Bulimia nervosa and major depression: a study of common genetic and environmental factors

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SYNOPSIS A genetic analysis of the co-occurrence of bulimia and major depression (MD) was performed on 1033 female twin pairs obtained from a population based register. Personal interviews were conducted and clinical diagnoses made according to DSM-III-R criteria.

Additive genes, but not family environment, are found to play an important aetiological role in both bulimia and MD. The genetic liabilities of the two disorders are correlated 0.456. While unique environmental factors account for around half of the variation in liability to both bulimia and MD, these risk factors appear to be unrelated, i.e., each disorder has its own set of unique environmental risk factors. Thus, the genetic liability of bulimia and MD is neither highly specific nor entirely nonspecific. There is some genetic correlation between the two disorders as well as some genetic and environmental risk factors unique to each disorder. Limitations and directions for future research are discussed.

INTRODUCTION

The frequent co-occurrence of bulimia and major affective disorder as noted by clinicians has led investigators to consider the possibility that the two disorders may share important risk factors. Since studies show that both disorders have a familial component (Tsuang & Fararone, 1990; Kendler et al. 1991, 1992a), the possibility that the two share some common genetic basis is a question of considerable interest.

Several family studies provide support for the presence of shared genetic and/or environmental factors for these two disorders. Lee et al. (1985) reported that 58.9% of bulimic probands had at least one first-degree relative with a history of major affective disorder, although no control group was examined for comparison.

Two studies by Hudson et al. (1983a, 1987) report the morbidity risk for major affective disorder in relatives of bulimics to be significantly greater than the risk in relatives of non-psychiatric, as well as certain psychiatric controls. Logue et al. (1989) and Kassett et al. (1989) both report higher rates of major affective disorder in relatives of bulimic probands than in relatives of normal controls.

Examining only the group of bulimics without major affective disorder, both Hudson et al. (1987) and Kassett et al. (1989) report higher rates of major affective disorder in the relatives of this group than in relatives of controls. Additionally, Hudson et al. (1987) found the rate of familial major affective disorder to be significantly greater in relatives of those with a history of both disorders than in those with bulimia alone. These results suggest the possibility of an underlying liability to major affective disorder in bulimics and their families.

Only two studies have examined rates of bulimia in relatives of depressed probands. Hudson et al. (1987) report the morbidity risk for bulimia in relatives of probands with major depression to be 0% and Logue et al. (1989) found one case of bulimia in 75 relatives of 16 depressed probands. These results do not support the hypothesis that the disorders share certain risk factors. However, because of the low...
prevalence rate of bulimia in the general population, a larger sample would be required to determine accurately if there is an increased rate in the relatives of depressed probands. It should also be noted that many of the relatives of depressed probands may be middle-aged or older. Because bulimia nervosa has only recently been recognized as an illness, it is expected that fewer cases would be reported or diagnosed in an older cohort.

Although the co-morbidity of bulimia and major affective disorder has often been noted, no studies have attempted to quantify the genetic and environmental components shared by the two disorders. In an effort to do this, we present the results of a twin study concentrating specifically on the co-morbidity of bulimia and major depression (MD). Unlike family studies, twin studies can discriminate whether familial co-aggregation is due to shared genetic or familial environmental factors.

METHOD

Data for this analysis were obtained from Caucasian same-sex female twin pairs identified through the Virginia Twin Register. This is a population-based register constructed from a systematic review of public birth records in the Commonwealth of Virginia. Current addresses are obtained by matching these records with other public records.

Twin pairs were eligible to participate in the personal interview phase of the study if both members responded to an initial questionnaire. While the individual response rate to this questionnaire was 64%, this is probably an underestimate of the true cooperation rate since a proportion of the questionnaires were not received by the twins due to incorrect addresses. Of the 1176 twin pairs who responded to the initial questionnaire, personal interviews pertaining to genetic and environmental risk factors for common psychiatric disorders were given to both members of 1033 pairs of twins. In an additional 97 pairs, one member was interviewed and the other refused to participate. The mean age (± s.d.) of the sample at interview was 30.1 ± 7.6 and ages ranged from 17 to 55. Of the sample, 93.8% reported that they were high school graduates while 27% had completed a four-year college degree. The median family income was $32000, with 40.0% of the sample earning less than $15000 and 15.4% earning more than $50000. This sample has been described in detail elsewhere (Kendler et al. 1991, 1992).

Twin pair zygosity was determined, based on a combination of self-report information and photographs. When zygosity was uncertain an attempt was made to examine DNA samples from both members of the pair. Of the 186 pairs classified as uncertain, blood samples were obtained from both members of 117 pairs. Final zygosity diagnoses gave 590 MZ twin pairs, 440 DZ twin pairs, and 3 pairs of unknown zygosity.

Clinical diagnoses of lifetime major depression were made based on a blind review of the interviews using DSM-III-R criteria. This included the review of an adapted version of the Structured Clinical Interview for DSM-III-R diagnosis (Spitzer et al. 1987) as well as any related information recorded by the interviewer. Because of the low prevalence rate of bulimia, an expanded definition of bulimia was used. An individual was diagnosed as bulimic if she met full DSM-III-R criteria, or if most, but not all diagnostic criteria were met and the disorder was thought to be clinically significant. While 83.3% of narrowly defined bulimics met the DSM-III-R criterion of a minimum of two binge-eating episodes a week for at least three months, this criterion was met by only 33.3% of broadly defined bulimics. Kendler et al. (1991) have previously shown that in this sample, from both genetic and epidemiological perspectives, groups defined by strict versus broader criteria are not qualitatively different.

Two variables were created indicating the presence or absence of lifetime bulimia and MD. A phenotypic correlation was calculated between bulimia and MD as well as the rate of co-morbidity expressed as an odds ratio.

A bivariate genetic analysis was then performed on the correlations between these two variables. Three types of tetrachoric correlations between the variables exist: within-twin cross-trait, cross-twin within-trait, and cross-twin cross-trait. Each of these correlations was calculated separately for MZ and DZ twins. The estimation of these correlations assumes that there is an underlying continuous normal distribution of risk for each variable with some
threshold on the distribution of risk determining the point at which a person becomes affected. It also assumes that these underlying latent variables have a bivariate normal distribution. The tetrachoric correlation is an estimate of the correlation of these latent variables and is obtained from the computer program PRELIS (Jöreskog & Sörbom, 1986).

Models were fitted to the correlations using the computer program LISREL (Jöreskog & Sörbom, 1989). These models estimate the components of variance for each variable in terms of additive genetic (A), common familial environmental (C) and unique environmental (E) components. In addition, they estimate the additive genetic ($r_a$), familial environmental ($r_c$), and unique environmental ($r_e$) correlations between the variables.

If the two disorders share only a genetic liability, the cross-twin cross-trait correlation will be twice as high in MZ twins as in DZ twins. In addition, the MZ within-twin cross-trait and cross-twin cross-trait correlations will be the same. If the same familial environmental factors cause both disorders to occur, the cross-twin cross-trait correlation will be the same in MZ and DZ twins. In the absence of genetic effects, if the same specific environmental factors cause both disorders to occur there will be no cross-twin cross-trait correlation and the MZ and DZ within-twin cross-trait correlations will be high.

The full model includes estimates of all these components (A, C, E, $r_a$, $r_c$, $r_e$) and is shown in Fig. 1. Two submodels of these parameters were also fitted to the data. Submodels were compared by Akaike’s Information Criterion (AIC) (Akaike, 1987). The AIC for a model is obtained by subtracting twice the degrees of freedom from the goodness-of-fit chi-square and the model that minimizes this value is the most parsimonious explanation of the observed correlations.

RESULTS

Of the 2163 interviewed twins, 677 (31.3%) were diagnosed with lifetime MD, 123 (5.7%) with broadly defined lifetime bulimia and 62 (2.9%) with both. The phenotypic tetrachoric correlation between bulimic and MD liabilities is
0.234. The resulting odds ratio of 2.36 comparing the rates of co-morbidity in cases with that in non-cases is significant with a 95% confidence interval of (1.636, 3.401).

The parameter estimates of the full model (I) are shown in Fig. 2, and those of the best fitting submodel (III) are shown in Fig. 3. MZ and DZ correlations are listed in Table 1 and the results of the model fitting in Table 2. The full model fitted well with a χ² goodness-of-fit of 4.39 (AIC = -5.61). The model had an additive genetic correlation (r_a) between bulimia and MD of 0.258 and a common environmental correlation (r_c) of 1.

The second model (II) sets both the bulimia and MD familial environmental paths to 0, based on the results of univariate analyses of these variables (Kendler et al. 1991, 1992a). This
Table 1. Tetrachoric correlation matrix for bulimia nervosa (Bul) and major depression (MD)

<table>
<thead>
<tr>
<th></th>
<th>Twin 1</th>
<th>Twin 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bul</td>
<td>MD</td>
</tr>
<tr>
<td>Twin 1</td>
<td>0.20</td>
<td>0.50</td>
</tr>
<tr>
<td>Twin 2</td>
<td>0.23</td>
<td>0.19</td>
</tr>
</tbody>
</table>

MZ twins above diagonal, DZ twins below.

Table 2. Results of bivariate twin models for bulimia nervosa and major depression

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameters</th>
<th>$\chi^2$</th>
<th>df</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>$\rho_a$, $\rho_c$, $\rho_e$</td>
<td>4.39</td>
<td>5</td>
<td>-5.61</td>
</tr>
<tr>
<td>II</td>
<td>$\rho_a$, $\rho_e$</td>
<td>4.87</td>
<td>8</td>
<td>-11.13</td>
</tr>
<tr>
<td>III</td>
<td>$\rho_c$</td>
<td>5.03</td>
<td>9</td>
<td>-12.97</td>
</tr>
<tr>
<td>IV</td>
<td>$\rho_a = 1$</td>
<td>17.06</td>
<td>10</td>
<td>-2.94</td>
</tr>
<tr>
<td>V</td>
<td>$\rho_a = 0$, $\rho_e$</td>
<td>12.52</td>
<td>9</td>
<td>-5.48</td>
</tr>
</tbody>
</table>

$\rho_a$ = additive genetic correlation; $\rho_c$ = common environmental correlation; $\rho_e$ = unique environmental correlation; AIC = Akaike's Information Criterion (Akaike, 1987).

forces the familial environmental correlation to 0. This model is an improvement over the full model, with an AIC of -11.13 ($\chi^2 = 4.87$).

Model (III) sets the unique environmental correlation to 0. This again improves the fit with an AIC of -12.97 ($\chi^2 = 5.03$) and estimates the additive genetic correlation ($r_{ae}$) between bulimia and MD to be 0.456. Model IV sets the genetic correlation to 1. This model (AIC = -2.94) was significantly worse than the best fitting model (III). The model (V) that fixes the genetic correlation to 0 and estimates the environmental correlation was also significantly worse than the best fitting model (AIC = -5.48).

DISCUSSION

As previously found, additive genes account for a substantial proportion of variance of MD (43%) and bulimia (50%). Unique environmental effects account for the remaining variance since the effects of common familial environment can be disregarded without harming the fit of the model.

Since the unique environmental correlation can be set to zero, it appears, within the power of our sample size, that the co-morbidity of the two disorders is not the result of the same unique environmental risk factors predisposing to both disorders. However, the genetic correlation of 0.46 suggests the presence of some genes that do predispose to both disorders. Although, due to the small number of co-morbid cases, the standard error of this estimate is quite large, model fitting suggests that it is significantly different from both zero and one. Thus, while bulimia and MD share some genetic factors, there are also some genetic factors which are specific to each disorder.

Despite our large sample size, the number of co-morbid cases in this study is small due to the low base rate of bulimia in the general population. The possibility that common familial environmental factors play some role in the co-morbidity of bulimia and MD remains. This analysis may not have the power to discriminate between the effects of genetic and familial environmental factors.

It should be noted that all studies referenced in the introduction examined subjects ascertained in a clinical setting or through newspaper advertisements. Such samples may not be representative of the general population. Our sample, however, was ascertained independent of treatment status. Thus, our results are more appropriate for extension to the general female population.

Additional work is needed before the co-morbidity of bulimia and major affective disorder is completely understood. The question of causation is one such area. Laesle et al. (1987) report that major affective disorder follows the onset of eating disorder by at least one year in the majority of cases, while the findings of Hudson et al. (1983b) and Lee et al. (1985) do not support this. In this sample, 7 of the co-morbid cases reported onset at the same age, 11 reported bulimia prior to MD and 45 MD prior to bulimia. Methods have been proposed for using cross-sectional twin design to determine direction of causality (Heath et al. 1989). However, due to the small number of co-morbid cases in this sample, these methods are not appropriate for our data.

A second important issue to be resolved is that of heterogeneity. Do the depressive symptoms in bulimics differ from those in primary depressives and do those individuals
with a history of both bulimia and major affective disorder belong to a group aetologically distinct from those with either bulimia or major affective disorder alone?

Additionally, it must be noted that the observed phenotypic correlation between bulimia and major affective disorder may be partially due to diagnostic overlap in the two disorders. An associated feature of bulimia is a depressed mood and associated symptoms of major affective disorder include appetite disturbance and weight change. Further study is necessary to determine to what extent these overlapping symptoms affect the co-morbidity of the two disorders.

Studies have also shown the effectiveness of treating bulimia with antidepressant medication. Hudson & Pope (1990) review over 25 studies testing the efficacy of several classes of antidepressant including tricyclic type, MAOIs, and serotonin uptake inhibitors. While such pharmacological studies provide support for the theory that bulimia and MD share an underlying biological mechanism, further work is necessary to identify such a mechanism.

In contrast to the results of a study of the co-morbidity of MD and generalized anxiety disorder (GAD) which determined that the genes affecting the two disorders are entirely non-specific ($r_a = 1$) (Kendler, unpublished data), the genetic liability of MD and bulimia is neither highly specific nor entirely non-specific. A woman vulnerable to both MD and GAD develops one or the other entirely as a result of her environmental experiences. However, genes shared by both disorders, genes specific to both disorders and unique environmental influences all play a role in determining if a woman will develop MD, bulimia, or both.

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REFERENCES


