

Binge-Eating Disorder as a Distinct Familial Phenotype in Obese Individuals

James I. Hudson, MD, ScD; Justine K. Lalonde, MD; Judith M. Berry, MA; Lindsay J. Pindyck; Cynthia M. Bulik, PhD; Scott J. Crow, MD; Susan L. McElroy, MD; Nan M. Laird, PhD; Ming T. Tsuang, MD, PhD; B. Timothy Walsh, MD; Norman R. Rosenthal, MD; Harrison G. Pope, Jr, MD, MPH

Context: Binge-eating disorder (BED)—a syndrome that only recently has attracted scientific attention—is often seen in obese individuals, especially those with severe obesity. However, it remains unclear whether BED represents an etiologically distinct behavioral phenotype of obesity or simply a nonspecific eating pattern sometimes seen in obese individuals.

Objective: To test whether BED aggregates in families independently of obesity, and if so, whether familial factors for BED also independently increase the risk of obesity.

Design, Patients, and Setting: Blinded family interview study of overweight or obese probands with (n=150) and without (n=150) BED, and their first-degree relatives (n=888) in a community setting evaluated between October 2002 and July 2004.

Main Outcome Measures: Lifetime diagnosis of BED; current and highest lifetime body mass index (calculated as the weight in kilograms divided by the square of the height in meters).

Results: Binge-eating disorder aggregated strongly in families independently of obesity (odds ratio, 2.2; 95% confidence interval, 1.4-3.6; $P<.001$). Furthermore, relatives of probands with BED displayed a markedly higher prevalence of severe obesity in adulthood (body mass index ≥ 40) than relatives of probands without BED even when controlling for proband body mass index (odds ratio, 2.5; 95% confidence interval, 1.4-4.4; $P=.002$).

Conclusions: Binge-eating disorder is a familial disorder caused in part by factors distinct from other familial factors for obesity. Furthermore, these BED-specific familial factors may independently increase the risk of obesity, especially severe obesity. It follows that targeted interventions capable of preventing or treating traits influenced by these BED-specific familial factors could reduce the public health burden of obesity.

Arch Gen Psychiatry. 2006;63:313-319

OBESITY IS A GLOBAL EPIDEMIC with profound medical and social consequences,¹ but its complex causes remain incompletely understood. Binge-eating disorder (BED), a syndrome that only recently has attracted scientific attention,²⁻⁴ may contribute to obesity in some individuals.⁵ Individuals with BED exhibit frequent eating binges characterized by a loss of control over eating, during which the individual consumes an unusually large amount of food within a short period of time, typically less than 2 hours. Current diagnostic criteria² for BED require that these binges occur at least twice per week for a minimum of 6 months.

Individuals with BED are frequently obese.^{3,5-8} Conversely, BED is often observed in obese populations, especially the severely obese.^{3,5-10} Binge-eating disorder also appears to be associated with substantial medical^{11,12} and psychiatric^{3,6,12-16} morbidity, some likely mediated through obesity and some independently associated with BED itself.^{4,12-14,16} Collectively,

these findings suggest that BED is a major public health problem and a contributor to the obesity epidemic.

However, it remains unclear whether BED represents an etiologically distinct behavioral phenotype of obesity⁴ or simply a nonspecific eating pattern, seen in some obese individuals with no particular etiologic significance. It is known, for example, that various pharmacological,¹⁷⁻¹⁹ psychological,^{20,21} and surgical²² treatments are efficacious in BED, but it is unknown whether these treatments work via a direct effect on BED per se or merely via a generic effect on appetite or eating patterns.^{4,16} One way to discriminate among these possibilities is to determine whether BED aggregates in families independently of obesity. Evidence for such aggregation would suggest that BED is caused in part by familial factors distinct from those for obesity itself.

Few investigations have assessed the familial aggregation of BED. Two small nonblinded studies,^{23,24} using information obtained from probands²³ or from telephone interviews of relatives,²⁴ found an elevated

Author Affiliations are listed at the end of this article.

prevalence of BED in the relatives of probands with BED, but only one²³ produced statistically significant results. The other study²⁴ yielded an odds ratio (OR) of 1.9 for the aggregation of BED in families, but this OR had a very wide confidence interval (0.42-12) because only 10 cases of BED were identified among relatives. Several twin studies have used questionnaires to examine binge eating, but not the full syndrome of BED.²⁵⁻²⁷ These studies have suggested a strong genetic contribution to binge eating in general^{25,26} and binge eating without compensatory behaviors.²⁷ One genetic study²⁸ found BED associated with mutations in the melanocortin-4 receptor gene (a gene implicated in the development of hyperphagia and obesity^{29,30}) although a subsequent study³¹ failed to replicate this finding.

To augment these limited data, we conducted a blinded family interview study of 300 probands with and without BED and 888 of their first-degree relatives.

METHODS

SUBJECTS

Using radio and print advertising, we recruited 2 groups of probands aged 18 years and older who were all overweight or obese, defined here as a body mass index (BMI) (weight in kilograms divided by the square of the height in meters) of 25 or greater for women and 27 or greater for men. We chose the higher cut-off value for men on the basis of several studies suggesting that the BMI threshold for being overweight or obesity should be higher in men than in women.³²⁻³⁴ Probands in the first group met DSM-IV² criteria for a lifetime diagnosis of BED. Probands in the second group were frequency matched in age and sex to probands with BED, but reported no lifetime diagnosis of bulimia nervosa or anorexia nervosa, and no more than 5 lifetime eating binges as defined by criterion A for BED in DSM-IV. We required that all probands have at least 2 living first-degree relatives aged 18 years and older who are potentially able to come to our laboratory for interviews; in both groups, we particularly tried to secure female relatives because BED is more common in women,^{3,8} and therefore we expected female relatives to be more informative.

PROCEDURES

Probands who qualified on telephone screen were invited to a personal interview with the proband interviewer (H.G.P.) who was blinded to information about the proband's relatives. The interviewer confirmed that the subject met all inclusion criteria and then assessed for a lifetime diagnosis of BED (including retrospective assessment of age at onset) in the subject by DSM-IV criteria, using the Structured Clinical Interview for DSM-IV (SCID).³⁵ Although we used the SCID to assess a wide range of other DSM-IV disorders, the present article is restricted to the diagnosis of BED; data on other disorders in this sample will be presented in a separate report.

A study coordinator then scheduled all available and consenting first-degree relatives for an interview with a family interviewer (J.I.H. or J.K.L.) who was blinded to information about the proband. The family interviewers assessed lifetime BED in relatives by the same method used for the probands. Consenting relatives unable to come to McLean Hospital, Belmont, Mass, were interviewed by telephone.

When probands and relatives were evaluated in person, we measured the height by ruler to the nearest 1.3 cm, and weight by beam balance to the nearest 0.2 kg. For relatives evaluated by telephone,

we obtained self-reported height and weight. We also asked all subjects to report their highest adult body weight at any time since age 18 years; from this value we in turn estimated their highest adult BMI because height after age 18 years is relatively stable.

To maximize reliability, the family interviewers discussed all cases together and assigned consensus diagnoses. When these interviewers disagreed, cases were presented to H.G.P. under blinded conditions and his diagnosis was taken as final.

All subjects gave written informed consent for this study, which was approved by the McLean Hospital institutional review board.

STATISTICAL ANALYSIS

To evaluate the familial aggregation of BED, we used a univariate proband predictive logistic regression model, which is described elsewhere,^{36,37} where the outcome was the presence of BED in a relative and the predictor was BED in the corresponding proband. In a secondary analysis, we applied a proportional hazards model for time to onset of BED.

The analyses reported here used data from interviewed relatives only; we also performed additional analyses using data for all relatives aged 18 years and older, based on information about noninterviewed relatives provided by the interviewed relatives. In analyses restricted to interviewed relatives, missing data from noninterviewed relatives can be a source of bias, but serious bias is unlikely in our case because our statistical models are valid even if a relative's probability of selection into the study depends on the outcome (eg, BED in a relative).³⁸ By contrast, analyses using all relatives, while having no missing data, may be biased because information given by informants may depend on the informants' outcome (eg, relatives who have BED themselves might be more likely to detect or report it in a fellow relative).^{39,40}

To compare characteristics between probands with and without BED, and between relatives with and without BED, we used linear regression for continuous variables and logistic regression for binary variables. In all models for outcomes in probands, we adjusted for sex and age, using the following 5 age categories (years): 18 to 30, 31 to 40, 41 to 50, 51 to 60, and 60 and older. In models for outcomes in relatives, we adjusted for the proband's sex, age, and BMI (modeled as categories representing quintiles of the distribution of BMI in probands); relative's age, sex, and relationship to the proband (parent, sibling, or child); and interview type (in person or telephone). In the case of relatives, because observations within families are correlated, we used generalized estimating equations⁴¹ to estimate standard errors with independence as the working covariance structure.

We fitted all models using Stata 7.0 statistical software (Stata Corp, College Station, Tex). We set α at .05, 2-tailed. The statistical analysis was performed by J.I.H. in collaboration with N.M.L. and H.G.P.

RESULTS

CHARACTERISTICS OF PROBANDS AND RELATIVES

Between October 2002 and July 2004, we evaluated 300 probands and 888 relatives. Our advertisements for probands generated 1830 respondents, of whom 1376 were excluded at telephone screen (fewer than 2 available relatives [n=924]; failed to meet full diagnostic criteria for either BED group or non-BED comparison group [n=436]; declined to participate [n=16]). Of the 199 qualifying for the BED group, we rejected 49 (no match in non-BED group [n=29]; did not show for appointment [n=14];

Table 1. Characteristics of Probands and Relatives, by Proband Group

	BED	Non-BED
Probands		
Total, No.	150	150
Age \pm SD, y	49.5 \pm 12.8	50.2 \pm 12.6
Range	18-75	21-75
Female sex, No. (%)	114 (76.0)	114 (76.0)
BMI \pm SD	35.8 \pm 6.7*	33.3 \pm 5.2
Relatives		
Total, No.	431†	457‡
Age \pm SD, y	45.7 \pm 17.4	47.8 \pm 17.4
Range	18-87	18-91
Female sex, No. (%)	295 (68.5)	294 (64.3)

Abbreviations: BED, binge-eating disorder; BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters).

*The mean estimated difference in BMI (adjusted for age and sex) between probands with BED and without BED is 2.4 (95% confidence interval, 1.1-3.8; $P < .001$).

†We conducted 371 in-person interviews and 60 telephone interviews; we interviewed 68 mothers, 29 fathers, 122 sisters, 50 brothers, 105 daughters, and 57 sons.

‡We conducted 370 in-person interviews and 87 telephone interviews; we interviewed 65 mothers, 31 fathers, 128 sisters, 85 brothers, 101 daughters, and 47 sons.

failed to meet diagnostic criteria at in-person interview [$n = 3$]; and no relatives obtained [$n = 3$]); of the 255 qualifying for the non-BED group, we rejected 105 (no match in BED group [$n = 91$]; did not show for appointment [$n = 9$]; failed to meet diagnostic criteria at in-person interview [$n = 2$]; and no relatives obtained [$n = 3$]).

The 300 probands had 1593 living relatives aged 18 years and older, of whom we obtained permission to contact 1192. Of these, 587 were relatives of probands with BED; 154 were unwilling to participate and 431 were evaluated (in person [$n = 371$]; by telephone [$n = 60$]). Of the 605 relatives of non-BED probands, 148 were unwilling to participate and 457 were evaluated (in person [$n = 370$]; by telephone [$n = 87$]).

Subject characteristics are presented in **Table 1**. Probands with BED displayed a significantly higher mean BMI than probands without BED.

FAMILIAL AGGREGATION OF BED

A lifetime diagnosis of BED was found in 87 (20.2%) of the 431 relatives of probands with BED, and 44 (9.6%) of the 457 relatives of probands without BED. Binge-eating disorder aggregated strongly in families; the OR for BED among relatives of probands with BED as compared with relatives of probands without BED was 2.2 (95% confidence interval, 1.4-3.6; $P < .001$). The hazard for onset of BED in relatives of probands with BED was double that for relatives of probands without BED ($P = .001$) (**Figure**).

The estimated OR for aggregation of BED remained stable (changing less than 5%) when (1) restricting to the 114 probands with BED and 108 probands without BED who were obese (BMI ≥ 30); (2) weighting relatives by inverse probability of selection based on age, sex, and type of relative to adjust for oversampling of female

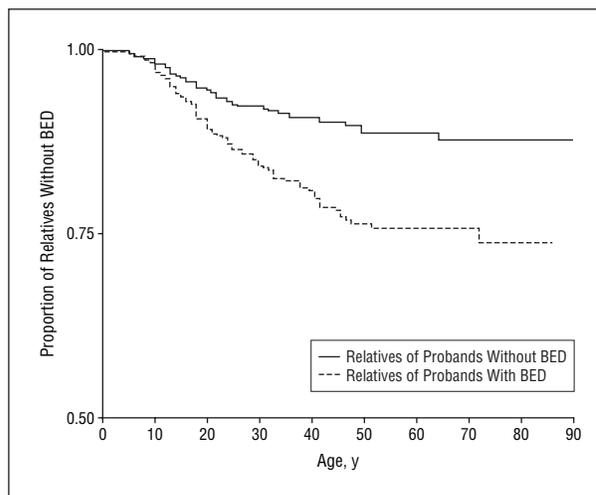


Figure. Kaplan-Meier estimates of time to onset of binge-eating disorder (BED) among relatives, according to proband group.

relatives and other deviations from the characteristics of all first-degree relatives that resulted from sampling; and (3) including information on noninterviewed relatives. In connection with the last of these 3 analyses, we also found that interviewed relatives with BED were not significantly more likely to report information supportive of BED in a noninterviewed fellow relative than interviewed relatives without BED (76.2% vs 68.6%, respectively; OR, 1.6; 95% confidence interval, 0.77-3.3; $P = .21$) in a logistic regression analysis that adjusted for the informants' age, sex, and relationship to proband, and that accounted for the correlation of observations within families using generalized estimating equations.

BMI AND OBESITY IN RELATIVES

We first compared the relatives associated with each of the 2 groups of probands (**Table 2**). Relatives of probands with BED, compared with relatives of probands without BED, displayed a significantly higher mean current BMI, mean highest adult BMI, and a higher current prevalence of obesity. Most strikingly, these relatives displayed a much higher lifetime prevalence of severe obesity (BMI ≥ 40). It should be recalled that all of these comparisons controlled for proband BMI.

In a second analysis, we split the relatives in a different way and compared those with and without a lifetime diagnosis of BED, regardless of the proband group with which they were associated (**Table 3**). Relatives with a lifetime diagnosis of BED, compared with relatives with no lifetime BED, exhibited a strikingly higher mean current and highest adult BMI, and prevalence of current and lifetime adult obesity. Indeed, the prevalence of severe obesity, whether assessed on a current or lifetime adult basis, was nearly 5 times as great among relatives with BED vs those without BED.

COMMENT

We performed a blinded family interview study of 150 overweight or obese probands with BED and an age-

Table 2. BMI and Obesity Among Relatives, by Proband Group

Measure	Relatives of Probands With BED (n = 431)	Relatives of Probands Without BED (n = 457)	Difference Between Groups*		
			Estimate	95% CI	P Value
BMI					
Current ± SD	29.5 ± 7.6	28.0 ± 5.8	1.1	0.11-2.1	.029
Highest adult ± SD	32.2 ± 8.4	30.4 ± 6.3	1.3	0.09-2.4	.034
Current obesity					
None, No. (%)	253 (58.7)	320 (70.0)
Moderate, No. (%)†	141 (32.7)	118 (25.8)	1.4	1.0-2.0	.038
Severe, No. (%)‡	37 (8.6)	19 (4.2)	2.1	1.1-4.2	.029
Lifetime adult obesity					
None, No. (%)	203 (47.1)	239 (52.3)
Moderate, No. (%)†	153 (35.5)	186 (40.7)	0.88	0.63-1.2	.46
Severe, No. (%)‡	75 (17.4)	32 (7.0)	2.5	1.4-4.4	.002

Abbreviations: BED, binge-eating disorder; BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters); CI, confidence interval.

*The measure of difference for BMI is the mean difference between groups. For obesity categories, the measure of difference is the odds ratio for a given obesity category, with no obesity as the reference group, with both measures adjusted for proband's age, sex, and BMI; relative's age, sex, and relationship to the proband; and interview type.

†Moderate obesity is defined by a BMI between 30 to 39.

‡Severe obesity is defined by a BMI of 40 or more.

Table 3. BMI and Obesity Among Relatives, by Lifetime BED Status

Measure	Relatives With BED (n = 131)	Relatives Without BED (n = 757)	Difference Between Groups*		
			Estimate	95% CI	P Value
BMI					
Current ± SD	33.3 ± 8.5	28.0 ± 6.1	5.2	3.7-6.7	<.001
Highest ± SD	37.7 ± 8.4	30.2 ± 6.7	7.4	6.0-8.9	<.001
Current obesity					
None, No. (%)	54 (41.2)	519 (68.6)
Moderate, No. (%)†	52 (39.7)	207 (27.3)	2.5	1.6-3.8	<.001
Severe, No. (%)‡	25 (19.1)	31 (4.1)	8.5	4.1-18	<.001
Lifetime adult obesity					
None, No. (%)	25 (19.1)	417 (55.1)
Moderate, No. (%)†	58 (44.3)	281 (37.1)	4.0	2.5-6.5	<.001
Severe, No. (%)‡	48 (36.6)	59 (7.8)	16	8.8-29	<.001

Abbreviations: BED, binge-eating disorder; BMI, body mass index (calculated as the weight in kilograms divided by the square of height in meters); CI, confidence interval.

*The measure of difference for BMI is the mean difference between groups. For obesity categories, the measure of difference is the odds ratio for a given obesity category, with no obesity as the reference group, with both measures adjusted for proband's age, sex, and BMI; relative's age, sex, and relationship to the proband; and interview type.

†Moderate obesity is defined by a BMI between 30 to 39.

‡Severe obesity is defined by a BMI of 40 or more.

matched and sex-matched group of 150 overweight or obese probands with no history of an eating disorder, together with 888 of their first-degree relatives. We restricted the study to overweight or obese probands, and further adjusted for proband BMI, to ensure that any observed familial aggregation of BED would be independent of familial factors for obesity itself.

The study produced 3 principal findings. First, our primary hypothesis—that BED aggregated in families independently of obesity—was strongly supported, with an estimated aggregation OR of 2.2. When interpreting this finding, it should be recalled that familial aggregation is fully explained by a combination of genetic and family environmental factors. Family studies such as this one

cannot quantify the relative contributions of these 2 sets of factors. However, given (1) evidence from twin studies suggesting a significant contribution of genetic factors in binge eating, separate from those for obesity²⁶; (2) further twin-study data finding virtually no evidence for a contribution of familial environmental factors in binge eating²⁵⁻²⁷; and (3) theoretical evidence suggesting that aggregation ORs of this magnitude cannot easily be explained by purely environmental factors,⁴² it seems likely that at least some of the independent familial factors for BED are genetic.

It should be noted here that we are discussing the contributions of genetic and environmental factors to the familial aggregation of BED, as distinguished from

their contribution to individual liability for BED. More technically, the familial aggregation of BED is determined by a combination of genetic and shared environmental factors, whereas BED itself is determined by a combination of these factors plus additional unique or nonfamilial environmental factors. Twin studies²⁵⁻²⁷ suggest that the contribution of shared environmental factors to the liability for BED is minimal, whereas the contribution of unique environmental factors is substantial. Among the many environmental factors potentially contributing to BED are prenatal factors, which may be either shared or unique.

Second, we found that relatives of probands with BED displayed a higher prevalence of obesity—particularly of severe obesity—than relatives of probands without BED, even when controlling for proband BMI. For example, our findings suggest that if an individual has an overweight or obese first-degree relative with BED, as compared with having an equally overweight or obese relative without BED, then that individual faces a 2.5-fold increase in his or her odds of lifetime adult severe obesity.

Third, when we compared relatives with and without BED, regardless of proband group, we found a marked association of BED with obesity, consistent with previous community-based studies.⁶⁻⁸ Notably, this association was much stronger with severe obesity than with moderate obesity—a result that reinforces previous impressions^{3,10,43} that the association of BED with obesity becomes stronger with increasing levels of BMI. The only other study to examine the association of BED with severe obesity in a community-based sample was the National Comorbidity Survey Replication,¹⁰ which produced results consistent with those presented here. Other previous studies of BED and severe obesity are not directly comparable to ours because they have been confined to clinical samples of patients undergoing gastric bypass surgery.^{9,22,44}

Our first 2 findings suggest that there are familial factors associated with BED, independent from any additional familial factors for obesity, and that these familial factors themselves increase the risk of obesity. It is likely that familial endophenotypes represent links in this causal chain. For example, 1 candidate endophenotype is impulsivity, a personality trait associated with BED,⁴⁵ which could lead to impulsive binge eating and then to BED, which could in turn lead to obesity. Another candidate endophenotype is hyperphagia, which has known genetic determinants, including melanocortin-4 receptor mutations²⁹⁻³¹ that are possibly shared with BED.²⁹ Hyperphagia might lead to both obesity and BED in some individuals and might lead to obesity, even in the absence of BED, in others.

Our cross-sectional data cannot discriminate among these various causal models. In particular, although there is a striking association between BED and severe obesity, as demonstrated by our third finding, our data do not allow us to determine the degree to which BED mediates the effect of genetic factors on the development of obesity. A possible mechanism is that genetic factors increase the risk of binge-eating behavior, thus increasing caloric intake, leading to substantial weight gain and culminating in severe obesity.

In any event, regardless of the causal sequence, it would still follow that interventions to prevent or treat traits influenced by these putative BED-specific familial factors could decrease the prevalence of obesity in the population. Effective interventions might operate at various points in the causal sequence. For example, they might correct abnormal endophenotypes such as impulsivity or hyperphagia, which in turn might reduce or prevent binge eating. Finally, since these familial determinants likely interact with nonfamilial (ie, unique) environmental factors to produce obesity, interventions might correct facilitating nonfamilial environmental factors. Given that BED affects a substantial minority of obese individuals,^{3,5-9} a successful intervention could reduce the public health burden of obesity.⁵

We consider 4 limitations of our design. First, selection factors may have influenced the characteristics of probands and relatives who agreed to participate in this study. Selection bias seems unlikely, however, because selection factors would be expected to be similar across groups. Second, to assess whether BED aggregated in families independent of obesity, we intentionally restricted our study to overweight or obese probands. Thus our results might not be generalizable to individuals of normal weight with BED. However, many or most individuals with BED are obese, as demonstrated by previous studies^{3,5,6} and by our findings in relatives with BED, and obese individuals are the group of greatest public health importance in any case. Third, we relied on self-report to assess maximum adult body weight in all subjects, and additionally to assess current height and weight in all relatives evaluated by telephone. While self-report is less accurate than objective measurements, the resulting measurement error would be expected to be nondifferential, and thus would tend to bias the results toward the null (ie, produce overly conservative findings). Fourth, we did not assess the age at onset of obesity in participants, because we judged that retrospective determinations of this variable would be inaccurate. Thus, we were unable to use the relative timing of BED and obesity to aid in the assessment of possible causal relationships.

Finally, we found a high prevalence of BED among relatives of probands with BED and even among relatives of non-BED probands who showed a lifetime prevalence of 9.6% as compared with only 2% to 5% in population-based studies.^{3,8,10} Several factors may explain this difference. First, we interviewed more female than male relatives; when adjusting for the sex distribution, the lifetime prevalence of BED among the relatives of probands without BED falls to 8.6%. Second, all relatives were related to an overweight or obese proband, and familial obesity, independent of BED, may increase the risk of BED. Third, administration of the SCID by clinicians with expertise in eating disorders may be more sensitive to BED than other techniques.⁴⁶ Fourth, there may have been selection in favor of greater overall psychopathology among probands or relatives. Weighing against this last possibility, however, is our finding that the lifetime prevalence of other conditions—such as major depressive disorder, bipolar disorder, panic disorder, and substance abuse or dependence—among probands without BED (16.0%, 1.3%, 4.0%, and 24.0%, respectively) and rela-

tives of probands without BED (25.0%, 2.4%, 6.4%, and 21.9%, respectively) was fairly similar to results from the National Comorbidity Study^{47,48} (17.1%, 1.6%, 3.5%, and 26.6%, respectively), a large population-based study of the prevalence of psychiatric disorders in the United States. Furthermore, none of these 4 factors would limit the conclusions drawn from the study in any event because the conclusions are based not on the absolute prevalence of BED, but rather the relative prevalence of BED between groups. Only bias owing to differential selection (selection that operated more strongly on the relatives of 1 proband group than the other) would affect the conclusions, and differential selection seems unlikely.

In summary, BED appears to represent a distinct familial phenotype in obese individuals, associated with familial factors independent in part from those for obesity. Elucidation of these familial factors, leading to targeted interventions, could reduce the public health burden of obesity.

Submitted for Publication: June 3, 2005; final revision received July 19, 2005; accepted September 8, 2005.

Author Affiliations: Department of Psychiatry, Harvard Medical School and McLean Hospital, Belmont, Mass (Drs Hudson, Lalonde, and Pope, and Ms Berry and Ms Pindyck); Departments of Psychiatry and Nutrition, University of North Carolina, Chapel Hill (Dr Bulik); Department of Psychiatry, University of Minnesota, Minneapolis (Dr Crow); Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio (Dr McElroy); Department of Biostatistics, Harvard School of Public Health, Boston, Mass (Dr Laird); Institute of Behavioral Genomics, Department of Psychiatry, University of California, San Diego, and the Harvard Institute of Psychiatric Epidemiology & Genetics, Boston (Dr Tsuang); Department of Psychiatry, New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons, New York (Dr Walsh); and Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ (Dr Rosenthal).

Correspondence: James I. Hudson, MD, ScD, Psychiatric Epidemiology Research Program, McLean Hospital, 115 Mill St, Belmont, MA 02478 (jhudson@mclean.harvard.edu).

Funding/Support: This study was supported by a grant from Ortho-McNeil Pharmaceutical Inc, Raritan, NJ.

Acknowledgment: We thank Steven Barry, Geoffrey Cohane, Rebecca Hudson, Rachel Placidi, and Michaela Vine for their assistance with data collection and data entry; and Julie Capece and Frances Nestor for assistance with the administration of the project.

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