The Clinical Characteristics of Major Depression as Indices of the Familial Risk to Illness

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Background. From both a clinical and an aetiological perspective, major depression (MD) is probably a heterogeneous condition. We attempt to relate these two domains.

Method. We examined which of an extensive series of clinical characteristics in 646 female twins from a population-based register with a lifetime diagnosis of MD predicts the risk for MD in co-twins. MD was defined by DSM-III-R criteria.

Results. Four variables uniquely predicted an increased risk for MD in the co-twin: number of episodes, degree of impairment and co-morbidity with panic disorder or bulimia. One variable uniquely predicted decreased risk: co-morbidity with phobia. Variables that did not uniquely predict risk of MD in the co-twin included age at onset, number and kind of depressive symptoms, treatment seeking, duration of the longest episode and co-morbidity with generalised anxiety disorder and alcohol dependence.

Conclusions. Our results suggest that the clinical features of MD can be meaningfully related to the familial vulnerability to illness, particularly with respect to recurrence, impairment and patterns of co-morbidity.

Major depression (MD) is an aetiological heterogeneous condition with a wide range of documented risk factors (Gershon et al., 1975; Brown & Harris, 1978; Parker, 1979; Kessler et al., 1985; Lin et al., 1986; Tennant, 1988; Tsuang & Faraone, 1990). MD is also clinically heterogeneous with widely varying patterns of symptoms, severity, duration, recurrence and patterns of co-morbidity. Little is known of the relationship in MD between aetiological and clinical heterogeneity.

Since familial factors are aetiological important in depression (Tsuang & Faraone, 1990), it may be useful to relate clinical features of the disorder to familial risk of illness. Using this approach, investigators have examined the relationship between the familial risk to depression and: age at onset (Hopkinson, 1964; Winokur, 1973; Cadoret et al., 1977; Mendlewicz & Baron, 1981; Bland et al., 1986; Weissman et al., 1986; McGuffin et al., 1987; Stancer et al., 1987; Kupfer et al., 1989); recurrence (Bland et al., 1986; Gerston et al., 1986); severity of impairment (Gershon et al., 1986); number of kind of depressive symptoms (Leckman et al., 1984; Klein, 1990); and co-morbidity (Weissman et al., 1986; Grove et al., 1987).

These studies have two important limitations. First, all but one (Gershon et al., 1986) utilised depressed probands who were patients. Since help-seeking is probably influenced by both family history and clinical variables, an association between these variables could result from their interaction in predicting help-seeking. Second, with one exception (Weissman et al., 1986), previous studies examined only a few clinical features of MD. Examining a broad array of clinical characteristics of depression is a better way to ensure detection of the individual clinical variables which uniquely and maximally index the familial liability to depression.

In this study, we examined the relationship between an extensive array of clinical features in 646 female twins (ascertained from a population-based register) who meet DSM-III-R criteria for MD, and the risk for MD in their co-twins.

Method

The characteristics of this study have been outlined elsewhere (Kendler et al., 1992a). Caucasian female same-sex twins were ascertained from the population-based Virginia Twin Registry, formed from a systematic review of state birth records from 1915 onward in the Commonwealth of Virginia. Twins were eligible to participate if both members of the pair had previously responded to a mailed questionnaire, with an individual response rate of 64%. (The cooperation rate was higher, as an undetermined number of questionnaires never reached the twin due to faulty addresses.) Of the 2352 individuals from 1176 twin pairs meeting these criteria, we personally interviewed 2163 (92%) of them (89.3% face to face and 10.7% by telephone), including both members of 1033 pairs. The mode of interview was unrelated
to the rate of MD. Zygosity was determined by the use of standard self-report questions, photographs, and when uncertain, genotyping. Final diagnoses yielded 590 monozygotic (MZ), 440 dizygotic (DZ) and three pairs of unknown zygosity.

For this present report, twin pairs where neither twin had MD \((n = 530)\) are uninformative. Our analyses are, therefore, restricted to twins from the remaining 500 pairs of known zygosity where either one \((n = 354)\) or both members \((n = 146)\) received a lifetime diagnosis of MD.

**Measures, interviewers and diagnostic review**

A lifetime diagnosis of MD was made using an adaptation of the Structured Clinical Interview (SCID) for DSM-III-R \((\text{Raskind et al., 1987; Spitzer et al., 1987)}\). All interviewers were carefully trained and had a minimum of either a master's degree in psychology or social work or a bachelor's degree and two years' clinical experience. The same interviewer never interviewed both members of a twin pair.

The lifetime diagnosis of MD was based on a blind review by KSK, an experienced psychiatric diagnostician, using DSM-III-R criteria \((\text{American Psychiatric Association, 1987). Depression was not diagnosed when the depressive syndrome was due to normal grief, medical illness or medication. In addition, lifetime diagnoses were made using DSM-III-R criteria for panic disorder, generalised anxiety disorder (GAD), alcohol dependence, anorexia nervosa and bulimia nervosa. With two exceptions, for these diagnostic categories we applied unmodified DSM-III-R criteria. For GAD, consistent with previous results (Breslau & Davis, 1985; Kendler et al., 1992b) we applied the DSM-III \((\text{American Psychiatric Association, 1980) one-month rather than the DSM-III-R six-month minimum duration of illness. For bulimia, we included 'subsyndromal' bulimic-like syndromes because we found that they closely resembled cases meeting full DSM-III-R criteria (Kendler et al., 1991). Phobia was defined as the presence of one or more irrational fears that objectively interfered in the respondent's life. Leckman et al. (1983a) divided their depressed probands with a lifetime diagnosis of anxiety disorder into those in whom the anxiety disorder was always associated with depressive episodes (here termed 'contemporaneous' co-morbid cases), and those in whom it was, at least some of the time, separate from the depressive episodes (here termed 'non-contemporaneous' cases). We make a similar distinction for panic disorder and GAD.

The SCID questions for MD were modified so that, from the 'A criteria' for depression \((\text{American Psychiatric Association, 1987)}\), we independently noted the presence of the 14 disaggregated symptoms (i.e. separately assessing weight loss, weight gain, decreased appetite, and increased appetite).

In addition to the symptomatic criteria, twins with a history of depression were asked about: (a) age at onset; (b) number of episodes; (c) length of longest episode; (d) degree of impairment during worst episode (none, moderate, or incapacitated); and (e) help-seeking behaviour related to the depressive episode.

Inter-rater reliability was assessed in 53 jointly conducted interviews and was quite high for MD, \(x = +0.96\) \((P < 0.001)\) \((\text{Cohen, 1960). x values for generalised anxiety disorder, phobia, bulimia and panic disorder ranged from +0.77 to +1.00, but could not be calculated for alcohol dependence or anorexia nervosa as no cases were so diagnosed in the reliability sample.**

**Treatment of individual symptoms**

To avoid possible spurious positive findings by treating each symptom individually, we submitted a product–moment correlation matrix for all 14 symptoms to a factor analysis and VARIMAX rotation \((\text{SAS Institute, 1985)}. Four meaningful factors were identified as follows: appetite loss (+ eating decreased, + weight loss, – eating increased, – weight gain), tiredness (+ retardation, + fatigue, – agitation), disturbed sleep (+ insomnia, + difficulty concentrating, – hypersonnia) and self-blame (+ guilt, + suicidal ideation).

**Statistical analysis**

We focused on pairs of observations: a proband twin with MD and her co-twin. Such pairs could be divided into (a) pairs where only one twin had a MD, which are 'counted' once; and (b) pairs where both twins had a MD, which are 'counted' twice (e.g. once when clinical characteristics of twin A predict risk in twin B and once vice versa).

Since the onset of MD depends on age, and our sample is variable with respect to age, we utilised the Cox proportional hazard model, as operationalised in the PHGLM procedure in the SAS program \((\text{SAS Institute, 1986), to predict the hazard rate (or risk) for MD in the co-twin as a function of clinical characteristics in the proband twin. Correction is required for assuming independence of the observations from the doubly counted twin pairs. If \(T\) is the total number of observations, \(N\) the number of doubly counted twin pairs, and \(P\) the number of parameters in our model, we multiplied the standard
errors obtained by \( \frac{(T-P)}{(T-N-P)} \)\(^{19} \). This approximate correction is likely to be conservative (Kish & Frankel, 1974). All significances reported are based on our corrected standard errors. In the stepwise proportional hazard model, we used entry and exit criterion of 0.50 and 0.10, respectively. We utilise the \( P \leq 0.05 \) criterion for significance, except for the stepwise analysis, where we report results at the \( P \leq 0.10 \) level.

Zygosity was included as an independent variable to control for modestly higher risk observed in MZ vs. DZ co-twins of affected twins (Kendler et al., 1992a). Year of birth and (year of birth\(^2 \)) both had a significant effect on risk for depression and were included to control for the possible cohort effect on MD.

Results

Key clinical characteristics of the 646 twins with MD, who had a mean (s.d.) age at interview of 31.5 (7.1), are seen in Table 1. In this group the age at onset was early, and the mean and median number of episodes were 6.4 and 2, respectively.

The proportion of twins meeting criteria for MD who also met criteria for a lifetime diagnosis of the other psychiatric disorders is seen in Table 2 and ranged from 1.5% for anorexia nervosa to 46.3% for phobia. The proportion of twins with MD who met criteria for generalised anxiety disorder and panic disorder only during depressive episodes was 17.8% and 1.4%, respectively.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>Clinical features of depression in the proband twin that predict risk for major depression in the co-twin(^1 )</td>
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<tr>
<td>Variable</td>
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<tr>
<td>Age at onset</td>
</tr>
<tr>
<td>No. of DSM-III-R A criteria</td>
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<tr>
<td>Maximum duration: weeks</td>
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<tr>
<td>Number of episodes</td>
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<td>Treatment seeking</td>
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<td>Impairment</td>
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1. Controlling for zygosity and year of birth; \( n = 646 \).
2. \% with incapacitation. 44.6% of twins had moderate impairment during their worst episode, while 24.0% reported no impairment.
3. Regression coefficient is negative, meaning that earlier treatment seeking predicts increased risk for depression in co-twin. All other coefficients are positive.
4. Value in proband twin with major depression.
5. All d.f. = 1.

Prediction of risk for major depression in the co-twin: variables taken one at a time

The relationship between the clinical characteristics of MD in the proband and the risk of MD in the co-twin is presented in Table 1. A larger number of episodes and a greater degree of impairment significantly predicted an increased risk for MD in the co-twin (\( P = 0.003 \) and 0.004, respectively). More DSM-III-R A criteria, a prolonged longest episode, treatment seeking and early age at onset predicted a non-significant increased risk of depression in the co-twin.

The impact of co-morbidity on the risk of MD in the co-twin is seen in Table 2. For all disorders, except contemporaneous panic disorder and phobia, co-occurrence in the proband twin increased the risk for depression in the co-twin. This effect was
statistically significant, however, only for non-contemporaneous panic disorder and bulimia (P = 0.01 for both).

The symptom factor of appetite loss was significantly and negatively related to risk of depression in the co-twin (χ² = 3.84, d.f. = 1, P = 0.05). This means that depressed twins with increased appetite and/or weight gain had a higher risk of MD in their co-twin than depressed twins who reported decreased appetite and/or weight loss. No significant relationship was found between risk of MD in the co-twin and the three other symptom factors: levels of tiredness (χ² = 0.04, d.f. = 1, not significant (NS)), poor sleep (χ² = 0.07, d.f. = 1, NS) or self-blame (χ² = 0.82, d.f. = 1, NS).

Prediction of risk for major depression in the co-twin: multivariate analysis

In the stepwise proportional hazards regression (Table 3), four clinical features in the proband twin uniquely predicted the risk of MD in the co-twin at the 5% level, and one at the 10% level. The most significant unique predictor was the number of episodes, followed by lifetime co-morbidity with bulimia, non-contemporaneous co-morbidity with panic disorder, and lifetime co-morbidity with phobia. Recurrence, impairment and co-morbidity with panic and eating disorders predicted an increased risk of depression in the co-twin. By contrast, co-morbidity with phobia predicted a decreased risk of depression in the co-twin.

Table 3 also gives the relative risk for depression in the co-twin associated with each of these six variables, controlling for zygosity, year of birth and the other predictors. The calculation of comparable relative risks required that the two variables, number of episodes and impairment, be reduced to a dichotomy for which we used, respectively, less than or greater than the mean number of episodes (i.e. ≤6 v. >6) and no or mild impairment v. incapacitation.

Co-morbidity with bulimia and panic disorder had the greatest predictive power for the rates of depression in the co-twin, increasing their risk to 61% and 53%, respectively. Number of episodes and degree of impairment predicted a 46% and 33% increased risk of depression in the co-twin, respectively. A lifetime history of phobia was associated with a 21% decrease in the risk of depression in the co-twin. It is noteworthy that depressed twins with more than one as compared to only one episode of illness had only an 11% increased risk for depression in their co-twins.

Monozygotic v. dizygotic twins

We tested each of the potential predictor variables separately in MZ and DZ twins. Of the five unique predictor variables, all but one (co-morbidity with bulimia) were stronger predictors of risk for depression in MZ than in DZ co-twins, although these differences were not statistically significant.

Discussion

Three studies have previously examined the relationship between recurrence and risk of MD in relatives. Both Bland et al (1986) and Weissman et al (1986) found a significantly increased risk for MD in the relatives of treated depressed probands with recurrent v. single episodes of depression. Gershon et al (1986) found that significantly more depressed relatives of depressed than of control probands had recurrent depression. Interestingly, our results suggested that the major difference in risk to relatives was not seen in relatives of those with one v. more than one episode of illness. Rather, the trend was for the risk of illness in co-twins to keep increasing with an increasing number of episodes of illness in the proband.

The degree of impairment during the worst episode also significantly predicted the risk of depression in the co-twin. We know of only one study that addressed this question; Gershon et al (1986) found that a significantly higher proportion of depressed relatives of depressed than of control probands were impaired or incapacitated during their episode.

Symptoms of depression and co-morbidity

Neither the number nor the kind of depressive symptoms endorsed in our sample uniquely related to the risk for depression in the co-twin. Appetite loss was a modest predictor on its own, but lost significance when analysed with other predictors. We could not replicate previous results that the risk of depression in relatives is correlated with the number of DSM-III criteria in the depressed proband (Klein, 1990).

The risk of depression in the relatives of depressed probands was significantly related to co-morbidity with bulimia, panic disorder and phobia. Weissman and colleagues (Leckman et al, 1983a,b; Weissman et al, 1986) found that in depressed probands panic disorder and GAD, but not agoraphobia, significantly predicted increased risk of depression in relatives. Like us, they found that co-morbid panic disorder was a stronger predictor than co-morbid GAD.

We could not, by contrast, replicate their finding that co-morbidity with alcohol dependence predicted
a significant increase in risk for depression in relatives (Weissman et al, 1986). We are unaware of any previous study that bears on our finding of a substantial impact of co-morbidity with bulimia on the risk for depression in the relatives of depressed probands.

Our results, which suggest that with respect to familial factors co-morbidity with depression is not a unitary phenomenon, raise questions about the validity of the diagnostic concept of secondary depression. Grove et al (1987) found that the rates of depression in relatives of probands with primary and secondary depression were approximately equal. This may have occurred because some of the primary disorders (e.g., panic disorder) carried increased familial vulnerability to depression and others (e.g., phobia) carried decreased familial vulnerability.

Age at onset

We did not replicate previous findings that early age at onset of depression predicts an increased risk of illness in relatives (Hopkinson, 1964; Winokur, 1973; Cadoret et al, 1977; Mendlewicz & Baron, 1981; Bland et al, 1986; Weissman et al, 1986; McGuffin et al, 1987; Stancer et al, 1987; Kuper et al, 1989). We suggest three possible reasons for this. First, ours was the only study which examined a non-treated sample. If the combination of early onset and positive family history commonly causes the subject to seek help (e.g., a parent with prior depression insisting that a depressed teenager get treatment), the association in treated samples might be artefactual. Second, unlike most, but not all (Bland et al, 1986; Weissman et al, 1986) previous reports, we corrected for year of birth. Without this correction, age at onset significantly predicts risk of depression in the co-twin. Since year of birth is correlated both with age at onset and risk of depression, it can induce a non-causal association between age at onset and risk in relatives. Third, our sample is young, with few onsets of depression after 40, thereby restricting our power to detect an association between age at onset and risk in relatives.

Implications for nosology and aetiology of depression

Family history is an important validator for psychiatric diagnostic categories (Robins & Guze, 1970). Our results suggest that to increase validity (from a familial perspective), criteria for MD should require multiple episodes of illness and impairment of functioning. Both these changes have previously been suggested (Perris, 1966; Mazure & Gershon, 1979). Our results would not support a longer minimum duration of illness or a higher minimum number of symptoms, both required by the Washington University Criteria (Feighner et al, 1972). Finally, our results argue against excluding cases on the basis of co-morbidity; eliminating 'secondary' cases of depression does not appear to result in a syndrome which is more familial.

Our results also provide some insight into the aetiology of MD. In individuals with one or a few depressive episodes, transient risk factors that are largely non-familial, such as stressful life events, are likely to play the major aetiological role. In recurrent MD, by contrast, enduring risk factors, such as genetics or childhood parental loss, which are largely familial, are likely to be particularly important. Furthermore, depressions substantially influenced by enduring familial factors are likely to be more severe, but not longer in duration, than those more associated with transient non-familial factors. Finally, like the results of Leckman et al (1984), our findings suggest that unlike recurrence and severity, symptomatic variability in depression is a poor index of aetiological variability, at least with respect to familial factors.

Limitations

Our results have four potential limitations. (1) Our sample was restricted to females. (2) Lifetime prevalence rate for MD is higher in this study than in most previous samples. As discussed elsewhere (Kendler et al, 1992a; Kendler et al, 1993), our high rates are probably due to several factors including the breadth of the DSM-III-R criteria (American Psychiatric Association, 1987), the youth of our sample, the use of professional interviewers, and specific statements in the interview used to augment memory for lifetime disorders. In addition, several recent population-based studies, including at least one with very similar methods (Weissman & Myers, 1978), report lifetime prevalence rates for MD in women in the range of those reported here (Bebbington et al, 1989; Rorsman et al, 1990). (3) Our interview did not include an assessment of manic episodes, so we are unable to separate unipolar from bipolar depressions. In previous epidemiological studies, only a small fraction of individuals with a history of depression in the general population also had a history of mania (Robins et al, 1984; Tsuang & Faraone, 1990). (4) We related clinical characteristics of depression to the tendency for depression to aggregate in families. We have previously shown that the pattern of twin resemblance in this sample suggests that the familial aggregation of MD results from genetic factors (Kendler et al, 1992a). Hence
the indices of familial depression detected in this report probably reflect the genetic, and not just the familial, liability to depression. The finding that four of the five significant predictor variables were stronger predictors of risk in MZ vs. DZ co-twins is consistent with this hypothesis. While it would have been more elegant to have demonstrated this directly, the kinds of analyses reported here cannot currently be performed either in specially parameterised regression analyses which, with twins, can separate genetic and familial–environmental factors (DeFries & Fulker, 1988), or with more formal model-fitting approaches. A more definitive resolution of the issues addressed in this report must await the availability of new models, which may, however, require quite large sample sizes, to discriminate definitively between competing hypotheses.

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References


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