	7 <sub>b</sub>	5.54	.07
Panic disorder	4	4	0	2.02	.36
Posttraumatic stress disorder	8	30 <sub>a</sub>	7 <sub>b</sub>	9.71	.01
Obsessive-compulsive disorder	62 <sub>a</sub>	21 <sub>b</sub>	5 <sub>c</sub>	29.47	<.001
Personality disorders					
Obsessive-compulsive	46 <sub>a</sub>	4 <sub>b</sub>	5 <sub>b</sub>	23.52	<.001
Any cluster B disorder	8	17 <sub>a</sub>	0 <sub>b</sub>	8.84	.02

\*AN indicates anorexic probands; BN, bulimic probands; and CW, control women. Overall comparisons are shown by row using  $\chi^2$  with 2 df or Fisher exact tests where appropriate. Individual group comparisons are made by row using  $\chi^2$  with 1 df and Yates correction for discontinuity, or Fisher exact tests where appropriate. Rates are given per 100. Rates with different subscript letters differ significantly from each other at  $P < .05$ . Rates without any subscripts do not differ significantly from any other rate in that row.

mission. Similar findings emerged for OCD. The findings for GAD were mixed, as risk ratios were significantly elevated among relatives of AN probands who themselves had GAD, but were not elevated among relatives of either group of BN probands. The risk ratios for social phobia among relatives of both groups of AN probands were similarly nonsignificant. Rates of OCPD among relatives of AN probands with and without OCPD were virtually identical and significantly greater than among relatives of CW probands, suggesting shared familial transmission of AN and OCPD. Cluster B personality disorders occurred at rates too low to include in the PH analyses. However, in a more extended consideration of cluster B personality disorders reported elsewhere,<sup>38</sup> we found that these disorders were significantly elevated among BN probands with a coexisting lifetime diagnosis of substance dependence and their relatives ( $P = .01$ ). A more extended consideration of BN and substance dependence is also reported elsewhere,<sup>12</sup> where we found that these 2 disorders were independently transmitted in families.

#### SEX, AGE, AND INTERVIEW STATUS OF THE RELATIVES

When the effects of sex, age, and interview status were examined, rates of ED not otherwise specified ( $P = .001$ ), GAD ( $P = .02$ ), and simple phobia ( $P = .001$ ) were significantly higher among female than male relatives, while rates of substance dependence were significantly higher among male than female relatives ( $P = .001$ ), in accordance with re-

**Table 4. Unadjusted Lifetime Rates of Psychiatric Disorders Among First-Degree Relatives of Probands With Eating Disorders and Control Probands\***

Diagnosis in Relatives	AN (n = 93)	BN (n = 177)	CW (n = 190)	$\chi^2$	P
Eating disorders					
Anorexia nervosa	1	1	0	2.39	.30
Bulimia nervosa	1	2	0	4.20	.12
Binge eating disorder	3	6	3	2.20	.33
Eating disorder NOS	7 <sub>a</sub>	12 <sub>a</sub>	1 <sub>b</sub>	22.13	<.001
Any eating disorder	12 <sub>a</sub>	20 <sub>a</sub>	4 <sub>b</sub>	23.49	<.001
Mood disorders					
Major depressive disorder	15	16 <sub>a</sub>	7 <sub>b</sub>	6.55	.04
Substance disorders					
Alcohol abuse	8	11	12	1.38	.50
Alcohol dependence	13	19	15	2.31	.31
Drug abuse	4	10	5	4.58	.11
Drug dependence	4	8	6	1.53	.47
Anxiety disorders					
Generalized anxiety disorder	17 <sub>a</sub>	12 <sub>a</sub>	6 <sub>b</sub>	9.53	.01
Social phobia	16 <sub>a</sub>	11	8 <sub>b</sub>	4.44	.11
Simple phobia	15	16	12	0.92	.63
Panic disorder	5 <sub>a</sub>	7 <sub>a</sub>	1 <sub>b</sub>	11.86	.01
Posttraumatic stress disorder	4	7 <sub>a</sub>	2 <sub>b</sub>	4.83	.09
Obsessive-compulsive disorder	10 <sub>a</sub>	7	3 <sub>b</sub>	6.77	.04
Personality disorders					
Obsessive-compulsive	19 <sub>a</sub>	7 <sub>b</sub>	6 <sub>b</sub>	14.89	.001
Any cluster B disorder	1	5 <sub>a</sub>	1 <sub>b</sub>	5.97	.05

\*AN indicates relatives of anorexic probands; BN, relatives of bulimic probands; CW, relatives of control women; and NOS, not otherwise specified. Overall comparisons are shown by row using  $\chi^2$  tests with 2 df or Fisher exact tests where appropriate. Individual group comparisons are made by row using  $\chi^2$  tests with 1 df and Yates correction for discontinuity, or Fisher exact tests where appropriate. Rates are given per 100. Rates with different subscript letters differ significantly from each other at  $P < .05$ . Rates without any subscripts do not differ significantly from any other rate in that row.

cent epidemiological findings.<sup>26</sup> Rates of MDD ( $P = .001$ ), substance dependence ( $P = .001$ ), ED not otherwise specified ( $P = .001$ ), panic disorder ( $P = .05$ ), and posttraumatic stress disorder ( $P = .01$ ) were significantly higher among younger relatives. Finally, rates of social ( $P = .05$ ) and simple ( $P = .01$ ) phobias were significantly higher among directly interviewed relatives. There were no significant differences in the rates of any disorders between those relatives who were directly interviewed face-to-face compared with those who were directly interviewed by telephone.

#### COMMENT

This is the first study, to our knowledge, to compare diagnostically "pure" groups of restricting-type AN probands, normal-weight BN probands, and matched community controls by means of contemporary family-epidemiological methods. Our data support other studies<sup>39</sup> suggesting a common familial vulnerability for both AN and BN, which may manifest on a spectrum from clinically subthreshold forms (eg, ED not otherwise specified) to full-blown EDs. Both MDD and OCD, which commonly co-occur with EDs, appeared to be transmitted

**Table 5. Adjusted Risk Ratios (95% Confidence Interval) for Disorders Among First-Degree Relatives of Probands With Eating Disorders and Control Probands\***

	AN vs CW	BN vs CW	AN vs BN
Mood disorders			
Major depressive disorder	2.3 (1.1-4.8)†	2.3 (1.2-4.4)†	1.0 (0.5-1.9)
Substance disorders			
Alcohol and/or drug dependence	0.7 (0.4-1.3)	1.3 (0.8-2.0)	0.5 (0.3-1.0)†
Eating disorders			
Eating disorder NOS	15.0 (1.8-125.1)‡	30.7 (4.1-228.0)§	0.5 (0.2-1.2)
Anxiety disorders			
Generalized anxiety disorder	3.1 (1.5-6.8)‡	2.3 (1.1-4.7)†	1.4 (0.7-2.7)
Social phobia	2.1 (1.0-4.3)†	1.5 (0.7-2.9)	1.3 (0.7-2.8)
Obsessive-compulsive disorder	4.1 (1.4-12.2)†	3.0 (1.1-8.5)†	1.3 (0.6-3.1)
Personality disorders			
Obsessive-compulsive	3.6 (1.6-8.0)‡	1.2 (0.5-2.8)	3.3 (1.5-7.2)‡

\*AN indicates relatives of anorexic probands (n = 93); BN, relatives of bulimic probands (n = 177); CW, relatives of control women (n = 190); and NOS, not otherwise specified. Sex, age, and interview status were controlled for in these analyses. These results represent 3 separate models calculated for each disorder for each pairwise group comparison.

†P < .05.

‡P < .01.

§P < .001.

||A logistic regression rather than proportional hazards model was used for this variable; hence, the odds ratio rather than the relative risk ratio is reported in the table.

**Table 6. Effect of Proband Comorbidity on Unadjusted Lifetime Rates of Disorders Among First-Degree Relatives of Probands With Eating Disorders vs Those of Control Probands\***

Proband Comorbidity Status	Disorders in Relatives, No. (%)				
	Major Depressive Disorder	Generalized Anxiety Disorder	Social Phobia	Obsessive-compulsive Disorder	Obsessive-compulsive Personality Disorder
AN +	8/42 (19)†	7/30 (23)‡	5/32 (16)	7/53 (13)‡	10/49 (20)‡
BN +	20/99 (20)‡	3/19 (16)	2/25 (8)	4/34 (12)†	4/11 (36)‡
CW	14/190 (7)	11/190 (6)	15/190 (8)	5/190 (3)	11/190 (6)
AN -	6/51 (12)	9/63 (14)§	10/61 (16)§	2/40 (5)	8/44 (18)†
BN -	7/77 (9)	19/157 (12)§	17/151 (11)	9/142 (6)	9/165 (6)
CW -	13/188 (7)	11/185 (6)	14/185 (8)	5/183 (3)	10/182 (6)

\*AN indicates anorexic probands; BN, bulimic probands; CW, control women; plus sign, probands with the same comorbid disorder as that measured in the relatives; and minus sign, probands without the same comorbid disorder as that measured in the relatives.

†P < .05 vs CW relatives.

‡P < .01 vs CW relatives.

§P < .07 vs CW relatives.

independently from AN and BN in families. Similarly, substance dependence appeared to be transmitted independently from BN. Thus, our findings do not suggest a common cause between these disorders and EDs.

However, certain personality traits may reflect a source of liability for particular phenotypes of disordered eating. Our results suggest a shared familial transmission of AN and OCPD, which raises the possibility that it is necessary to have a risk for both OCPD and an ED to develop restricting-type AN. Our data also suggest that impulsivity and affective instability are important in the development of BN and substance dependence.

### EATING DISORDERS

Few relatives met DSM-III-R criteria for AN or BN. Instead, relatives of AN and BN probands had a 7 to 12 times higher rate of ED not otherwise specified diagnoses (which encompassed subthreshold forms or "broad" diagnostic categories of AN and BN), compared with relatives of CW pro-

bands. Our findings and those of Walters and Kendler<sup>39</sup> suggest familial aggregation of a broad spectrum of EDs.

### DEPRESSION

Lifetime rates of MDD were in the low to midrange of those previously reported for ED probands<sup>16,18</sup> and their first-degree relatives.<sup>4,5,8,40</sup> We found that depression and EDs were transmitted independently in families, confirming some findings in this area,<sup>4,6</sup> and contrary to some findings suggesting that EDs may be a variant expression of affective disease.<sup>5,7,23</sup> Other studies' findings have been inconclusive.<sup>8,10</sup> The familial coaggregation of depression and EDs may best be explained by some common familiarly transmitted factors and some factors that are distinct.<sup>9</sup>

### SUBSTANCE DEPENDENCE

There were elevated rates of substance dependence among BN probands and their relatives, within the ranges pre-

**Table 7. Effect of Proband Comorbidity on Adjusted Risk Ratios (95% Confidence Interval) for Disorders Among First-Degree Relatives of Probands With Eating Disorders vs Those of Control Probands\***

Proband Comorbidity Status	Disorders in Relatives				
	Major Depressive Disorder	Generalized Anxiety Disorder	Social Phobia	Obsessive-compulsive Disorder	Obsessive-compulsive Personality Disorder†
AN + vs CW	4.2 (1.4-12.4)‡	4.0 (1.3-12.8)§	1.8 (0.5-6.3)	6.6 (1.2-36.4)§	3.6 (1.2-11.3)§
AN - vs CW	1.7 (1.1-7.6)	1.3 (0.4-3.7)	1.6 (0.5-4.5)	0.7 (0.1-5.7)	2.0 (0.6-6.5)
BN + vs CW	5.3 (2.5-11.3)	2.4 (0.5-11.7)	0.8 (0.1-5.6)	4.2 (0.6-31.5)¶	..#
BN - vs CW	1.2 (0.6-3.8)	1.4 (0.5-4.0)	1.7 (0.5-5.4)	1.3 (0.3-6.1)	..#

\*AN indicates anorexic probands; BN, bulimic probands; CW, control women; plus sign, probands with the same comorbid disorder as that measured in the relatives; and minus sign, probands without the same comorbid disorder as that measured in the relatives. Sex, age, and interview status were controlled for in these analyses.

†A logistic regression rather than proportional hazards model was used for this variable; hence, the odds ratio rather than the relative risk ratio is reported in the table.

‡P < .01.

§P < .05.

||P < .001.

¶P < .07.

#Sample size after stratification was too small to conduct this analysis.

viously reported.<sup>41,42</sup> Specifically, rates were elevated only among relatives of BN women who themselves were substance dependent.<sup>12</sup> Together, these findings and those of others<sup>9,13,14</sup> suggest that BN and substance use disorders do not share a common transmissible factor.

#### ANXIETY DISORDERS

Nearly every AN proband, more than two thirds of BN probands, and almost half of their relatives had a lifetime history of an anxiety disorder. Proband rates are somewhat higher than in some previous studies<sup>15,16,18</sup> and similar to those from another well-controlled study.<sup>43</sup> Differences may result from greater diagnostic sensitivity with direct interviews than with other, less-sensitive techniques (eg, chart review), or from the fact that we used the Schedule for Affective Disorders and Schizophrenia—Lifetime Version rather than the Structured Clinical Interview for *DSM-III-R*.<sup>44</sup> Only a few previous studies have conducted a limited assessment of anxiety disorders among the relatives of ED probands,<sup>45,46</sup> and none have examined patterns of familial transmission. We found that OCD and EDs were independently transmitted in families; specifically, the rate of OCD was elevated among relatives of ED probands who themselves had OCD. Thus, although OCD and EDs frequently co-occur within individuals and within families, we found no evidence of a shared causative factor. While we found some suggestion of a common familial transmissible factor between AN and social phobia, sample size after stratification was too small to clarify this association. Future research should further examine the relationship between anxiety disorders and EDs with a larger ED sample selected for stratification on anxiety disorders of interest.

#### OBSESSIVE-COMPULSIVE PERSONALITY DISORDER

The AN probands had high rates of OCPD. This supports clinical reports of perfectionism and inflexibility among individuals with restricting-type AN,<sup>1-2,47</sup> as well as past research.<sup>19-22</sup> Of our AN probands, 31% had OCPD and OCD.

Although OCPD is not necessary for the development of OCD, these individuals may be more prone to OCD than those without this personality pattern.<sup>48</sup> Our study is the first, to our knowledge, to investigate OCPD among the relatives of women with EDs. Rates were elevated among relatives of AN probands, irrespective of the presence of OCPD among the probands themselves. These findings raise the possibility that OCPD and AN represent a continuum of phenotypic expressions of a similar genotype. Alternatively, restricting-type AN may occur only in the presence of risk factors for both an ED and OCPD. However, it is important to note that the reliability of personality disorder diagnoses is questionable. It is not clear whether the discrete category of OCPD or some dimensional component (eg, perfectionism or rigidity) is truly operative.

#### CLUSTER B PERSONALITY DISORDERS

Affective dysregulation often occurs in BN probands.<sup>47,49,50</sup> We found elevated rates of cluster B personality disorders among BN probands, which were within the lower bounds of rates reported in the literature.<sup>19,21,22</sup> Additional analyses suggest that affective instability and impulsivity are particularly present in a subset of BN women who have substance dependence.<sup>38</sup>

#### LIMITATIONS

One limitation of the present study is the relatively small number of AN probands, which may have limited the power to detect cases of full-blown EDs among relatives. Therefore, a more definite conclusion regarding the relationship between AN and BN awaits a similar pattern of findings for threshold cases of AN and BN among relatives from future family studies with larger sample sizes. The small number of AN probands is likely to have also restricted the power of the PH analyses conducted on stratified proband groups. A second limitation is that, although unbalanced sample sizes were somewhat unavoidable given the nature of our clinical study, this is likely to have affected the results of pairwise comparison significance tests for some of the analyses. In addition,

$\chi^2$  and PH model analyses may have ignored potential statistical dependency among relatives within each family, which may result in an increased type I error rate. A third limitation is that screening out EDs among our control group may have decreased the rates of EDs, as well as other forms of psychopathological conditions, among their relatives. A fourth limitation is that relatives of ED probands may have a higher rate of detection or false-positive reporting of EDs than do relatives of control probands. A fifth limitation is that although there were clear advantages to our selection of pure AN and BN proband groups, the findings may not be completely generalizable to those with a history of both disorders. A sixth limitation is the potential bias introduced by the use of family history interviews. However, we found no significant differences in the rates of any disorders among those relatives with whom we conducted direct interviews (more than two thirds of the total sample) compared with the entire sample of relatives. A likely reason this bias was not present is that we obtained multiple informants (4 on average) for every relative, which lessened the chance of inaccurate information from one informant making a large contribution to the final best-estimate diagnoses.

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## REFERENCES

1. Strober M. Personality and symptomatological features in young, nonchronic anorexia nervosa patients. *J Psychosom Res.* 1980;24:353-359.
2. Srinivasagan NM, Plotnicov KH, Greeno C, Weltzin TE, Rao R, Kaye WH. Persistent perfectionism, symmetry, and exactness in anorexia nervosa after long-term recovery. *Am J Psychiatry.* 1995;152:1630-1634.
3. Pollice CP, Kaye WH, Greeno CG, Weltzin TE. Relationship of depression, anxiety, and obsessionalism to state of illness in anorexia nervosa. *Int J Eat Disord.* 1997;21:367-376.
4. Strober M, Lampert C, Morrell W, Burroughs J, Jacobs C. A controlled family study of anorexia nervosa. *Int J Eating Disord.* 1990;9:239-253.
5. Logue CM, Crowe RR, Bean JA. A family study of anorexia nervosa and bulimia. *Br J Psychiatry.* 1989;30:179-188.
6. Biederman J, Rivinus T, Kemper K, Hamilton D, MacFadyen J, Hartz J. Depressive disorders in relatives of anorexia nervosa patients with and without a current episode of nonbipolar major depression. *Am J Psychiatry.* 1985;142:1495-1496.
7. Gershon ES, Schreiber J, Hamovit JR, Dibble ED, Kaye W, Nurnberger JI Jr, Andersen AE, Ebert MH. Clinical findings in patients with anorexia nervosa and affective illness in their relatives. *Am J Psychiatry.* 1984;141:1419-1422.
8. Hudson JI, Pope HG, Jonas JM, Yurgelun-Todd D, Frankenburg FR. A controlled family history study of bulimia. *Psychol Med.* 1987;17:883-890.
9. Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC, Eaves LJ. The structure of the genetic and environmental risk factors for six major psychiatric disorders in women. *Arch Gen Psychiatry.* 1995;52:374-383.
10. Kasset JA, Gershon ES, Maxwell ME, Guroff JJ, Kazuba DM, Smith AL, Brandt HA, Jimerson DC. Psychiatric disorders in the relatives of probands with bulimia nervosa. *Am J Psychiatry.* 1989;146:1468-1471.
11. Bulik CM. Drug and alcohol abuse by bulimic women and their families. *Am J Psychiatry.* 1987;144:1604-1606.
12. Kaye WH, Lilienfeld LR, Plotnicov K, Merikangas KR, Nagy L, Strober M, Bulik CM, Moss H, Greeno CG. Bulimia nervosa and substance dependence. *Alcohol Clin Exp Res.* 1996;20:878-881.
13. Strober M. Substance abuse disorder and bulimia nervosa: familial vulnerability. Presented at the International Conference on Eating Disorders; April 27, 1996; New York, NY.
14. Schuckit MA, Tip JE, Anthenelli RM, Bucholz KK, Hesselbrock VM, Nurnberger JI. Anorexia nervosa and bulimia nervosa in alcohol-dependent men and women and their relatives. *Am J Psychiatry.* 1996;153:74-82.
15. Braun DL, Sunday S, Halmi KA. Psychiatric comorbidity in patients with eating disorders. *Psychol Med.* 1994;24:859-867.
16. Brewerton TD, Lydiard RB, Herzog DB, Brotman AW, O'Neil PM, Ballenger JC. Comorbidity of axis I psychiatric disorders in bulimia nervosa. *J Clin Psychiatry.* 1995;56:77-80.
17. Thiel A, Broocks A, Ohlmeier M, Jacoby GE, Schubler G. Obsessive-compulsive disorder among patients with anorexia nervosa and bulimia nervosa. *Am J Psychiatry.* 1995;152:72-75.
18. Garfinkel PE, Lin E, Goering P, Spegg C, Goldbloom DS, Kennedy S, Kaplan AS, Woodside DB. Bulimia nervosa in a Canadian community sample. *Am J Psychiatry.* 1995;152:1052-1058.
19. Kennedy SH, Katz R, Rockett W, Mendlowitz S, Ralevski E, Clewes J. Assessment of personality disorders in anorexia nervosa and bulimia nervosa. *J Nerv Ment Dis.* 1995;183:358-364.
20. Gillberg C, Rastam M, Gillberg C. Anorexia nervosa 6 years after onset, part I: personality disorders. *Compr Psychiatry.* 1995;36:61-69.
21. Herzog DB, Keller MB, Lavori PW, Kenny GM, Sacks NR. The prevalence of personality disorders in 210 women with eating disorders. *J Clin Psychiatry.* 1992;53:147-152.
22. Gartner AF, Marcus RN, Halmi K, Loranger AW. *DSM-III-R* personality disorders in patients with eating disorders. *Am J Psychiatry.* 1989;146:1585-1592.
23. Keck PE, Pope HG Jr, Hudson JI, McElroy SL, Yurgelun-Todd D, Hundert EM. A controlled study of phenomenology and family history in outpatients with bulimia nervosa. *Compr Psychiatry.* 1990;31:275-283.
24. American Psychiatric Association. Committee on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.* Washington, DC: American Psychiatric Association; 1987.
25. Bulik CM, Sullivan PF, Fear J, Pickering A. Predictors of the development of bulimia nervosa in women with anorexia nervosa. *J Nerv Ment Dis.* 1997;185:704-707.
26. Metropolitan Life Insurance Company. New weight standards for men and women. *Stat Bull Metrop Insur Co.* 1959;40:1-11.
27. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshelman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of *DSM-III-R* psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry.* 1994;51:8-19.
28. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. *The Biology of Human Starvation.* Minneapolis: University of Minnesota Press; 1950.
29. Eckert ED, Goldberg SC, Halmi KA, Casper RC, Davis JM. Depression in anorexia nervosa. *Psychol Med.* 1982;12:115-122.
30. Endicott J, Spitzer RL. A diagnostic interview. *Arch Gen Psychiatry.* 1978;35:837-844.
31. Merikangas KR, Stevens DS, Fenton B, O'Malley S, Woods S, Stolar M, Risch N. Comorbidity and familial aggregation of alcoholism and anxiety disorders. *Psychol Med.* In press.
32. Puig-Antich J, Orvaschel H, Tabrizi MA, Chambers W. *The Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version (Kiddie-SADS-E).* 3rd ed. New York, NY: New York State Psychiatric Institute and Yale University School of Medicine; 1980.
33. Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria. *Arch Gen Psychiatry.* 1977;34:1229-1235.
34. Spitzer RL, Williams JBW, Gibbon M, First MB. *Structured Clinical Interview for DSM-III-R Personality Disorders (SCID II).* Washington, DC: American Psychiatric Press; 1990.
35. Loranger AW. *Personality Disorder Examination (PDE) Manual.* Yonkers, NY: DV Communications; 1988.
36. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data.* New York, NY: John Wiley & Sons; 1980.
37. Dixon WJ. *BMDP Statistical Software Manual.* Berkeley: University of California Press; 1988.
38. Lilienfeld LR, Kaye WH, Greeno CG, Merikangas KR, Plotnicov K, Pollice C, Rao R, Strober M, Bulik CM, Nagy L. Psychiatric disorders in women with bulimia nervosa and their first-degree relatives. *Int J Eating Disord.* 1997;22:253-264.
39. Walters EE, Kendler KS. Anorexia nervosa and anorexic-like syndromes in a population-based twin sample. *Am J Psychiatry.* 1995;152:64-71.
40. Winokur A, March V, Mendels J. Primary affective disorder in relatives of patients with anorexia nervosa. *Am J Psychiatry.* 1980;137:695-698.
41. Holderness CC, Brooks-Gunn J, Warren WP. Co-morbidity of eating disorders and substance abuse. *Int J Eating Disord.* 1994;16:1-34.
42. Bulik CM, Sullivan PF, Epstein LH, McKee M, Kaye WH, Dahl RE, Weltzin TE. Drug use in women with anorexia and bulimia nervosa. *Int J Eating Disord.* 1992;11:213-225.
43. Bulik CM, Sullivan PF, Joyce PR. Eating disorders and antecedent anxiety disorders. *Acta Psychiatr Scand.* 1997;96:101-107.
44. Spitzer RL, Williams JBW, Gibbon M, First MB. *Structured Clinical Interview for DSM-III-R (SCID).* Washington, DC: American Psychiatric Press; 1990.
45. Halmi KA, Eckert E, Marchi P, Sampugnaro V, Apple R, Cohen J. Comorbidity of psychiatric diagnoses in anorexia nervosa. *Arch Gen Psychiatry.* 1991;48:712-718.
46. Pasquale L, Sciuto G, Cocchi S, Ronshi P, Bellodi L. A family study of obsessive compulsive, eating and mood disorders. *Eur Psychiatry.* 1994;9:33-38.
47. Vitousek K, Manke F. Personality variables and disorders in anorexia nervosa and bulimia nervosa. *J Abnorm Psychol.* 1994;1:137-147.
48. Pollack J. Relationship of obsessive-compulsive personality to obsessive-compulsive disorder. *J Psychol.* 1987;121:137-148.
49. DaCosta M, Halmi KA. Classifications of anorexia nervosa. *Int J Eating Disord.* 1992;11:305-313.
50. Cooper JL, Morrison TL, Bigman OL, Abramowitz SI, Blunden D, Nassi A, Krener P. Bulimia and borderline personality disorder. *Int J Eating Disord.* 1988;7:43-49.