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BRIEF COMMUNICATION

Family study of the aggregation of eating disorders and mood disorders[1]

B. MANGWETH, J. I. HUDSON,[2] H. G. POPE, A. HAUSMANN, C. DE COL, N. M. LAIRD, W. BEIBL AND M. T. TSUANG

From the Department of Psychiatry, University of Innsbruck and Innsbruck University Clinics, Innsbruck, Austria; and Department of Psychiatry, Harvard Medical School, Departments of Biostatistics and Epidemiology, Harvard School of Public Health and Massachusetts Mental Health Center, Boston and the Biological Psychiatry Laboratory, McLean Hospital, Belmont, MA, USA

ABSTRACT

Background. Family studies have suggested that eating disorders and mood disorders may coaggregate in families. To study further this question, data from a family interview study of probands with and without major depressive disorder was examined.

Method. A bivariate proband predictive logistic regression model was applied to data from a family interview study, conducted in Innsbruck, Austria, of probands with ($N=64$) and without ($N=58$) major depressive disorder, together with 330 of their first-degree relatives.

Results. The estimated odds ratio (OR) for the familial aggregation of eating disorders (anorexia nervosa, bulimia nervosa and binge-eating disorder) was 7·0 (95% CI 1·4, 28; $P=0·006$); the OR for the familial aggregation of mood disorders (major depression and bipolar disorder) was 2·2 (0·92, 5·4; $P=0·076$); and for the familial coaggregation of eating disorders with mood disorders the OR was 2·2 (1·1, 4·6; $P=0·035$).

Conclusions. The familial coaggregation of eating disorders with mood disorders was significant and of the same magnitude as the aggregation of mood disorders alone – suggesting that eating disorders and mood disorders have common familial causal factors.

INTRODUCTION

Family studies have consistently found an elevated prevalence of mood disorders among the relatives of probands with eating disorders, including even those probands who do not have a mood disorder themselves (Gershon *et al.* 1984; Biederman *et al.* 1985; Hudson *et al.* 1987, 2001*a*; Kassett *et al.* 1989; Logue *et al.* 1989; Keck *et al.* 1990; Lilenfeld *et al.* 1998). These observations suggest that eating disorders and mood disorders may cluster together, or coaggregate, in families. However, the interpretation of these studies is subject to two main limitations (reviewed in Hudson *et al.* 2001*a*): (1) because of small samples, the confidence intervals for the estimated coaggregation effect are wide and in some cases include the null value; and (2) statistical analyses in these studies do not correct for the correlation of observations within families, and use univariate models that have less flexibility and power than bivariate models.

To assess further the familial coaggregation of eating disorders and mood disorders, we applied a bivariate logistic regression model to data from a recent family interview study.

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[2] Address for correspondence: Dr James I. Hudson, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA.

METHOD

We analysed data from a family interview study, described previously (Hudson *et al.* 2003), of 64 probands admitted to psychiatric units for treatment of major depressive disorder (MDD), and 58 probands without MDD admitted to surgical and ophthalmology units, at Innsbruck University Clinics in Innsbruck, Austria. In this study, designed to test the aggregation of 'affective spectrum disorder' (Hudson & Pope, 1990), we interviewed all probands and their consenting first-degree relatives (parents, siblings and children) age 18 or over, using a German translation (Wittchen *et al.* 1996) of the *Structured Clinical Interview for DSM-IV* (First *et al.* 1994). Before administration of any study procedures, subjects signed informed consent forms approved by the McLean Hospital Institutional Review Board and the Ethikkommission of the University of Innsbruck.

A single interviewer, blinded to proband diagnosis, assessed all first-degree relatives. We used data from interviewed relatives only; information about eating disorders in non-interviewed relatives was insufficient to allow confident diagnoses. We have discussed the issues dealing with non-interviewed relatives in this sample previously (Hudson *et al.* 2003).

To assess the familial coaggregation of mood disorders (MDD and bipolar disorder) with eating disorders (anorexia nervosa, bulimia nervosa and binge eating disorder), we used a logistic regression model with bivariate disorder status of a relative as the outcome and bivariate disorder status of the proband as the predictor. We have discussed elsewhere (Hudson *et al.* 2001*a*, *b*) this bivariate proband predictive model and its application to studies of the familial aggregation of eating disorders and mood disorders. The model allows for combining information from individuals with a single disorder and individuals with both disorders in the absence of certain interactions. Thus, we estimate a single coaggregation effect, with greater precision and generality of interpretation than separate effects. The model accounts simultaneously for four main associations of interest: (1) the within-person association of eating and mood disorders; (2) the familial aggregation of eating disorders; (3) the familial aggregation of mood disorders; and (4) the familial coaggregation of eating disorders with mood disorders.

This basic model makes two assumptions. First, it assumes that the ORs for aggregation and coaggregation are not affected if a proband or a relative simultaneously displays an eating disorder and a mood disorder, over and above the additive effects of these two disorders individually. In other words, it assumes that there are no interaction effects caused by the simultaneous presence of the two disorders. We have applied an augmented model with terms for these interactions (see model 7 in Hudson *et al.* 2001*b*) to the data in this study; we found no statistically significant interactions.

Secondly, the model posits 'interchangeability' of probands and relatives; specifically, that the coaggregation of eating disorders with mood disorders is independent of whether the proband has an eating disorder and the relative has a mood disorder, or vice versa. In statistical terms, the model assumes that the association parameters are the same for probands and relatives, when adjusted for the covariates in the model. This assumption is reasonable if we can view probands with a given combination of disorders (eating disorder, mood disorder, both disorders, or neither disorder) as randomly selected from among all family members with the same combination of disorders (discussed further in Hudson *et al.* 2001*a*, *b*). We can test this assumption by estimating two coaggregation parameters – one for the association between eating disorder in a proband and mood disorder in a relative, and one for the association between eating disorder in a relative and mood disorder in a proband – and then testing whether these two parameters are equal, as they are when interchangeability holds (Hudson *et al.* 2001*b*). In analysis of the present data, we found no evidence to reject the hypothesis that these parameters were equal.

When applying the model, we adjusted for age, sex, and the relative's relationship to the proband (parent, sibling, or child). Because observations within families are correlated, we used generalized estimating equations (Liang & Zeger, 1986) to estimate standard errors, with independence as the working covariance structure. We fitted the models using Stata 7.0 software (further details of fitting and testing

Table 1. *Prevalence of eating disorders*[a] *and mood disorders*[b] *in interviewed relatives by proband group*

	Proband group			
	No eating or mood disorder ($N=57$)	Eating disorder alone ($N=1$)[c]	Mood disorder alone ($N=50$)	Eating disorder and mood disorder ($N=14$)[d]
Total relatives, *N*	150	2	142	36
Relatives, %				
No eating disorder or mood disorder	91	100	78	67
Eating disorder alone	1[e]	0	4[f]	8[g]
Mood disorder alone	8	0	15[h]	11
Eating disorder and mood disorder	0	0	3[i]	14[j]

[a] Anorexia nervosa (AN), bulimia nervosa (BN), or binge eating disorder (BED); number of cases of each disorder in footnotes. Note that all cases listed as 'AN and BN' displayed BN at times that they did not display AN.
[b] Major depressive disorder or bipolar disorder; all cases are major depressive disorder unless otherwise stated.
[c] BN = 1.
[d] AN = 8; BN = 1; AN and BN = 5.
[e] One relative had BN; and one had BED.
[f] Two relatives had AN; two had BN; and one had BED.
[g] Two relatives had BN; and one had BED.
[h] One relative had bipolar disorder.
[i] Two relatives had BN; one had BED; one had AN and BN; and one had bipolar disorder.
[j] Two relatives had BN; one had BED; and two had AN and BN.

procedures can be found elsewhere (Hudson *et al*. 2001*a*, *b*)).

RESULTS

We interviewed 178 relatives of 64 probands with MDD and 152 relatives of 58 probands without MDD (detailed demographic data on this sample are presented elsewhere (Hudson *et al*. 2003). The mean (S.D.) age for depressed and control probands, respectively, was 39·5 (15·0) and 40·9 (14·1) years, and for relatives of depressed and control probands was 39·6 (13·7) and 37·4 (13·1). The number of relatives with each combination of mood and eating disorder status, by proband group, is shown in Table 1.

The estimated odds ratios (ORs) for the association parameters are displayed in Table 2. We found that ORs were statistically significant for the within-person association of eating disorders with mood disorders ($P=0{\cdot}011$), the familial aggregation of eating disorders ($P=0{\cdot}006$) and the familial coaggregation of eating disorders with mood disorders ($P=0{\cdot}035$); and approached significance for the familial aggregation of mood disorders ($P=0{\cdot}076$). Notably, the familial coaggregation of eating disorders with mood disorders was of the same magnitude as the aggregation of mood disorders alone (2·2 in both cases). To give a specific example, the odds of an individual developing a mood disorder increase equally (by a factor of 2·2) whether he or she has a first-degree relative with an eating disorder or a first-degree relative with a mood disorder, compared to having a first-degree relative with neither disorder.

Table 2. *Estimated odds ratios and* 95% *CI for effects of interest from multivariate proband predictive logistic regression model*

Effect	OR*	95% CI	*P*
Within person association of eating disorders with mood disorders	3·8	1·4, 10	0·011
Aggregation of eating disorders in families	7·0	1·8, 28	0·006
Aggregation of mood disorders in families	2·2	0·92, 5·4	0·076
Coaggregation of eating disorders with mood disorders in families	2·2	1·1, 4·6	0·035

* Adjusted for age, sex and relationship of relative to proband.

The magnitude of the coaggregation of eating disorders with mood disorders changed little when we considered MDD alone (that is, not considering the two cases of bipolar disorder), yielding an OR of 2·5 (95% CI 1·2, 5·2; $P=0{\cdot}018$); or considered anorexia and bulimia

nervosa alone (that is, not considering the four cases of binge-eating disorder), yielding an OR of 2·2 (1·01, 4·8; $P=0·047$).

DISCUSSION

Applying a novel bivariate proband predictive model to data from a family interview study, we found a significant familial coaggregation of eating disorders with mood disorders, comparable in magnitude to the familial aggregation of mood disorders themselves. Thus, for example, the odds of an individual developing a mood disorder increase equally (by a factor of 2·2) whether he or she has a first-degree relative with an eating disorder or a first-degree relative with a mood disorder, compared to having a first-degree relative with neither disorder.

Our effect estimates for the familial coaggregation of mood disorders with eating disorders are the first obtained from a case–control study using probands with mood disorders. By contrast, all previous studies have used probands with eating disorders. There are seven studies that have provided data on the coaggregation of mood disorders and eating that control adequately for the effects of proband diagnosis (see Hudson *et al.* 2001*b*). These studies have compared the prevalence of mood disorders among relatives of probands with eating disorders, but no mood disorders, *versus* relatives of probands with neither eating disorders nor mood disorders (and who also were not selected to have other psychiatric disorders). Initially, these studies would appear to have produced mixed results, with three (Gershon *et al.* 1984; Kassett *et al.* 1989; Keck *et al.* 1990) reporting a significant coaggregation of eating and mood disorders, one (Hudson *et al.* 1987) reporting an effect approaching statistical significance ($P<0·10$), two reporting non-significant findings (Biederman *et al.* 1985; Lilenfeld *et al.* 1998) and one (Logue *et al.* 1989) not providing the results of a statistical test for this type of coaggregation.

Although the studies reported a variety of measures of effect, including risk ratios, ORs, hazard ratios, and relative morbidity risks, the results presented can all be reanalysed to generate a coaggregation OR that estimates the same effect as the coaggregation OR estimated above. Using the ORs computed by reanalysis of original data (detailed in Hudson *et al.* 2001*a* for Hudson *et al.* 1987 and Keck *et al.* 1990) or published data (for the other studies), we found that the coaggregation ORs in the seven previous studies ranged from 1·3 to 3·1, with a median of 2·2 (Hudson *et al.* 2001*a*). Furthermore, the 95% CIs for all studies included the median value of 2·2. (An analogous analysis using the risk ratio as the measure of effect is presented in Hudson *et al.* 2001*a*.) Using a random effects model for meta-analysis (DerSimonian & Laird, 1986), as implemented in Stata 7.0, the combined coaggregation OR from these studies is 2·0 (95% CI 1·5, 2·7), with no evidence for lack of homogeneity of the OR. Thus, the apparent discrepancies in reported results between previous studies can be accounted for the fact that these studies have low power due to relatively small sample sizes, and hence some of them fail to find a statistically significant effect because of the large CIs around the estimates. In summary, the weight of previous evidence suggests a moderately strong coaggregation, and the coaggregation OR of 2·2 in the present study is clearly compatible with the previous seven studies that have used the opposite approach of starting with probands with eating disorders.

Our results therefore augment previous data showing that the familial coaggregation of eating disorders with mood disorders is independent of the aggregation of either eating disorders alone or mood disorders alone. This finding suggests that eating disorders and mood disorders have common familial, and perhaps common genetic factors – a hypothesis also supported by twin studies (Walters *et al.* 1992; Wade *et al.* 2000).

Simultaneously, our analysis supports familial aggregation for eating disorders alone, consistent with previous studies (Hudson *et al.* 1987, 2001*a*; Kassett *et al.* 1989; Keck *et al.* 1990; Strober *et al.* 2000); and for mood disorders alone, also consistent with previous studies (reviewed in Tsuang & Faraone, 1990; Sullivan *et al.* 2000). While our OR of 2·2 for familial aggregation of mood disorders narrowly does not achieve statistical significance, the magnitude of the effect is similar to the combined OR of 2·4 obtained by Sullivan *et al.* (2000) in a meta-analysis of all family studies of MDD using similar sampling of probands.

Thus, it likely that the failure to achieve statistical significance reflects the low statistical power to detect this effect, rather than an absence of this effect in our sample.

The present study is limited by its modest sample size, resulting in wide confidence intervals for effect estimates, especially for the aggregation of eating disorders. It might also be argued that the study is limited by ascertainment bias, because our probands with MDD were seeking in-patient treatment. In other words, these probands and their relatives might be expected to display a higher prevalence of comorbid eating disorders than individuals with MDD in the general population – a phenomenon sometimes called 'spurious comorbidity' (Smoller *et al*. 2000). However, as we have explained previously (Hudson *et al*. 2001*a*, *b*, 2003), our proband predictive model does not depend on the assumption that the prevalence of eating disorders in our in-patient probands with MDD be the same as that of individuals with MDD in the general population. Thus, our findings cannot reasonably be explained as an artefact of spurious morbidity between eating disorders and mood disorders in the proband sample studied.

Further genetic epidemiological research – such as twin studies and genetic linkage and association studies – will be required to characterize the combination of genes, environmental factors, and gene–environment interactions responsible for the familial coaggregation of eating disorders with mood disorders.

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