

Familiality and Heritability of Binge Eating Disorder: Results of a Case-Control Family Study and a Twin Study

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ABSTRACT

Objective: To estimate the familiality and heritability of binge eating disorder (BED).

Method: We used a new ACE structural equation model to estimate heritability from a case-control family study of BED conducted in the Boston area. The sample consisted of 150 overweight/obese probands with lifetime BED by *DSM-IV* criteria, 150 overweight/obese probands without lifetime BED, and 888 of their first-degree relatives. We compared our findings with those from a study of binge eating (in the absence of compensatory behaviors) among 7,831 Norwegian twins.

Results: The prevalence of BED differed by sex and by age. In the case-control

family study, BED was found to aggregate in families, and heritability was estimated as 57% (CI: 30–77%). Including shared environment did not substantially improve the model's fit, nor did allowing sex-specific heritability. Findings from the twin study were similar.

Conclusion: BED appears to aggregate in families and have a significant genetic component. © 2007 by Wiley Periodicals, Inc.

Keywords: binge eating disorder; binge eating; case-control family study; twin study; familial aggregation; heritability

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Introduction

Binge eating disorder (BED) has a lifetime prevalence of ~3% in the United States and is associated with obesity and psychiatric comorbidity.^{1–3}

The disorder appears to aggregate in families,⁴ but the contribution of genetic factors to this aggregation is unclear. A population-based study⁵ of Norwegian twins between 18- and 31-years old found a heritability estimate of 41% for binge eating without compensatory behaviors (BE), with the

remaining variance in liability to BE attributable to unique environment. The Norwegian study is the only extant twin study exploring the contribution of genetic and environmental factors to liability to a phenotype that closely approximates *DSM-IV*⁶ BED.

To further explore the role of various familial factors in BED, we used a novel ACE (A = additive genetic effects, C = common or shared environment, E = unique environment) structural equation model (Javaras et al., submitted for publication) to analyze data from a case-control family study of BED conducted in the Boston area.⁴ We compared the findings with those from the Norwegian twin study.⁵

Method

Participants and Assessments

The case-control family study was conducted in the Boston area from 2002 to 2004.⁴ Radio and print advertising were used to recruit probands who were overweight or obese. Researchers selected 150 “case” probands who met all the *DSM-IV* criteria for current or past BED within

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TABLE 1. Summary statistics for Boston family and Norwegian twin data

	Boston Families				Norwegian Twins			
	Proband (<i>n</i> = 300)	Parents (<i>n</i> = 195)	Siblings (<i>n</i> = 379)	Children (<i>n</i> = 314)	MZ Twins (Both Included) (<i>n</i> = 2482)	DZ Twins (Both Included) (<i>n</i> = 3870)	MZ Twins (One Included) (<i>n</i> = 396)	DZ Twins (One Included) (<i>n</i> = 1083)
Sex distribution								
Female	227	136	245	209	1486	2175	186	633
Male	73	59	134	105	996	1695	210	450
Age distribution								
18–31 years	26	0	29	155	2482	3870	396	1083
32–40 years	38	0	65	94				
41–50 years	81	13	130	64				
51–60 years	92	34	97	1				
61–91 years	63	148	58	0				
BMI distribution								
9–15.9	0	0	0	0	4	2	0	0
16–17.9	0	2	4	3	55	64	7	23
18–24.9	0	40	106	125	1104	1659	147	427
25–29.9	78	70	128	95	125	233	24	55
30–34.9	94	53	75	47	13	21	3	13
35–39.9	73	19	40	25	1	5	0	0
40–44.9	36	6	16	13	0	1	0	0
45–62.9	19	5	10	6	0	0	0	0
Unknown	0	0	0	0	1180	1885	215	565

their lifetime and 150 “control” probands reporting no lifetime history of BED or other *DSM-IV* eating disorder. The control probands were frequency-matched in age and sex to the case probands. All probands were administered the Structured Diagnostic Interview for *DSM-IV* (SCID)⁷ by an investigator blinded to information about relatives. Subsequently, all consenting adult first-degree relatives of the probands were administered the SCID by interviewers blinded to the status of the proband. The sample we analyzed included the 300 probands and only those 888 relatives who were personally interviewed. The participants included ranged in age from 18 to 91 years.

The twin study⁵ was conducted in Norway in 1998. Questionnaires assessing binge eating, along with other variables, were sent to twins listed in the Norwegian Twin Panel, a population-based twin registry.⁸ Binge eating (BE) was defined as “binge eating with a feeling of a loss of control in the absence of compensatory behaviors such as vomiting, laxative use, fasting, and excessive physical exercise.” This definition did not require *DSM-IV* BED criterion B (behavioral aspects of BE) or C (distress regarding BE). Twins who met the definition of BE within the past 6 months but did not have anorexia nervosa or bulimia nervosa were diagnosed with subthreshold BE if they reported eating binges one to four times a month, and full BE if they reported binges at least twice a week. The sample we analyzed included only those 7,831 twins who responded to the questionnaire and were not missing BE data. Although each subject belonged to a same-sex or opposite-sex twin pair, 1,479 included participants were “single twins” whose cotwin was not included in our sample; the remaining 6,352 participants

belonged to 3,176 “complete twin pairs.” The participants ranged in age from 18 to 31 years.

Table 1 presents summary statistics for sex, age, and body mass index (BMI) by relative type for the Boston family and the Norwegian twin data.

Statistical Analysis

For the Boston family data, estimates of BED prevalence by sex and age were calculated using a novel method of prevalence estimation for binary case-control family data.⁹ Then, estimates of heritability and shared environment were obtained using an ACE structural equation model for binary case-control family data (Javaras et al., submitted for publication). ACE models for binary data assess the extent to which additive genetic factors (A), common or shared environment (C), and unique environment (E) contribute to the variation in liability to the binary outcome (e.g., BED diagnosis); their relative contributions are measured by the parameters a^2 , c^2 , and e^2 , respectively. The classic ACE model for twin data¹⁰ (with a liability-threshold model for binary outcomes¹⁰) can be generalized to family data.¹¹ Several technical issues arise when fitting the generalized model to family data sampled via case-control probands, but these issues can be addressed by conditioning on the proband’s disease status and using independently-obtained estimates of prevalence (Javaras et al., submitted for publication). Importantly, our approach to estimating heritability and shared environment requires no additional assumptions beyond those of the standard meth-

TABLE 2. Prevalence (%) of binge eating disorder by sex and age

Sex	Age (yr)	Boston Families	Norwegian Twins	
		Lifetime Binge Eating Disorder ^a	Six-Month Subthreshold ^b or Full ^c Binge Eating ^d	Six-Month Full ^c Binge Eating ^d
Male	18–31	7.4	11.5	3.8
	32–40	6.4	—	—
	41–60	10.1	—	—
	61–91	1.5	—	—
Female	18–31	12.9	16.4	5.2
	32–40	17.8	—	—
	41–60	14.4	—	—
	61–91	8.7	—	—

^a Binge eating disorder was diagnosed in personal interviews by psychiatrists, according to DSM-IV criteria, using the Structured Clinical Interview for DSM-IV.

^b Subthreshold binge eating requires binge eating one to four times a month.

^c Full binge eating requires binge eating at least twice a week.

^d Binge eating was diagnosed by mail-in questionnaire and was defined as “binge eating with loss of control but in the absence of vomiting, laxative use, fasting, and excessive exercise.”

ods,^{10,11} except for the usual assumptions that pertain to the validity of case-control sampling for family studies.¹²

We fitted different variants of the model, specifically the full model (ACE) and three reduced models (AE, CE, and E). For all variants, we allowed thresholds to be age- and sex-specific; during the estimation of the contribution parameters, we fixed these thresholds at values based on the sex-age prevalence estimates. For variants AE, CE, and ACE, we first constrained a^2 or c^2 (or both) to be the same for both sexes and then allowed them to differ by sex. For variants CE and ACE, we assumed that all sibling pairs shared a family environment equally and that all other relative pairs did not share a family environment at all. We tested the latter assumption by allowing husband–wife and parent–child pairs to share a family environment in our model. The inclusion of these two terms changed model fit by a negligible amount (both were estimated to be close to zero), and their inclusion did not change our conclusions about the presence and magnitude of a^2 and c^2 .

For the Norwegian twin data, estimates of BED prevalence for sex–age groups were calculated from the data on complete twin pairs and single twins, using proportions of affected twins. Estimates of heritability and shared environment were obtained from the data on complete twin pairs, using E, AE, CE, and ACE variants of the classic ACE model for twins.¹⁰ To create a binary outcome variable with a nontrivial number of positive values, the “subthreshold BE” and “full BE” categories were combined into one “BE” category. We used a liability-threshold model for the resulting binary outcomes. For all variants, we allowed the thresholds to be sex- and age-specific and fixed them (when estimating the contribution parameters) at values based on the sex–age prevalence estimates. For variants AE, CE, and ACE, we first constrained the other parameters to be the same for both sexes and then allowed them to differ by sex. We

expected our results to differ slightly from the published results,⁵ since the latter were produced using the BE outcome variable in its original three-category form.

Results

Both the Boston and the Norwegian estimates of BED prevalence (**Table 2**) were higher for females than for males in every age bracket. The prevalence estimates peaked in the 30s age bracket for females and in the 40s and 50s age bracket for males. The Boston estimates were higher than the Norwegian (“full BE”) estimates, not surprisingly since the former estimated lifetime (rather than 6-month) prevalence and came from personal interviews of individuals ascertained through an overweight or obese relative.

Table 3 presents goodness of fit statistics for all models fitted to the Boston family data or the Norwegian twin data. In both the Boston and Norwegian studies, constraining a^2 and c^2 , a^2 , or c^2 to be the same for both sexes did not significantly worsen the fit of variants ACE, AE, or CE, respectively. Thus, in the remainder of this article, we focus exclusively on the combined-sex version of each variant. **Table 3** presents estimates and standard errors of heritability, shared environment, and unique environment for the combined-sex models.

For both the Boston and Norwegian studies, comparing the fit of Model E to that of Model AE, Model CE, or Model ACE allowed us to reject the hypothesis that BED does not aggregate in families.

For the Boston family study, there was some evidence that Model AE fit the data best: the 0.95 CI

TABLE 3. Estimates (standard errors) and goodness of fit for ACE models

Model	Boston Families ^a					Norwegian Twins ^b				
	a^2	c^2	e^2	Parameters ^c	-2ML ^d	a^2	c^2	e^2	Parameters ^c	-2ML ^d
ACE (sex-specific)	NR	NR	NR	4	701.4	NR	NR	NR	4	3937.0
ACE (sex-combined)	0.45 (0.18)	0.14 (0.13)	0.41	2	706.0	0.39 (0.07)	0.00	0.61	2	3937.7
CE (sex-specific)	NR	NR	NR	2	721.0	NR	NR	NR	2	3941.0
CE (sex-combined)	—	0.36 (0.09)	0.64	1	721.0	—	0.28 (0.05)	0.72	1	3941.6
AE (sex-specific)	NR	NR	NR	2	706.4	NR	NR	NR	2	3937.0
AE (sex-combined)	0.57 (0.12)	—	0.43	1	708.9	0.39 (0.07)	—	0.61	1	3937.7
E	—	—	1.00	0	758.7	—	—	1.00	0	3965.3

Notes: NR, not reported.

^a In all variants for Boston families, the thresholds were sex- and age-specific.

^b In all variants for Norwegian twins, the thresholds were sex-specific.

^c Number of parameters in model not including thresholds, which are fixed.

^d Minus two times the maximum value of the log likelihood.

for c^2 in Model ACE (0–53%) included zero, and the test statistic (=2.9) for the likelihood ratio test (LRT) comparing Model AE to Model ACE did not exceed the conservative cutoff ($\chi_{1,0.95} = 3.84$) required to reject the hypothesis that Model AE fit best. However, there was also some evidence in favor of Model ACE: both a Monte Carlo test and an LRT with an anticonservative cut-off ($\chi_{1,0.90} = 2.71$) allowed us to reject the hypothesis that Model AE fit best. Although we selected Model AE as the best fitting model because of its greater parsimony, shared environment may play a small but non-negligible role in BED. For the Norwegian twin study, Model AE clearly fit the data best.

The best fitting model from the Boston family study (Model AE) yielded an estimate for the heritability of BED of 57%. This value did not differ significantly from the Norwegian twin study estimate of 39%. Further, the Boston family study 0.95 CI for a^2 (30–77%) overlapped with the Norwegian twin study 0.95 CI for a^2 (26–52%).

Conclusion

We fitted ACE structural equation models to data from a case-control family interview study conducted in Boston and also to data from a population-based twin study conducted in Norway. Both analyses provide strong evidence that BED aggregates in families. This finding agrees with a previous analysis⁴ of the Boston family data using a univariate proband predictive logistic regression model,¹² which found significant evidence of family aggregation (odds ratio of 2.2 for the odds of BED in a relative of a proband with BED vs. the odds of BED in a relative of a proband without

BED). In two smaller family studies of BED conducted earlier, one¹³ found significant evidence for familial aggregation, and the other¹⁴ found an effect size (odds ratio of 1.9) similar to the Boston family study, although the value was not statistically significant, probably because the study did not have sufficient power to detect effects of that magnitude.

The Boston and Norwegian analyses also suggest that additive genetic effects are responsible for a substantial part of the familial aggregation of BED: the heritability of BED appears to fall between 30 and 80%, most likely in the middle of this range. Although these are the only analyses thus far that have assessed the heritability of BED, previous studies^{15,16} have suggested that BE in general (i.e., with or without purging or other compensatory activities) is heritable. It is likely that the genetic factors for BED are in part shared with and in part distinct from those for obesity. This speculation is based in part on previous analysis⁴ of the Boston family data, which demonstrated that the familial factors for BED (which our present analysis reveals to be largely, if not exclusively, genetic) overlap only partially with those for obesity. In addition, a previous twin study¹⁶ has found evidence for separate, as well as shared, genetic factors for BE in general and obesity. Additional studies will be needed to determine the specific genes involved in BED, including those shared with obesity. There have only been a few genetic studies of BED. A candidate gene study¹⁷ found an association of melanocortin 4 receptor mutations with BED in obese individuals, whereas two subsequent studies^{18,19} failed to replicate this finding. Other studies have reported an association of BED with the Leu72Met polymorphism of the ghrelin gene²⁰ and with a polymorphism of the promoter of the serotonin transporter gene.²¹

The Boston and Norwegian analyses did not completely agree on whether shared environment plays a role in BED. The Norwegian twin study indicated a negligible role, whereas the Boston family study indicated a small but perhaps non-negligible role. Clearly, the role of shared environment warrants further study.

Both of the analyses in this article have limitations. Beginning with the Boston family study, the requirement that the probands be overweight or obese meant that all probands and almost all relatives had a body mass index above 25. Since BED tends to be comorbid with obesity, the estimates of BED prevalence were likely larger than the corresponding population estimates. The over-representation of individuals with a high body mass index would be expected to attenuate the estimates of BED familiarity and heritability.⁴ In addition, it is more difficult to estimate the effect of shared environment from family data. For example, if two siblings differ greatly in age, they probably do not share their environment to the same extent as two twins.

Turning to the Norwegian twin study, the definition of BE did not correspond completely to the *DSM-IV* criteria for BED. In addition, BE was assessed only on a current basis, and thus past cases were not identified. Finally, BE was assessed by questionnaire responses and not confirmed by personal interview. When compared with a lifetime *DSM-IV* diagnosis of BED, the limitations of the Norwegian study phenotype represent measurement error. Since measurement error is included in the unique environment term (E) of ACE models, the estimates of heritability (and possibly also shared environment) would be expected to be lower for the Norwegian study than the Boston study.

Although previous analysis⁵ of the Norwegian twin data used three-category outcomes (“no BE;” “subthreshold BE;” “full BE”), we chose to combine the “subthreshold” and “full” categories in order to make the outcomes binary like the Boston family study BED outcomes. Doing so resulted in a loss of power and in estimates slightly different from those reported in the previous analysis.⁵

These limitations aside, the Boston family and Norwegian twin studies provide strong evidence that BED aggregates in families and that additive genetic factors play a substantial role in the observed aggregation.

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