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# The Risk of Minor Depression in Families of Probands with Major Depression: Sex Differences and Familiality

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**Summary.** Currently it is not clear whether minor forms of unipolar depression not matching the criteria of "major depression" should be considered as a separate diagnostic category. A controlled family study examined the familial aggregation of minor depression among probands with unipolar major depression. In the families of these probands the relative risk for minor depression was elevated by a similar magnitude to the risk for major depression. Threrefore, the diagnostic category "minor depression" would not increase diagnostic sensitivity at the expense of diagnostic specificity as far as familiality is the criterion. In agreement with recent epidemiological studies, minor depression did not reveal a similar excess prevalence in females compared with males as major depression does. The variation of the sex ratio for any subtype of unipolar depression was not associated with the familiality of this disorder.

**Key words:** Unipolar minor depression – Major depression – Sex ratio – Familial aggregation

## Introduction

Recent epidemiological studies have found high prevalence rates of minor depression in the community with a substantial proportion of cases seeking treatment for this condition (Ernst and Angst 1992). Although included in the Research Diagnostic Criteria (RDC) (Spitzer et al. 1978), this syndrome was not recognized as a diagnostic category by the more recently designed diagnostic schedules such as DSM-III (American Psychiatric Association 1980) and DSM-III-R (American Psychiatric Association 1987). This change is hard to understand given the high rate of cases with minor depression in primary care settings (Kessler et al. 1985, Barrett et al. 1988). One reason for the reluctance to accept the validity of this putative diagnostic entity might be the possibility of a loss of specificity with increasing sensitivity of the concept of unipolar depression. If this suggestion is correct, family studies should demonstrate a lack of familiality in minor as compared to major depression. Previous family studies revealed a familial aggregation of minor depression in families of probands with unipolar major depression, but only two controlled studies were informative in this respect, and further evidence is required (Gershon et al. 1982, Weissman et al. 1982).

The concept of minor depression is of considerable scientific interest as some epidemiological studies have shown that the definition of depression might be critical for the sex ratio to be found among cases with depression (Angst and Dobler-Mikola 1984). These studies give rise to the hypothesis that lowering the number of cross-sectional symptoms required for defining a case would increase the relative proportion of male cases. Recently, the Zurich Study systematically tested this hypothesis by repeated follow-up assessments and found this prediction to be true (Ernst and Angst 1992). Family studies might clarify to what extent a changing sex ratio is associated with changing familiality of depression. However, studies reporting the sex ratio in affected relatives as a function of the diagnostic threshold are rare (one controlled study: Weissman et al. 1982, one uncontrolled study: Young et al. 1990), and their results are ambiguous, i.e. sex ratio in affected relatives varies with probands' type of depression. Most informative in this regard are the figures of the Yale Family Study (Weissman et al. 1982): the sex ratio was balanced among interviewed cases with any type of depression (minor and major depression), but not so among interviewed cases with major depression in the control group; major depression was twice as common among females compared with males in this sample. The same study was unable to find a similar pattern among families of probands with unipolar depression: female relatives of patients were more likely to present with any type of depression than male relatives. This observation triggers the question whether familiality of depression increases the prevalence particularly in females, and especially so in the minor subtype. No further published family study data

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set is able to examine the validity of this tentative conclusion.

The present family study examines whether the sex ratio is attenuated with a reduction of the stringency of the diagnostic definition and whether the familiality of minor depression depends on the subject's gender.

## Methods

### *Recruitment and Assessment*

Study design, recruitment, psychopathological assessment, and the samples of probands and relatives have extensively been described in a previous paper in this journal (Maier et al. 1991).

Inpatients with affective, schizoaffective, or schizophrenic disorder consecutively admitted to the Department of Psychiatry, Mainz, with at least one first degree relative available for personal interview were recruited for this study ($n = 525$). One hundred and eighty-four patients (index cases) presented with unipolar major depressive disorder (MDD) according to RDC. These MDD patients had 609 living first degree relatives of whom 514 (84.4%) were personally interviewed.

The control probands with at least one first degree relative available for personal interview were matched by sex, age, educational status, and area of residence to a random subsample of the patients selected as index cases (probands). Within the particular stratum, the control probands were recruited in a representative manner in the general population. Among 109 control probands 80 presented without a lifetime history of any disorder according to RDC (including minor depression); these healthy control probands ($n = 80$) had 262 living first-degree relatives of whom 221 (84.4%) could be personally interviewed and served as a control group in this study.

Interviews were performed by using the structured clinical interview SADS-LA. Family history information on other family members than the proband was also collected during the interview. The final diagnostic assessment was based on a best estimate procedure joining together the information obtained by direct interview, by family history reports, and eventually by medical records. Interviews and diagnostic assessments in relatives were conducted blindly to the assessments in probands, and vice versa.

Compared with the family study method, depressive disorders can be identified only with reduced sensitivity by the family history method (Andreasen et al. 1986). As the major topic of this report is minor depression in families we only refer to those relatives who were directly interviewed.

### *Evaluation*

Major depression was defined as the presence of depressed mood for at least 2 weeks with at least four associated symptoms as listed by RDC; minor depression was defined as the presence of depressed mood for at least 2 weeks with at least two but less than four associated symptoms. A disorder was diagnosed only if the psychopathological syndrome was associated with a significant degree of psychosocial impairment or treatment seeking behaviour.

No significant differences with regard to current age and sex were found between relatives of probands with recurrent unipolar major depression, relatives of probands with single episodes of unipolar major depression, and relatives of healthy control probands (F-tests, $P = 0.01$). Thus, crude lifetime prevalences were compared across the three groups of relatives (because of their similarity by mean age and sex).

The calculation of relative risks for disorders in families and the comparison of prevalence rates between groups of relatives was based on methods of life-table analysis (Cox regression analysis, proportional hazard model). The dependent variable was age of onset in affected relatives and current age in non-affected relatives; the non-affected subjects were considered as censored observations in terms of the life-table analysis (i.e. no critical event occurred during the observation period). This method allows one to control simultaneously for age and gender in probands (and, if required, gender in relatives) as covariates (Lee 1980). As age at onset is a crucial variable for the proportional hazard model we only applied this technique to disorders (including minor disorders) but not to symptoms (such as episodes of depressed mood); the retrospective assessment of age at first onset of a symptom is especially likely to be prone to errors of measurement.

## Results

As shown in Table 1 male as well as female relatives of probands with either recurrent major depression or with

**Table 1.** Lifetime risk (%, not adjusted for age) of major and minor affective disorders (RDC) in relatives by sex and proband type

| | Female relatives by proband type | | | Male relatives by proband type | | |
|---|---|---|---|---|---|---|
| | MDD recurrent ($n = 157$) | MDD single ($n = 109$) | Healthy control ($n = 121$) | MDD recurrent ($n = 149$) | MDD single ($n = 99$) | Healthy control ($n = 100$) |
| *Diagnoses in relatives:* | | | | | | |
| Bipolar I disorder | 1.3 | 0 | 0.8 | 0.7 | 1.0 | 0 |
| Bipolar II disorder | 0 | 1.8 | 0 | 0.7 | 0 | 1.0 |
| MDD recurrent | 11.6 | 7.3 | 3.3 | 5.3 | 5.0 | 3.0 |
| MDD single | 9.6 | 11.0 | 6.6 | 4.7 | 6.0 | 3.0 |
| Cyclothymia[a] | 1.3 | 1.8 | 1.7 | 1.3 | 1.0 | 1.0 |
| Hypomania[a] (incl. cyclothymia) | 3.8 | 3.7 | 5.8 | 4.7 | 4.0 | 5.0 |
| Intermittent depression[a] | 3.2 | 4.6 | 1.7 | 3.4 | 2.0 | 3.0 |
| Minor depression[a] (incl. intermittent) | 5.7 | 6.4 | 3.4 | 7.5 | 5.0 | 6.0 |
| Any bipolar disorder | 5.1 | 5.5 | 5.8 | 6.1 | 5.0 | 6.0 |
| Any unipolar depression | 26.7 | 24.8 | 13.3 | 17.4 | 16.2 | 12.0 |
| Any Episode (> 2 weeks) of depressed mood: | 31.2 | 31.2 | 18.2 | 25.4 | 26.2 | 18.0 |

[a] Only if no lifetime diagnosis of bipolar disorder or MDD

**Table 2.** Relative risks for major and minor unipolar depression in relatives

**a** Relative risk by sex by probands' type of depression: Female versus male relatives

| | Probands' type | | |
|---|---|---|---|
| | MDD recurrent | MDD single | Healthy control |
| Major unipolar | 2.17[a] | 1.75[b] | 1.65[b] |
| Minor unipolar | 0.84 | 1.22 | 0.68[b] |
| All unipolar | 1.57[b] | 1.56[b] | 1.20 |

**b** Familiality of major and minor depression in relatives of patients with major depression by sex of relatives (relative risks): Relatives of patients versus relatives of controls

| | Relatives' Gender | |
|---|---|---|
| | Female | Male |
| Major unipolar | 2.00[a] | 1.62[b] |
| Minor unipolar | 1.93[b] | 1.40 |
| All unipolar | 1.93[b] | 1,54[b] |

[a] $0.001 < P < 0.01$
[b] $0.01 < P < 0.05$
Different from balanced risk (1.0) by Cox regression model with age, sex of proband, sex of relative as covariates

a single major depressive episode were distinct from relatives of healthy controls by elevated lifetime morbid rates of all types of unipolar depression ($P < 0.01$ by proportional hazard model), but not of bipolar disorder ($P > 0.10$). Independently of relatives' gender, all subtypes of unipolar disorder (including minor depression) were more frequent among relatives of probands with unipolar depression than among relatives of controls. In both gender groups recurrent major depression as well as single episodes of major depression showed a trend for being familial. However, in both gender groups also recurrent major depression was significantly more frequent in relatives of probands with single episode unipolar depression compared to contols, and vice versa.

Major depression was more frequent among female than among male relatives independently of whether the proband was a patient or a control. The relative risk by sex (i.e. female/male ratio of the relative frequeny) of minor depression neglecting intermittent depression was more balanced (0.92 in families of patients of each type; 0.68 in families of controls) compared with major depression (Table 2a). Chronic cases of minor depression diagnosed as intermittent depression did not consistently reveal a systematic predominance of any gender. However, owing to the low base rate the number of cases was relatively low, and random fluctuation is likely to occur.

In summary, minor depression did not reveal a strong female predominance. When the definition of caseness was extended beyond the scope of major and minor depression, the sex ratio of relative frequencies of cases was additionally attenuated. This was reflected by the sex-specifc relative frequency of subjects with any episode of depressed mood lasting longer than two weeks in the absence of the diagnosis of minor or major depression or bipolar affective disorder, which was more often reported by males than by females: by 4.9% of the female and 6.0% of the male relatives of control probands, by 5.3% of the female and 10.0% of the male relatives of probands with single episode MDD, and by 4.5% of the female and 7.9% of the male relatives of probands with MDD (multiple episodes).

Table 2 shows the relationship between sex ratio, severity of the disorder, and proband's type by means of the proportional hazard model. The first question is whether the sex ratio in ill relatives of patients and in ill relatives of healthy controls differs by the severity of the disorder in relatives (upper part of Table 2). The relative risk by sex for major and for minor unipolar depression in relatives are reported for the three comparison groups controlled for proband's and relative's gender and for the proband's age (Table 2). As already apparent from the comparison of the crude rates between male and female relatives in Table 1, major depression was consistently more frequent in females, but no so minor depression which showed a more balanced sex distribution.

Table 2 is also concerned with the extent to which the risk of major and minor depression is higher in relatives of patients compared with relatives of controls. These relative risks are presented as a function of the relatives' gender in the lower part of Table 2. Familiality was found to be slightly more pronounced in females independently of the subtype after controlling for proband's gender and age. The familiality of minor forms of unipolar depression was only slightly lower than of major forms. Given the limitations of the sample size it cannot be decided if these trends are systematic or if they just reflect random variation.

Combining female and male relatives, major depression as well as minor depression are familial by the proportional hazard model ($P < 0.01$ for both levels of severity). Therefore it can be concluded that minor depression clusters in families of probands with major depression and does not occur at random. The elevation of relative risks (i.e. higher than 1.0 which indicates balanced risk) presented as a function of gender in the lower part of Table 2 was significant ($P = 0.05$) for major depression in male as well as in female relatives and for minor depression in male relatives. The sex specific significances of familiality, however, are of questionable validity given the multiplicity of testing.

## Discussion

### *Familiality of Minor Versus Major Depression*

The present study is in agreement with previous controlled family studies by Gershon et al. (1982) and Weissman et al. (1982) with regard to the prevalence of unipolar minor or intermittent depression in the control families (ranging from 2.5% to 5.3% in these two previous studies and between 3.4% and 6.0% in this study). The risk for minor or intermittent depression in families of probands with unipolar major depression varied between 3.8% and 9.0% in previous family studies (Weissman et al.

1982, Gershon et al. 1982, Andreasen et al. 1987, Endicott et al. 1985) and was found to range between 5.7% and 7.5% in the present study. There is also agreement with regard to the elevation of risk for minor depression in the families of probands with unipolar major depression as compared with control families (Gershon et al. 1982, Weissman et al. 1982). The present study furthermore indicated that the occurrence of depressed mood lasting for at least two weeks without requiring additional associated symptoms was also more frequent in families of probands with major depression than in control families. This evidence supports the view that what is transmitted in families are not the diagnostic entities themselves but dimensions of liability to depression.

The impact of the familiality of depression on the risks in relatives of probands is not substantially stronger for the major as compared with the minor variant independently of the relatives' gender. Therefore, our family data reveal that minor forms of depression do not lack specificity in comparison with the major form with respect to the criterion of familiality. This conclusion is an argument against the reluctance to include unipolar minor depression into diagnostic manuals as was the case with DSM-III and DSM-III-R.

### *Sex Ratio in Minor and Major Depression*

In agreement with the NIMH collaborative family study (Young et al. 1990) the predominance of females among cases affected with a depression became more attenuated with the reduction of the number of symptoms to be fullfilled for being a case. If only presence of depressed mood for at least two weeks was required the sex ratio became nearly balanced. Epidemiological studies (Ernst and Angst 1992) and the control group in the Yale Family Study (Weissman et al. 1982) also pointed in this direction.

Another strategy to increase the severitiy of a disorder is to consider only longstanding conditions. Based on previous prospective epidemiological surveys which reported a higher prevalence of chronic depression (dysthymia) in females compared with males (discussed by Ernst and Angst 1992) it was expected that chronic minor depression (intermittent depression) would be more frequent in females. However, the results of this report were not consistently in line with this expectation. The number of cases with intermittent depression in relatives may be too low for a reliable estimate of the sex ratio; it is worthwhile to note that some extensive prospective epidemiological studies (Ernst and Angst 1992) also were ambiguous in this respect.

The variation of the sex ratio was consistent within groups of relatives defined by a particular diagnostic subtype independently of the proband's status. The evidence for a different sex ratio in familial as compared with control cases was convincing neither for major depression nor for minor depression nor for episodes with depressed mood (not requiring additional symptoms). In contrast to the Yale Family Study (Weissman et al. 1982) we did not find sex ratio to be a function of familiality if caseness was defined by an episode of *any* depressive disorder.

A variety of explanations can be offered for the variation of sex ratio by subtypes of depression (i.e. with the variation of numbers of symptoms associated with depressed mood) as observed in this as well as in other family studies (Young et al. 1990): e.g., differential recall of associated features of depression, less severe impairment, modifying factors such as social roles (Ernst and Angst 1992). The present study is not informative in this respect and can only contribute to this discussion by showing that differential familiality in male and female subjects cannot explain the differential sex ratio in cases of depression.

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