Controlled Family Study of Anorexia Nervosa and Bulimia Nervosa: Evidence of Shared Liability and Transmission of Partial Syndromes

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Objective: Lifetime rates of full and partial anorexia nervosa and bulimia nervosa were determined in first-degree relatives of diagnostically pure proband groups and relatives of matched, never-ill comparison subjects. **Method:** Rates of each eating disorder were obtained for 1,831 relatives of 504 probands on the basis of personal structured clinical interviews and family history. Best-estimate diagnoses based on all available information were rendered without knowledge of proband status and pedigree identity. Only definite and probable diagnoses were considered. **Results:** Whereas anorexia nervosa was rare in families of the comparison subjects, full and partial syndromes of anorexia nervosa aggregated in female relatives of both anorexic and bulimic probands. For the full syndrome of anorexia nervosa, the relative risks were 11.3 and 12.3 in female relatives of anorexic and bulimic probands, respectively. Bulimia nervosa was more common than anorexia nervosa in female relatives of comparison subjects, but it, too, aggregated in the families of ill probands; the corresponding relative risks for bulimia nervosa were 4.2 and 4.4 for female relatives of anorexic and bulimic probands, respectively. When partial syndromes of anorexia nervosa and bulimia nervosa were considered, relative risks fell by one-half in each group of ill probands. **Conclusions:** Both anorexia nervosa and bulimia nervosa are familial. Their cross-transmission in families suggests a common, or shared, familial diathesis. The additional observation that familial aggregation and cross-transmission extend to milder phenotypes suggests the validity of their inclusion in a continuum of familial liability.

(Am J Psychiatry 2000; 157:393–401)

The eating disorders anorexia nervosa and bulimia nervosa are complex illnesses with multiple determinants of risk and susceptibility (1, 2). Psychosocial influences are assumed to play a role, but familial transmission of risk has emerged as an increasingly strong focus of research attention. In 10 studies that used a case-control design to investigate the familiality of eating disorders (3–12), cases of anorexia nervosa were found only among relatives of anorexia nervosa probands in all but one (8). Of added note, the frequency of bulimia nervosa was greater in the relatives of anorexic probands than in the relatives of comparison subjects in five (3, 4, 9, 10, 12) of the six studies that included the bulimia nervosa diagnosis, suggesting coaggregation of the two eating disorder phenotypes in families. Of four family studies (5, 7, 8, 12) of bulimia nervosa, this diagnosis was more frequent in the probands' relatives than in the relatives of comparison subjects in three (5, 7, 12), whereas in two studies (5, 7), isolated cases of anorexia nervosa were observed in the families of the bulimic probands but not in the families of the comparison subjects. Also, in two family studies (4, 12) the frequency of partial eating disorder syndromes was higher in the relatives of ill probands than in the relatives of comparison subjects. The coaggregation of anorexia nervosa and bulimia nervosa in families is in accord with clinical accounts of binge eating in underweight anorexic patients (13–15), continuities between the two syndromes shown in longitudinal, prospective follow-up studies (16–18), their common patterns of association with gender and

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Supported in part by grant AA-08983 from the National Institute on Alcohol Abuse and Alcoholism.

personality traits (19), their comorbidity with mood and anxiety disorders (20, 21), and high spinal fluid levels of the serotonin metabolite 5-hydroxyindoleacetic acid after long-term clinical stabilization (22, 23). Hence, rather than being discrete entities, anorexia nervosa and bulimia nervosa appear to have common etiological factors.

The reliability of familial prevalence rates of eating disorders remains uncertain, however, because virtually all studies to date have been marred by small study groups and low statistical power. Likewise, the transmissibility of milder (i.e., partial) syndromes of anorexia nervosa and bulimia nervosa remains largely unexplored. We present herein initial results from what we believe is the largest case-control family study of eating disorders conducted to date. It was conducted in parallel with another controlled family study of eating disorders, results of which were published recently (12). We tested the following hypotheses: 1) anorexia nervosa and bulimia nervosa are each familial; 2) relatives of ill probands are also at higher than normal risk for partial syndromes; and 3) anorexia nervosa and bulimia nervosa, rather than breeding true, show cross-transmission of risk, indicative of at least some sharing of familial liability. This third hypothesis, based on models of familial coaggregation developed by others (24), predicts that the prevalence of bulimia nervosa and partial bulimia nervosa will be greater in relatives of probands with anorexia nervosa than in relatives of normal comparison subjects, and the converse. We plan separate reports on the rates of other axis I psychiatric disorders in these relatives.

METHOD

Probands

Three groups of Caucasian female probands, 18 to 28 years of age, were included in this study: 152 with pure (i.e., restricting subtype) anorexia nervosa, 171 with pure bulimia nervosa, and 181 without any lifetime axis I psychiatric illness. The ill probands were recruited over 4 years (January 1994 to December 1997) from patients consecutively admitted to the eating disorders program of the Neuropsychiatric Institute of the University of California, Los Angeles, who were willing to give informed consent and who had at least one first-degree relative available for direct interview. To rigorously test the hypothesis of familial cross-transmission of anorexia nervosa and bulimia nervosa, only diagnoses representing mutually exclusive classifications based on lifetime history were considered for this study (i.e., probands with comorbid anorexia and bulimia nervosa, whether cross-sectional or longitudinal, were excluded from the analyses reported herein; we plan to report familial aspects of this comorbid group later). As longitudinal studies of anorexia nervosa (16–18) show there is little, if any, switching to bulimia nervosa after 5 years of follow-up, we controlled for potential confounding due to latent comorbidity by selecting for this study only probands who had been ill with anorexia or bulimia nervosa alone for a minimum of 5 years. With respect to lifetime presence of other axis I conditions, only developmental disability, schizophrenia, and organic brain syndrome were exclusionary.

Diagnoses were made by two of the authors (M.S. and R.F.), who used the DSM-IV criteria at the definite level of certainty and based the diagnoses on direct examination of the patient and detailed review of the psychiatric history. The final group of 323 ill probands constituted 94% of the patients consecutively admitted during the period of recruitment who were eligible for study inclusion.

Never-ill comparison probands were identified by using a modification of an acquaintance method developed as a cost-efficient means of recruiting demographically matched comparison probands and relatives for family studies (25). With the original method, relatives of the probands provide the names of six adult acquaintances of the same gender and of comparable age and social class as themselves. Names on the list are then selected at random, and the persons are contacted for interview; the never-ill acquaintances thus identified serve as comparison probands, and lifetime rates of illness are determined in their first-degree relatives. However, strict application of the procedure was not possible in the present study since sibling acquaintances who were under 18 years of age could not be approached without parental consent, and that would have introduced potential selection biases in recruiting minor-age acquaintances as potential comparison probands. Accordingly, names of acquaintances were sought from the probands themselves; because of the large number of ill probands available, four, rather than six, names were requested per proband. A name from each list was selected randomly and then contacted by telephone for an interview with a modification of the lifetime version of the Schedule for Affective Disorders and Schizophrenia (SADS-L) (26) developed by Merikangas and colleagues (27). Acquaintances were eligible for inclusion as comparison probands if they were free of lifetime axis I psychiatric disorder and if they had at least one first-degree relative available for direct interview. The 323 ill probands generated lists totaling 947 names; 48.0% of these people refused participation outright. Of the remaining 492, 70.9% (N=349) had no axis I illness; of these remaining subjects, 51.9% each had at least one available consenting first-degree relative, yielding a final total of 181 comparison probands. Of these, 97 came from lists generated by the bulimic probands and 84 from lists generated by the anorexic probands. Each proband gave written informed consent to participate in the study interviews.

Relatives

Information on lifetime psychiatric history was sought on all first-degree relatives aged 12 and older. All interviewed relatives provided written informed consent. The three proband groups had a combined total of 1,831 living or deceased relatives on whom information was obtained. Of the 1,727 living relatives, 90.4% (N=1,561) were interviewed directly, the proportions being nearly equal across proband groups. Of these interviews, over two-thirds were conducted by telephone, with significantly greater reliance on telephone interviews for assessing the relatives of the comparison probands; accordingly, method of interview (face-to-face versus telephone) was controlled for in the statistical analysis. Source information for best-estimate diagnoses was obtained from direct interview of the relative and information provided by probands and interviewed relatives on other first-degree members of the family.

Interviews

Relatives 17 years and older were directly interviewed with the SADS-L and the Structured Clinical Interview for DSM-III-R Personality Disorders (28). Relatives under 17 years of age were interviewed by using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version, a juvenile counterpart to the SADS-L developed by Puig-Antich and colleagues (29). In addition, detailed information on diagnostic and clinical aspects of eating disorders was obtained by using the Eating Disorders Family History Interview, a semistructured interview developed by one of us (30). Lifetime psychiatric history was also obtained from each interviewed relative on other first-degree relatives by using the Family History Research Diagnostic Criteria (31), as updated and expanded by Merikangas and colleagues (27), and the Eating Disorders Family History Interview. All interviews were conducted by highly experienced clinicians with extensive knowledge of diagnostic psychopathology. Because of budget constraints and limited available personnel, it was not possible to conduct these interviews without knowledge of the proband's diagnostic status or the lifetime history of the other interviewed relatives within a family.

TABLE 1. Characteristics of Female Probands With Anorexia Nervosa, Bulimia Nervosa, or No Psychiatric Illness and of First-Degree Relatives

Characteristic	Proband Diagnosis: Anorexia Nervosa (N=152)		Bulimia Nervosa (N=171)		Never Ill (N=181)		Total (N=504)		p
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	
Proband age (years)	22.1	3.1	23.8	3.3	22.7	3.3	23.1	3.2	n.s.
Age of living relatives (years)	36.3	12.1	36.8	12.7	35.7	11.9	36.1	12.4	n.s.
	N	%	*N*	%	*N*	%	*N*	%	
Source of probands									0.0001[a]
Inpatient	111	73.0	43	25.1			154	47.7	
Outpatient	41	27.0	128	74.9			169	52.3	
Social class of probands[b]									n.s.
I or II	109	71.7	120	70.2	132	72.9	361	71.6	
III	43	28.3	51	29.8	49	27.1	143	28.4	
Relatives, total	574		610		647		1,831		—
Relatives, living	549		580		598		1,727		—
Interviewed	510	92.9	528	91.0	523	87.5	1,561	90.4	n.s.
Female	290	52.8	297	51.2	318	53.2	905	52.4	n.s.
Method of interview of relatives									0.0001[a]
Face-to-face	194	38.0	206	39.0	52	9.9	452	29.0	
Telephone	316	62.0	322	61.0	471	90.1	1,109	71.0	

[a] Fisher's exact test, two-tailed. [b] According to Hollingshead-Redlich Scale.

Diagnostic Procedures and Criteria for Partial Syndromes

Best-estimate diagnoses according to DSM-IV were made independently by two raters (M.S., R.F.) on the basis of all data compiled on each relative. Each rater was fully blind to proband diagnosis and the relative's pedigree. These assessments were then reviewed jointly by the two raters to render a final consensus diagnosis. Only diagnoses made at the probable or definite level of certainty were considered to be positive.

We decided a priori to conceptualize partial anorexia nervosa and partial bulimia nervosa as subthreshold illnesses, relaxing only the weight loss criterion for anorexia nervosa and the frequency criterion (for binge eating and compensatory behaviors) for bulimia nervosa, while requiring comparable minimum symptom durations (3 months) for both. We stipulated that a diagnosis of partial anorexia nervosa required, in an individual of normal body weight, unequivocal presence of anxiety regarding body weight that was judged to be extreme or irrational (persistent rumination or discomforting preoccupation about weight or shape appearance throughout much of the day and negatively affecting self-esteem or self-concept) *and* the concurrent presence for not less than 3 months of at least two of the following: 1) distraction from daily chores or life demands because of weight anxiety; 2) a seemingly unshakable conviction that one's weight was excessive and the belief that subjective discomfort could be reduced by weight reduction, regular and excessive vigilance about caloric intake, or frequent monitoring of weight that was driven by anxiety about weight or shape; 3) marked subjective distress precipitated by ingestion of meals deemed by the rater to be of normal or below-normal size, or comprising foods deemed by the subject to be "unsafe"; and 4) extreme distress occasioned by very minor fluctuations in body weight, extreme or rigid allegiance to exercise routines, or use of laxatives, diuretics, or anorexic agents because of weight anxiety. Similarly, the diagnosis of partial bulimia nervosa required, in accordance with DSM-IV guidelines, the joint presence of binge eating and abnormal compensatory behavior (e.g., self-induced vomiting). In keeping with these guidelines, a relative who met the criteria for anorexia nervosa, or partial anorexia nervosa, and who also gave a history of binge eating with purging was assigned lifetime diagnoses of anorexia nervosa and bulimia nervosa (or partial bulimia nervosa), whereas one who gave a history of binge eating in the absence of compensatory behavior was assigned only the single diagnosis of anorexia nervosa.

Kappa coefficients of agreement between the two raters were high across diagnoses: 0.96 for anorexia nervosa, 0.88 for bulimia nervosa, 0.89 for partial anorexia nervosa, and 0.81 for partial bulimia nervosa.

Statistical Analysis

The homogeneity of proband groups and relatives in regard to sampling and sociodemographic variables was assessed by using standard chi-square tests and simple analysis of variance. Unadjusted lifetime rates of illness in the three proband groups were compared by means of chi-square tests or Fisher's exact test for contrasts, when the cell sizes were under 5. We also obtained age-corrected lifetime rates of illness by using Kaplan-Meier survival analysis (32), and we compared survival curves by using log-rank chi-square tests. Since most relatives had already passed through or were well into the period of risk for anorexia and bulimia nervosa, the differences between age-adjusted and crude rates of illness turned out to be trivial; accordingly, only results from the comparisons of simple unadjusted rates of illness are reported herein for ease of exposition (age-adjusted rates of illness in the relatives are available on request). Given the a priori directional hypotheses, one-tailed tests of significance are reported throughout.

To control for potential confounding variables, we also tested familial aggregation with Cox proportional hazard models. The model yields a ratio (hazard) of the age-specific incidence of illness in the first-degree relatives of the ill probands to that for the relatives of the comparison probands, adjusted for covariates. A hazard ratio of 5 would indicate that the rate of illness is five times as high in the relatives of the ill probands as in the relatives of the comparison subjects. The Cox models were adjusted for the age of the relatives, interview type (direct versus family history), source of recruitment of the ill probands (inpatient versus outpatient), and method of interview (face-to-face versus telephone). Familial cross-transmission of disorders was similarly tested by fitting Cox models of anorexia nervosa and partial anorexia nervosa in the relatives of the bulimic probands compared to the relatives of the comparison probands, and bulimia nervosa and partial bulimia nervosa in the relatives of the anorexic probands compared to the relatives of the comparison probands. Because the nonindependence of diagnostic observations from relatives within a family violates an assumption of the proportional hazards model, all models were run by using the GENMOD procedure implemented in the generalized estimating equation method in SAS statistical software (33). This method approximates the variance of the estimated parameters when assumptions of the Cox model are violated.

TABLE 2. Unadjusted Lifetime Rates of Illness in Female First-Degree Relatives of Probands With Anorexia Nervosa, Bulimia Nervosa, or No Psychiatric Illness[a]

		Female Relatives With Diagnosis									
		Anorexia Nervosa		Partial Anorexia Nervosa		Bulimia Nervosa		Partial Bulimia Nervosa		Total Full and Partial Illness	
Proband Diagnosis	Number of Female Relatives	N	%	N	%	N	%	N	%	N	%
Anorexia nervosa	290	10	3.4††	10	3.4†	11	3.8***	10	3.4*	41	14.1‡
Bulimia nervosa	297	11	3.7†††	10	3.4†	12	4.0†	11	3.7**	44	14.8‡
Never ill	318	1	0.3	2	0.6	3	0.9	4	1.3	10	3.1

[a] Fisher's exact tests were used to compare relatives of probands with eating disorders and relatives of never-ill comparison subjects. *p=0.06. **p=0.04. ***p=0.02. †p=0.01. ††p=0.004. †††p=0.002. ‡p=0.0001.

TABLE 3. Number of Families of Probands With Anorexia Nervosa, Bulimia Nervosa, or No Psychiatric Illness That Contained Other Female Members With Eating Disorders

Proband Diagnosis	Number of Families	Families With One or More Ill Female Members Besides Proband	Families Without Other Ill Members
Anorexia nervosa	152	37	115
Bulimia nervosa	171	41	130
Never ill	181	9	172

RESULTS

Characteristics of the study groups are presented in table 1. The groups were well matched on relevant demographic and family variables. Not unexpected was the larger proportion of anorexia nervosa than bulimia nervosa probands recruited from the inpatient setting, and the larger proportion of relatives of comparison probands interviewed by telephone.

Unadjusted Rates of Illness in Relatives

A total of 95 relatives received a diagnosis of either full or partial eating disorder; all were female. Since cases of illness were absent among male relatives, all rates and statistical comparisons presented herein are for female relatives only and will be discussed in the text without specific reference to gender. Of these 95 diagnosed relatives, 85 (89.5%) were relatives of ill probands.

Unadjusted lifetime rates of mutually exclusive diagnoses among relatives by proband group are presented in table 2. The main effects of familial aggregation of full and partial syndromes were statistically significant. The rate of anorexia nervosa was 11.3 times as high in the relatives of anorexia nervosa probands as in the relatives of the comparison probands, and the relatives of the anorexic probands also had a prevalence of partial anorexia nervosa 5.7 times as high as that for the relatives of the comparison probands. Thus, the rate of anorexia nervosa spectrum disorders (i.e., anorexia nervosa plus partial syndrome) in the relatives of anorexia nervosa probands was 7.7 times that found in the relatives of the comparison subjects (6.9% versus 0.9%; Fisher exact p=0.0001). Of the 10 relatives of anorexic probands with anorexia nervosa, six were mothers and four were sisters, giving nonsignificantly different rates of 3.9% (six of 152) versus 2.9% (four of 138), respectively. Partial anorexia nervosa was diagnosed in 3.3% of the mothers (five of 152) and in 3.6% of the sisters (five of 138) of the anorexic probands.

The relatives of the probands with bulimia nervosa had a rate of bulimia nervosa that was 4.4 times as high as that for the relatives of the never-ill comparison probands (table 2). The rate of partial bulimia nervosa was 2.8 as high, a more modest difference. The overall rate of bulimia spectrum disorder (bulimia nervosa plus partial bulimia nervosa) was 3.5 times as high in the relatives of the bulimic probands as in the relatives of the comparison subjects (7.7% versus 2.2%) (Fisher's exact p=0.001). The 12 cases of bulimia nervosa among the relatives of bulimic probands included five (2.9%) of the 171 mothers and seven (5.6%) of the 126 sisters; the difference in rates was not statistically significant. The rates of partial bulimia nervosa in the mothers and sisters of bulimic probands were 3.5% and 4.0%, respectively.

When analyzed by families (table 3), 6.6% of the families of the probands with anorexia nervosa (10 of 152 families) had another relative with this illness, compared to 0.6% of the families of the comparison probands (one of 181 families) (Fisher's exact p=0.002). For partial anorexia nervosa, the corresponding proportions were 6.6% (10 of 152) and 1.1% (two of 181) (Fisher's exact p=0.008). Of the 171 families of the probands with bulimia nervosa, 12 (7.0%) contained another member with bulimia nervosa, compared to three (1.7%) of the 181 families of the comparison probands (Fisher's exact p=0.02). For partial bulimia nervosa, the corresponding proportions were 6.4% (11 of 171) and 2.2% (four of 181), respectively (Fisher's exact p=0.06). After aggregation of all full and partial diagnoses, the proportions of the families of the anorexic, bulimic, and comparison probands with at least one other ill member were 24.3%, 24.0%, and 5.0%, respectively (χ^2=29.8, df=2, p<0.0001).

Cross-Transmission of Disorders

The findings were consistent with the hypothesis of a shared familial component. As shown in table 2, the rate of bulimia nervosa was 4.2 times as high in the rel-

TABLE 4. Adjusted Hazard Ratios Comparing Rates of Eating Disorders in Female First-Degree Relatives of Probands With Anorexia Nervosa or Bulimia Nervosa to Rates for Female Relatives of Never-Ill Comparison Probands

Disorder in Female Relatives	Probands With Anorexia Nervosa				Probands With Bulimia Nervosa			
	Risk of Disorder in Female Relatives		Wald Chi-Square Analysis (df=1)		Risk of Disorder in Female Relatives		Wald Chi-Square Analysis (df=1)	
	Adjusted Hazard Ratio	95% CI	χ^2	p	Adjusted Hazard Ratio	95% CI	χ^2	p
Anorexia nervosa								
Full	11.4	1.1–89.3	5.3	<0.03	12.1	1.5–97.1	8.8	<0.005
Partial	5.2	1.1–25.2	4.7	<0.03	5.0	1.2–24.9	4.4	<0.004
Bulimia nervosa								
Full	3.5	1.1–14.1	3.9	<0.05	3.7	1.1–14.7	4.1	<0.05
Partial	2.4	0.7–8.1	2.6	<0.10	2.6	0.8–8.4	2.7	<0.10

atives of the anorexic probands as in the relatives of the normal comparison subjects, whereas for partial bulimia nervosa the difference fell just short of significance. In like manner, the rates of anorexia nervosa and partial anorexia nervosa were 12.3 times and 5.7 times as high, respectively, in the relatives of the bulimic probands as in the relatives of the comparison subjects; each contrast was statistically significant. There was no effect of the relative's generation on the rate of bulimia spectrum disorders in the relatives of the anorexic probands, or the converse. For the total of full and partial diagnoses (table 2), the relatives of the anorexic probands had a rate of eating disorders (14.1%) that was 4.5 times as high as the rate for the relatives of the normal comparison subjects (3.1%) (Fisher's exact test, p=0.0001), whereas the rate of illness among the relatives of the bulimic probands (14.8%) was 4.8 times that found in the relatives of the comparison subjects (3.1%) (Fisher's exact test, p= 0.0001). The proportions of anorexic, bulimic, and never-ill probands with at least one affected first-degree relative were 24.3%, 24.0%, and 5.0%, respectively; the differences were significant for the contrast between the anorexic and comparison probands and for the contrast between the bulimic and comparison probands (Fisher's exact test, p=0.0001). Families with multiple affected relatives other than the proband were rare, observed for only four anorexic probands and three bulimic probands.

Adjusted Hazard Ratios

Hazard ratios, adjusting for the effects of potential confounders, are given in table 4. The relatives of the probands with anorexia nervosa had a risk of developing anorexia nervosa 11.4 times as high as the risk for the relatives of the never-ill comparison probands, and they had a modestly higher, although still statistically significant, risk of partial anorexia nervosa. Likewise, the risk of bulimia nervosa for the relatives of the probands with bulimia nervosa was significantly higher than that for the relatives of the comparison subjects; the risk of partial bulimia nervosa was also higher, but the hazard ratio fell short of statistical significance.

The results of the cross-transmission analyses largely paralleled findings from the comparison of crude prevalence rates. The risk of bulimia nervosa in the relatives of the probands with anorexia nervosa was 3.5 times that for the relatives of the comparison subjects; the hazard of partial bulimia nervosa did not reach statistical significance. For the relatives of the bulimic probands, the diagnosis of anorexia nervosa was 12.1 times as common as in the relatives of the comparison subjects, and they also had a significantly greater risk of partial anorexia nervosa. Controlling for diagnostic comorbidity (coding for presence or absence of mood/anxiety disorder) in the proportional hazards models failed to alter any of the hazard ratios presented in table 4.

Associations of Anorexia Nervosa to Compensatory Behaviors in Relatives

Particularly surprising was the absence of comorbid lifetime diagnoses (i.e., anorexia nervosa plus bulimia nervosa or anorexia nervosa plus partial bulimia nervosa) among relatives of either group of ill probands. Accordingly, we undertook an exploratory analysis (results not shown but available on request) to determine 1) whether binge eating and the compensatory behaviors commonly associated with it (e.g., self-induced vomiting or use of laxatives, diuretics, or enemas, which, it has been speculated, may express a *forme fruste* of bulimia nervosa) co-occur in relatives with anorexia spectrum disorder (i.e., anorexia nervosa or partial anorexia nervosa) more often than expected by chance and 2) whether the magnitude of this association differs among relatives of the three groups of probands. For the relatives of the probands with anorexia nervosa and bulimia nervosa, the resulting odds ratios differed significantly from unity; however, these two odds ratios were comparable, indicating no difference in the strength of the association between relatives of anorexic probands and relatives of bulimic probands; that is, we found no evidence for a distinctive cosegregation of anorexic and bulimia spectrum behaviors among relatives of one eating disorder phenotype or the other.

DISCUSSION

The present analyses offer new evidence of the importance of familial factors in the risk for anorexia

nervosa and bulimia nervosa. A summary of the major findings follows.

1. The age-specific risk for anorexia nervosa in relatives of probands with anorexia nervosa was 11.4 times as high as the risk in relatives of normal probands, and the risk of bulimia nervosa was 3.7 times as high among relatives of probands with bulimia nervosa as in relatives of normal subjects. Affected subjects were found only among female relatives, a finding consistent with the disproportionate sex ratio for eating disorders found routinely in clinical and population samples.

2. Milder phenotypes of anorexia nervosa and bulimia nervosa also showed a tendency for familial aggregation, although of lesser magnitude; as with full syndromes, partial syndromes were seen only among female relatives. For relatives of anorexic probands, the age-corrected risk of partial anorexia nervosa was 5.2 times that for relatives of never-ill probands, whereas the risk for partial bulimia nervosa in relatives of bulimic probands was 2.6 times that for relatives of normal subjects.

3. Familial etiologic factors appear to be shared by anorexia nervosa and bulimia nervosa. This was reflected in significantly higher cross-prevalences of illness among relatives of the two groups of ill probands than among relatives of comparison subjects. Specifically, the age-corrected risk for bulimia nervosa was 3.5 times as high among relatives of anorexic probands as among relatives of comparison probands, whereas the risk for anorexia nervosa was 12.1 times as high among relatives of bulimic probands.

The greater frequency of eating disorders among relatives of ill probands than among relatives of normal comparison subjects accords with the results of most previous family studies of anorexia nervosa and bulimia nervosa. The absence, or near absence, of familial cases in two prior studies (8, 12) is likely the result of study groups that were too small to detect familial aggregation with any degree of confidence. By contrast, the large size of the comparison group in this current study, coupled with direct interview data obtained for the majority of living relatives, permitted statistically significant discrimination of rates of illness whose base rates in the general population are low. Two other observations give added support to the generalizability of our findings. First, the 3.4% risk for anorexia nervosa in first-degree female relatives of anorexic probands in this study is within the 1%–7% range reported in both uncontrolled series (34) and earlier case-control studies of anorexia nervosa (3–12), whereas the 0.3% risk in relatives of the comparison probands is virtually identical to the 0.1%–0.5% risk of anorexia nervosa found in community epidemiological samples (35). Similarly, the 4.0% risk of bulimia nervosa among female relatives of the present group of bulimic probands is in line with estimates from prior case-control studies (5, 7, 12), which range from 2% to 9%, just as the 0.9% risk found in relatives of the comparison subjects is comparable to the estimated 0.7%–1.6% lifetime risk of bulimia nervosa in the general female population (35).

The results concerning the occurrence of partial syndromes in these relatives are consistent with our earlier report (12) on the familial clustering of milder variants of eating disorder in probands with anorexia nervosa or bulimia nervosa. In the present study, female relatives of anorexic probands had six times the risk of partial anorexia nervosa and relatives of bulimic probands had nearly three times the risk of partial bulimia nervosa as the female relatives of the never-ill probands. That these rates are lower than the 34% rate of partial illness among relatives of the eating disorder probands reported earlier (12) is likely due to the more restrictive definition of partial phenotypes in the present study. It is interesting that, whereas the frequencies of partial syndromes were slightly greater than those for full syndromes of anorexia nervosa and bulimia nervosa among the relatives of the comparison probands, the rates of full and partial illness among the relatives of the ill probands were roughly equivalent. As a result, the recurrence risks for partial anorexia nervosa and partial bulimia nervosa (i.e., prevalences in relatives of ill probands versus those in relatives of normal subjects) are less robust than those based on use of the full syndrome as a threshold for affection. Even so, our results concur with findings from the Virginia Twin Study of eating disorders reported by Kendler and colleagues (36, 37). Regarding anorexia nervosa, Walters and Kendler (36) argued that full and partial syndromes of anorexia nervosa form a continuum given their observation that 1) the co-twin of a twin affected with severe anorexia nervosa was at higher-than-normal risk for subthreshold anorexia nervosa, 2) co-twins of twins with either severe or subthreshold illness had significantly lower body weights than did co-twins of unaffected twins, and 3) the distributions of putative risk factors for anorexia nervosa were similar across multiple thresholds of the anorexia nervosa diagnosis. Continuity between full and partial syndromes of bulimia nervosa with respect to purported risk factors has also been demonstrated (37). Results from the current study lend added support for a model of familial liability to eating disorders wherein risk is expressed individually along a continuum of clinical severity.

The mutually exclusive diagnostic categorization we used in recruiting probands for this study allowed for a rigorous test of the hypothesis of familial cross-transmission of illness. The results conformed with this prediction. The cross-transmission risks were balanced, with the risks for anorexia nervosa being roughly equal in the relatives of the anorexic and bulimic probands, respectively, and the converse. The findings suggest that anorexia nervosa and bulimia nervosa have common, or overlapping, etiologic determinants that can be expressed alternately in family members as one form of illness or the other. This finding is consistent with results from the Virginia twin sample studied by Kendler's group (36), which showed a higher than

normal risk for bulimia nervosa in the co-twin of a twin with either severe or mild anorexia nervosa, even after control for twin comorbidity with bulimia nervosa. At the same time, it is likely that distinct, syndrome-specific mediating genetic and environmental factors uniquely affect the developmental expression of phenotypic subtypes, their comorbidity, or the likelihood of progressing from one form of disordered eating behavior to the other.

The absence of familial cases of combined anorexia and bulimia nervosa was unexpected, considering that follow-up studies of pure anorexia nervosa (16–18) show that upwards of one-third of patients develop bulimia nervosa prospectively. One possible explanation is poor recall of bulimic symptoms (38), but this would not readily explain why relatives would preferentially recall pure bulimia nervosa but forget, or selectively ignore, occurrences of binge eating in the context of a history of anorexia nervosa. Still, the possibility that a lifetime history of anorexia nervosa can negatively bias the recall of other eating disorder symptoms cannot be dismissed outright. On the other hand, if, indeed, comorbidity of anorexia nervosa and bulimia nervosa, whether cross-sectional or prospective, represents an etiologically unique subform of eating disorder that is also familial, then failure to detect comorbid illness among relatives may reflect the absence in the present study of probands with anorexia and bulimia nervosa combined. An analysis of family data from a cohort of probands with comorbid anorexia nervosa and bulimia nervosa, now in progress, will address the question of whether there is a specific transmissibility of comorbid eating disorder phenotypes.

Our failure to find differences in rates of illness between mothers and sisters also has uncertain meaning. Birth cohort and period effects influencing the incidence of eating disorders have been shown in some, but not all, studies (35). If such effects are operative in anorexia nervosa and bulimia nervosa, the small number of familial cases observed in this study, coupled with the relatively truncated age structure of the study group, may have limited their detection.

The present findings do not allow for conclusive inferences regarding the role of genetic versus environmental sources of familial resemblance. Modeling or exposure effects cannot be discounted, at least with regard to proband-sister resemblance for bulimia nervosa, since Kendler and Gardner (39) showed that cosocialization was more common among monozygotic than dizygotic twins in the Virginia Twin Study and predicted concordance for bulimia nervosa independent of zygosity. Still, simple modeling of illness does not readily explain the discordance in illness phenotype in affected proband-sister pairs (i.e., anorexia nervosa in one, bulimia nervosa in the other), nor does it account for affected proband-mother pairs, as the history given by these mothers indicated that the disorders of all but a few mothers had remitted well before the onset of the proband's illness. In line with this observation, heritability estimates from twin studies of anorexia nervosa and of bulimia nervosa (40) have been reported to range from 0.5 to 0.8, suggesting that the additive gene effects on symptom development in eating disorders are significant. Thus, emerging efforts (41) to localize disease susceptibility genes underlying anorexia nervosa and bulimia nervosa have strong empirical support. Given the present findings on the familiality of subthreshold eating disorder syndromes, the range of phenotypes to be included in definitions of affection status for future genetic studies of eating disorders is in question. Since the base rates of the individual symptoms constituting the diagnoses of anorexia nervosa and bulimia nervosa are high in the general female population, precisely how to extend the phenotypic thresholds for affection status in molecular genetic studies is far from clear. The approach adopted for the present study is but one strategy.

A variety of limitations of the study deserve consideration. First, it has been argued (42) that use of screened, never-ill comparison subjects in studies of the familial coaggregation of two disorders can produce spurious support for common transmissible etiologic factors. However, we think it unlikely that the findings are significantly distorted by use of "super-normal subjects" in the present study. Since we selected probands for single forms of illness, bias that can result from overselection of comorbid cases among probands was eliminated. Furthermore, since the risks for anorexia nervosa and bulimia nervosa in the general population are relatively low, it is unlikely that use of unscreened comparison subjects would have altered the results to a substantial degree. More problematic is the possible differential effect on family transmission of eating disorders of comorbid mood or anxiety disorder among the anorexic and bulimic probands. However, we failed to observe any change in the proportional hazards analyses when they were rerun after inclusion of comorbid mood or anxiety disorder in probands as a covariate, and a prior family study of anorexia nervosa by two of the authors (9) showed no case of anorexia nervosa among a large sample of relatives of non-eating-disordered but psychiatrically ill comparison probands. Second, although we achieved excellent reliability of the best-estimate eating disorder diagnoses, we cannot discount the possibility that the nonblind interviewers inflated descriptions of the severity and functional significance of the eating difficulties and weight concerns reported by the relatives of the ill probands. Still, we doubt that a bias was operating to produce spurious evidence of familial aggregation, given the highly stringent, operationally defined criteria we used for defining the affection status of relatives and the fact that over 60% of the affected relatives of the probands reported having received some level of treatment for their conditions. Similarly, prior family studies (43, 44) have provided little evidence of significant bias resulting from a lack of blindness to proband diagnosis. A third limitation pertains to the use of probands selected from a specialty treatment facility. We acknowledge that family study findings can be sub-

stantially biased if treatment seeking is correlated with positive family history (45). In the absence of systematic ascertainment of probands from the general population, the degree of such bias remains unknown. However, screening of the general population to recruit probands for family studies is impractical for disorders as rare as anorexia nervosa, whereas family studies (45) of the impact of source of proband ascertainment on estimates of familiality of mood or anxiety disorders have not shown the differences in recurrence risk ratios to be significant. Finally, our use of telephone interviews raises the obvious question of whether thoroughness and honesty of self-disclosure of relatives in family studies is better assured through use of one method of interview or the other. However, the reliability and sensitivity of telephone interviews in assessing psychiatric disorders have been affirmed repeatedly (46, 47).

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