ORIGINAL CONTRIBUTIONS

Recurrence in Affective Disorder: Analyses with Frailty Models

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The risk of recurrence in affective disorder is influenced by the number of prior episodes and by a person's tendency toward recurrence. Newly developed frailty models were used to estimate the effect of the number of episodes on the rate of recurrence, taking into account individual frailty toward recurrence. The study base was the Danish psychiatric case register of all hospital admissions for primary affective disorder in Denmark during 1971–1993. A total of 20,350 first-admission patients were discharged with a diagnosis of major affective disorder. For women with unipolar disorder and for all kinds of patients with bipolar disorder, the rate of recurrence was affected by the number of prior episodes even when the effect was adjusted for individual frailty toward recurrence. No effect of episodes but a large effect of the frailty parameter was found for unipolar men. The authors concluded that the risk of recurrence seems to increase with the number of episodes of bipolar affective disorder in general and for women with unipolar disorder. *Am J Epidemiol* 1999;149:404–11.

affective disorders; bipolar disorder; depressive disorder; recurrence

The pathophysiology of affective disorder basically is unknown. One of the most significant theories involves application of the paradigm of sensitization and kindling. These concepts suggest that biochemical and anatomic substrates in the central nervous system evolve over time as a function of the recurrence of mood episodes (1, 2). It is hypothesized that mood episodes themselves stress the brain so that its sensitivity to biologic and psychosocial stressors increases. Thus, the likelihood of subsequent episodes increases with every new episode that occurs, and the duration of the intervals between mood episodes decreases during the course of the illness. This theory is based on observations from early epidemiologic studies of a recurrent and progressive course of the illness.

However, results of subsequent studies of the risk of recurrence in affective disorder in relation to the number of prior episodes have been contradictory (3, 4). The reason seems to be that the studies have the same analytical drawbacks as other epidemiologic studies of recurrence. First, as stated by Haghighat (4) in 1996, each group of subjects with a given number of episodes during a given period must be considered separately. Nevertheless, almost all studies combined all of their subjects in one pool, which may have led to serious miscalculations (4). We recently presented a case register study in which this fallacy was avoided, in that the risk of recurrence was estimated by following each new episode (3). The study revealed a progressive course of episodes in both unipolar and bipolar affective disorder. This progressive course was also found in different subgroups by gender and age (5) and when the rate of recurrence was adjusted for the effect of age, gender, and calendar time (6).

Second, in all studies including our own, estimation of recurrence was affected by selection. The statistical average course of the illness might have been dominated by the course of the episodes in those patients who were most ill. That is, if patients who have had several episodes already have a constant high risk of recurrence following their first episode, these patients will increasingly influence the pattern with each subsequent episode, because they will constitute a higher proportion of the remaining sample. Such a selection could

explain the progressive course of episodes that was found in our study and in others of affective disorder.

One might expect that a person's actual risk of recurrence is related to the risk of recurrence at former episodes. However, by using the standard survival techniques currently available, it is not possible to estimate the total risk accumulated over episodes, so the long-term effect of the illness is lost. Newly developed frailty models (7–9) represent a way to handle this problem in analyses of recurrent events in censored data. In these models, the frailty is a random effect reflecting the individual degree of illness; thus, it contributes to the heterogeneity of the course of affective disorder.

The aim of our study was to use frailty models to reanalyze the rate of recurrence in affective disorder. Recurrence was expressed as the number of readmissions found in the Danish psychiatric case register.

MATERIALS AND METHODS

The register

In Denmark, all psychiatric admissions have been listed in a nationwide register (10, 11) by using the same diagnostic system, the *International Classification of Diseases,* Eighth Revision (ICD-8) (12), from April 1, 1970, to December 31, 1993. For various reasons, and to achieve better diagnostic reliability over time, Denmark decided not to change to the *International Classification of Diseases,* Ninth Revision (ICD-9) (13) in 1978. Since there are no private psychiatric hospitals or clinics in Denmark, all admissions for the 5.1 million inhabitants are included in the register.

All Denmark inhabitants have a unique personal identification number that can be checked logically for errors, so it can be established with great certainty whether a patient has been admitted previously, irrespective of name changes, for example. Censoring because of death can also be established with equal certainty, because all public registration systems use the same identification number.

Subjects

To avoid the initial, slightly uncertain registration period, only those patients registered on or after January 1, 1971, were included. The study sample was defined as all inpatients (day and night patients) who had a diagnosis of manic depression (ICD-8 code 296), depressive or manic/circular episode at first discharge. (According to the glossary of ICD-8, a circular affective disorder is a bipolar disorder "that has appeared in both the depressed and the manic form, either succes-

sively or separated by an interval of normality" (14, p. 34)). On the basis of the diagnostic hierarchy of ICD-8 and the *International Classification of Diseases and Related Health Problems,* Tenth Revision (ICD-10), patients who were given a main diagnosis of organic psychosis (ICD-8 codes 290–294) or schizophrenia (ICD-8 code 295) at subsequent discharges were included in the analysis only until the original diagnosis was altered. These patients were then censored from further analysis because they were no longer considered primarily manic-depressive. Patients who were given other diagnoses (lower in the hierarchy) at subsequent discharges were still regarded as manic-depressive; thus, all data from these admissions were included.

The sample was divided dynamically into two groups according to the type of manic-depressive disorder present at a given time. Thus, patients were classified as unipolar (nonbipolar) as long as they had not been discharged with a diagnosis of manic or circular episode (ICD-8 codes 296.19 and 296.39); from the time that patients had such an episode, they were classified as bipolar. The type of disorder was thus time dependent and changed for some patients during the study.

Readmissions as an expression of recurrence

The risk of readmission to the hospital originates from a sum of two other risk factors: 1) the risk of relapse, that is, the return of an episode during remission (before recovery), and 2) the risk of recurrence, that is, the appearance of a new episode during recovery (15, 16). According to the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV) (17) and ICD-10 (18), episodes must be separated by at least 8 consecutive weeks without a significant mood disturbance to be considered two separate episodes. Analogously, since the scope of the investigation was to study the recurrence of episodes, the lengths of two admissions and the length of the period between the two admissions were added and counted as one episode if readmission occurred within 8 weeks of discharge. Thus, the first 8 weeks after discharge was defined as the remission period and readmission after these first 8 weeks was defined as a new episode (recurrence). Therefore, patients were not at risk of recurrence until 8 weeks after discharge, and recurrence was defined as readmission after that time.

Covariables

Since the rate of recurrence depends on age at first admission (Age1) (5) and on calendar time, as the available number of psychiatric inpatient beds in

Denmark declined from 9,016 in 1971 to 4,318 in 1993 (19), the rate of recurrence was adjusted for these covariables. Calendar time was divided into five periods (1971–1975, 1976–1980, 1981–1985, 1986–1990, and 1991–1994) because the alternative assumption of a linear effect was not justified. Because few patients had six or more episodes, the number of episodes was categorized as 1, 2, 3, 4, or ≥5.

Statistical analysis

The frailty model that was used is an extended Cox regression model (9). The time axis was defined as time since the last discharge, and the event was defined as readmission after being discharged for 8 weeks. The data were censored at a diagnosis of schizophrenia or organic psychosis, at death, and if readmission did not occur before December 31, 1993. Age at first admission (Age1), calendar time (period), and the episode number (k) were included as covariables.

In the model, the intensity of recurrence for a given person i at time t after episode k was $\lambda_{ik}(t) = \lambda_0(t) \, Z_i \, \exp(\text{Age1}_i \beta_{age1} + \beta_{period} + \beta_k)$. Here, β_{age1} is the effect of age at first admission, β_{period} is the effect of calendar time, and β_k is the episode effect, the parameter of interest. This formula can be interpreted as follows: For any given patient, $\exp(\beta_k)$, the relative hazard, is the ratio between his or her rate of recurrence following episode k (2, 3, 4, or ≥5) compared with the rate of recurrence following the reference episode, episode 1. Finally, Z_i is the frailty for patient i. Patients with a high Z_i value thus tend to have a high rate of recurrence after any episode, and the opposite is true for patients with a low Z_i value. The Z_i values are assumed to follow some distribution across the population of patients; thus, the variance σ^2 of this distribution is a measure of the heterogeneity of the patients.

Two distributions were studied in the analyses: a gamma distribution (20) and a log-normal distribution (21). In the latter, for mathematical convenience, the baseline hazard $\lambda_0(t)$ was assumed to be piecewise constant. For comparison, this paper also presents results from Cox regression models without inclusion of the frailty, corresponding to a variance of $\sigma^2 = 0$. All p values were based on Wald tests.

RESULTS

From 1971 to 1993, 20,350 patients were admitted to the hospital at least once; 17,447 presented with depression (ICD-8 codes 296.09 and 296.29) and 2,903 presented with mania or circular episode (ICD-8 codes 296.19 and 296.39). The sample included 7,254 men and 13,096 women who were admitted 1–30

TABLE 1. Eight subpopulations of psychiatric patients* admitted to the hospital, by type of affective disorder at first discharge, Denmark, 1971–1993

	No. of patients	No. of admissions
Unipolar		
Younger† men	2,608	4,651
Older‡ men	3,272	5,009
Younger women	4,409	8,862
Older women	7,158	12,783
Bipolar		
Younger men	1,081	3,160
Older men	558	1,094
Younger women	1,257	4,207
Older women	769	1,821

* Since patients can shift from unipolar to bipolar disorder, some patients contribute to the number of patients twice.
† Age at first admission, <52.38 years.
‡ Age at first admission, ≥52.38 years.

times, giving a total of 41,587 admissions (mean number of admissions, 2.43). The sample was divided into younger and older patients according to the median age at first admission (52.38 years). Data on the number of admissions within eight subpopulations of patients, by age, gender, and type of disorder at first discharge, are shown in table 1.

Twenty-six discharge dates were missing from the register, so data on these patients were included in the analyses only until the episode preceding the one with the missing date. Among the 20,350 patients who were included, 820 were classified as suffering from organic psychosis and 322 from schizophrenia when they were discharged later. Thus, the admission histories of 1,142 patients (5.6 percent of the sample) were censored when these patients were readmitted with a diagnosis of organic psychosis or schizophrenia, and more than 75 percent of these histories had been censored at the second or third discharge because the diagnosis had changed.

Tables 2 and 3 present Cox regression models in which the effect of episodes was adjusted for the effects of age at first admission and of calendar time for the four age- and gender-specified groups of patients with unipolar disorder and bipolar disorder, respectively. For both disorders and for all groups, the rate of recurrence increased with every episode. However, in these analyses the waiting times within patients (the lengths of time that elapsed between episodes for an individual patient) are (falsely) assumed to be independent. Therefore, these tables are included mainly for comparison with tables 4 and 5, which present the effects of episodes further adjusted for the effect of individual heterogeneity (a gamma-distributed frailty). For younger unipolar women, the rate of recurrence increased with the number of

TABLE 2. Effect of episodes, estimated by using Cox regression models without frailty, for patients admitted to the hospital with unipolar affective disorder, Denmark, 1971–1993

	Relative hazard*	95% confidence interval	p value
Younger† men			
Episode 1	1.000		
Episode 2	1.503	1.344–1.680	
Episode 3	1.964	1.702–2.267	<0.00001
Episode 4	2.341	1.946–2.816	
Episode ≥5	3.222	2.766–3.754	
Older‡ men			
Episode 1	1.000		
Episode 2	1.586	1.411–1.783	
Episode 3	1.767	1.501–2.081	<0.00001
Episode 4	2.185	1.750–2.728	
Episode ≥5	3.009	2.420–3.743	
Younger women			
Episode 1	1.000		
Episode 2	1.631	1.509–1.764	
Episode 3	2.024	1.839–2.228	<0.00001
Episode 4	2.264	2.013–2.547	
Episode ≥5	3.268	2.968–3.597	
Older women			
Episode 1	1.000		
Episode 2	1.506	1.409–1.609	
Episode 3	1.772	1.626–1.932	<0.00001
Episode 4	2.284	2.047–2.547	
Episode ≥5	2.527	2.291–2.786	

* All relative hazards were adjusted for the effect of age at first admission and for calendar time.
† Age at first admission, <52.38 years.
‡ Age at first admission, ≥52.38 years.

TABLE 3. Effect of episodes, estimated by using Cox regression models without frailty, for patients admitted to the hospital with bipolar affective disorder, Denmark, 1971–1993

	Relative hazard*	95% confidence interval	p value
Younger† men			
Episode 1	1.000		
Episode 2	1.177	1.034–1.340	
Episode 3	1.464	1.268–1.691	<0.00001
Episode 4	1.715	1.485–2.017	
Episode ≥5	2.350	2.070–2.668	
Older‡ men			
Episode 1	1.000		
Episode 2	1.391	1.103–1.753	
Episode 3	1.879	1.437–2.457	<0.00001
Episode 4	2.227	1.626–3.050	
Episode ≥5	2.530	1.939–3.302	
Younger women			
Episode 1	1.000		
Episode 2	1.216	1.080–1.370	
Episode 3	1.466	1.288–1.667	<0.00001
Episode 4	1.606	1.398–1.846	
Episode ≥5	2.194	1.965–2.450	
Older women			
Episode 1	1.000		
Episode 2	1.212	1.011–1.452	
Episode 3	1.314	1.069–1.614	<0.00001
Episode 4	1.762	1.407–2.206	
Episode ≥5	2.208	1.847–2.639	

* All relative hazards were adjusted for the effect of age at first admission and for calendar time.
† Age at first admission, <52.38 years.
‡ Age at first admission, ≥52.38 years.

episodes and the effect gained significance ($p <$ 0.0001) (table 4). Their rate of recurrence following episode ≥5 was 1.62 (95 percent confidence interval 1.269–2.066) times the rate of recurrence following episode 1. Similarly, a significant effect of episodes was found for older unipolar women, whose rate of recurrence tended to be lower after episode 1 than after subsequent episodes. For younger unipolar men, the rate of recurrence increased with the number of episodes, but the effect did not gain significance. No effect of episodes was demonstrated for older unipolar men. In contrast, the effect of the frailty gained significance among all four groups of unipolar patients. The estimated frailty parameter was the largest for older men, followed by the parameter for younger men.

Among all four groups of patients with bipolar disorder, the rate of recurrence increased with the number of episodes, although the effect was not significant for younger women (p = 0.17) and was marginally significant for younger (p = 0.064) and older (p = 0.053) men (table 5). For example, the rate of recurrence following episode ≥5 compared with the rate following

episode 1 was 1.982 (95 percent confidence interval 1.578–2.488) for older bipolar women and 1.802 (95 percent confidence interval 1.136–2.857) for older bipolar men. The estimated frailty parameters were the largest for younger patients, and the effect of the frailty gained significance for younger but not older patients (p = 0.127 for older men and p = 0.099 for older women). In summary, the effect of episodes was small when the estimated frailty parameter was large and vice versa.

When the frailty was assumed to follow a lognormal distribution instead of a gamma distribution, a smaller amount of the individual heterogeneity was explained (smaller σ^2), and there was a significant increasing effect of the episode number on the rate of recurrence in all age- and gender-specified groups (results not presented).

In all models, patients who were first admitted at the beginning of the observation period had a higher rate of readmission than patients who were first admitted later. Thus, the rate of recurrence decreased with calendar time (results not presented).

TABLE 4. Effect of episodes, adjusted for the effect of individual heterogeneity (frailty), for patients admitted to the hospital with unipolar affective disorder, Denmark, 1971–1993

	Relative hazard*	95% confidence interval	p value
Younger† men			
Episode 1	1.000		
Episode 2	1.022	0.810–1.290	
Episode 3	1.077	0.784–1.478	0.94
Episode 4	1.108	0.762–1.610	
Episode ≥5	1.136	0.749–1.723	
Frailty σ²	0.691	0.259–1.123	0.002
Older‡ men			
Episode 1	1.000		
Episode 2	1.052	0.974–1.396	
Episode 3	0.903	0.606–1.346	0.59
Episode 4	0.916	0.565–1.487	
Episode ≥5	0.991	0.581–1.688	
Frailty σ²	0.731	0.187–1.276	0.009
Younger women			
Episode 1	1.000		
Episode 2	1.333	1.180–1.505	
Episode 3	1.424	1.199–1.692	<0.0001
Episode 4	1.392	1.123–1.726	
Episode ≥5	1.620	1.269–2.066	
Frailty σ²	0.383	0.203–0.563	<0.0001
Older women			
Episode 1	1.000		
Episode 2	1.169	1.030–1.327	
Episode 3	1.154	0.960–1.386	0.03
Episode 4	1.290	1.029–1.617	
Episode ≥5	1.146	0.886–1.483	
Frailty σ²	0.453	0.244–0.663	<0.0001

* All relative hazards were adjusted for the effect of age at first admission and for calendar time.
† Age at first admission, <52.38 years.
‡ Age at first admission, ≥52.38 years.

TABLE 5. Effect of episodes, adjusted for the effect of individual heterogeneity (frailty), for patients admitted to the hospital with bipolar affective disorder, Denmark, 1971–1993

	Relative hazard*	95% confidence interval	p value
Younger† men			
Episode 1	1.000		
Episode 2	0.986	0.842 to 1.154	
Episode 3	1.103	0.912 to 1.333	0.064
Episode 4	1.162	0.930 to 1.452	
Episode ≥5	1.303	1.036 to 1.638	
Frailty σ²	0.448	0.262 to 0.634	<0.0001
Older‡ men			
Episode 1	1.000		
Episode 2	1.269	0.968 to 1.663	
Episode 3	1.603	1.132 to 2.269	0.053
Episode 4	1.790	1.170 to 2.738	
Episode ≥5	1.802	1.136 to 2.857	
Frailty σ²	0.217	−0.062 to 0.496	0.127
Younger women			
Episode 1	1.000		
Episode 2	1.068	0.933 to 1.223	
Episode 3	1.164	0.994 to 1.363	0.17
Episode 4	1.166	0.977 to 1.393	
Episode ≥5	1.252	1.043 to 1.503	
Frailty σ²	0.412	0.284 to 0.540	<0.0001
Older women			
Episode 1	1.000		
Episode 2	1.183	0.980 to 1.430	
Episode 3	1.267	1.018 to 1.575	<0.0001
Episode 4	1.667	1.307 to 2.127	
Episode ≥5	1.982	1.578 to 2.488	
Frailty σ²	0.074	−0.014 to 0.162	0.099

* All relative hazards were adjusted for the effect of age at first admission and for calendar time.
† Age at first admission, <52.38 years.
‡ Age at first admission, ≥52.38 years.

DISCUSSION

This study demonstrated that in frailty models, when the effect of episodes was adjusted for the individual tendency toward recurrence, no significant effect was found for unipolar men in general or for younger bipolar women. In previous analyses of the same data, we demonstrated a progressive course of the illness in general (3) and, by using another design and a subsample of the population included in the present study, found a significant effect of episodes on the rate of recurrence in unipolar and bipolar affective disorder (6). The present study showed that for younger bipolar women, the progressive course seemed to be explained partly by the individual frailty for recurrence and partly by the effect of episodes whereas for unipolar men, the progressive course was caused mainly by the frailty effect. It seems as if patients who had had many episodes already had a high risk of recurrence following the first episode and that these frail patients (with

a high frailty parameter) affected the analyses so that a general progressive course was found in unipolar men and younger bipolar women. In contrast, for unipolar women and bipolar men in general and for older bipolar women, the present study demonstrated that in frailty models, even when the effect of episodes was adjusted for the individual tendency toward recurrence, there was a substantial effect of episodes (although the effect did not increase consistently for older unipolar women).

In our analyses, two different frailty distributions were studied: a gamma distribution and a log-normal distribution. Since the aim of the study was to investigate whether the effect of episodes that was found in previous studies could be explained simply by individual heterogeneity, that is, the effect of the frailty, and since in all cases the model with the gamma distribution resulted in larger frailty parameters, we included results from only this model. Thus, a natural question is whether some third type of distribution might have

explained even more of the individual heterogeneity and have consequently resulted in smaller estimated effects of episodes. This possibility cannot of course be ruled out entirely. However, by using currently accepted methodology, we were able to identify an effect of episodes even after adjustment for individual heterogeneity. Further research must show whether this important result is sustained.

An alternative to frailty models could be a stratified Cox regression model that used the individual patient as the stratum. However, since the large number of patients who had only one episode would contribute no information to such an analysis, this approach should be considered less suitable.

In general, the present frailty analyses showed, as expected, that there was considerable individual heterogeneity in the rate of recurrence; thus, the waiting times within patients were mutually dependent. This is the reason that we did not compare estimations of the rate of recurrence across episodes previously (3, 5).

Epidemiologic advantages of our study are that it included 23 years of observation of the whole Danish population and that this population is ethnically and socially homogeneous and has a very low migration rate. Psychiatric care is well developed, so that persons with moderate to severe affective disorders can easily have access to a psychiatric hospital. Also, all psychiatric inpatient treatment in Denmark is free of charge, and as no private psychiatric inpatient facilities exist, our study was not biased by socioeconomic differences.

Problems related to the study design and to the use of a case register to research affective disorder have been discussed in a previous paper (3). It should be emphasized that the diagnoses in the register were made by different clinicians from all over Denmark and were not standardized for research purposes. However, for decades, all Danish specialists in psychiatry have completed identical courses in theoretical and clinical training, which helps to increase the reliability of the diagnoses. Additionally, diagnostic shifts due to the transfer to ICD-9 were avoided in our study, since ICD-8 was in use in Denmark during the entire 23-year study period.

In Denmark, ICD-10 was officially introduced on January 1, 1994. The concordance in the register between the clinical ICD-8 diagnoses of manic-depression made before 1994 and the clinical ICD-10 diagnoses of affective disorder made during 1994 has been found to be high (22). Additionally, a validation study (24) has found a high degree of concordance between the clinical ICD-8 diagnoses of manic-depression in the case register and the research diagnostic criteria according to ICD-10 (and the *Diagnostic and Statistical Manual of Mental*

Disorders, third edition, revised (DSM-IIIR) (23). Among 100 randomly selected patients discharged with a diagnosis of manic-depression according to ICD-8 and recorded in the register, 95 were found to have a diagnosis of major affective disorder according to ICD-10 research diagnostic criteria.

Furthermore, other studies have found a high degree of concordance between ICD-8 diagnoses and *Diagnostic and Statistical Manual of Mental Disorders,* third edition (DSM-III) diagnoses. Thus, the rate of agreement between unipolar affective psychosis according to ICD-8 and major depression according to DSM-III (25) has been found to be as high as 92.3 percent, and the rate of agreement between bipolar affective psychosis according to ICD-8 and bipolar disorder, mania according to DSM-III has been found to be as high as 97.4 percent (26). Similarly, in a study of 183 patients with functional psychoses, 94.3 percent of those who received a diagnosis of affective psychosis according to ICD-8 also had this diagnosis according to DSM-III (27). A diagnosis of bipolar II disorder (recurrent depression and hypomanic episodes but no manic episodes) was not delineated in the present study, since this diagnosis is not denoted in ICD-8.

In our analyses, censoring at death might have biased the results, since mortality in affective disorder is associated with suicide and suicide might be correlated with recurrence of affective episodes. However, suicide often occurs at the beginning of the disorder (28). Additionally, previous analyses of the present data have not shown any association between suicidal acts and the initial pattern of recurrence (29).

The rates of recurrence were adjusted for the effect of calendar time, since the number of available psychiatric inpatient beds and the admission rates for affective disorders in Denmark declined during the observation period (30, 31). As expected, the rates decreased with calendar time.

Our study concerned only those episodes severe enough to lead to hospitalization and may not reflect the absolute number of recurrences. We used a "naturalistic" approach. That is, patients may have received treatment at the discretion of the responsible clinician without any intervention by the researchers. Treatment interacts with the natural course of the illness, and a major problem in register studies is that the relation between treatment and episodes is unclear. However, in Denmark, patients with affective disorder who have had contact with a psychiatric hospital during the last few decades have been widely exposed to medical treatment. Early controlled studies found a prophylactic effect; thus, lithium with or without additional treatment such as antidepressants, electroconvulsive ther-

apy, and neuroleptics reduced the frequency of severe episodes in unipolar and bipolar disorder (32). In the present study, possible treatment did not prevent a progressive course of unipolar or bipolar disorder. Thus, naturalistic studies cast doubt on the extent of the prophylactic effectiveness of lithium and adjunctive treatment in clinical practice (33). One explanation seems to be noncompliance with treatment, which in general has been found to be an important factor in the frequency of hospitalization (34). Another explanation could be that antidepressants might accelerate the rate of recurrence (32, 35).

Our study fulfills the necessary conditions for analyses of the effect of episodes, as stated by Haghighat (4), and to our knowledge is the first study to take individual frailty into account. A progressive course of illness was found for women with unipolar disorder and for all kinds of patients with bipolar disorder, even when the rate of recurrence was adjusted for individual frailty toward recurrence. No effect of episodes but a large effect of the frailty parameter was found for unipolar men. In general, the frailty was greater for men than for women (tables 4 and 5), probably reflecting an increased disease heterogeneity among men.

The findings from our study partly confirm the results from other studies of unipolar and bipolar disorder, which investigated the effect of episodes (3, 4). Thus, from previous studies and the present one, and by using the best statistical methods currently available, it seems likely that the risk of recurrence increases with the number of episodes in bipolar affective disorder in general and for women with unipolar disorder.

The progressive course may in some ways reflect the illness process itself and thus is important in understanding the pathophysiology of affective disorder. As mentioned previously, the paradigm of sensitization and kindling in affective disorder is based on observations of such a recurrent and progressive course of the illness. In addition, the present study also found that the risk of recurrence was partly laid down at onset, before the deteriorating effect of the illness itself occurred, reflecting the premorbid probability of illness for the person. Our study suggests that after the onset of the illness, this individual premorbid probability, frailty, or diathesis is modified by the illness process itself, creating a time-dependent total risk of recurrence of new episodes of illness.

According to the sensitization and kindling theories, biochemical and anatomic substrates underlying affective disorders evolve over time, possibly in the hippocampus and elsewhere in the limbic system, as a function of prior episodes (2, 36). The inducing principles, the neurophysiologic processes, and the behaviors induced in the animal kindling models are, at best,

only rough analogies to those observed in affective disorder (37–39), and no direct neurophysiologic evidence has been provided for these theories. However, preliminary brain imaging studies indirectly support the episode effect, which is central to the sensitization theories, as an association between the number of affective episodes (40) and the duration of the illness (41), and subcortical brain abnormalities, including those in the hippocampus, have been found. Additionally, it seems as if recurrent and chronic stress may induce atrophy of neurons in these brain regions (36). The longitudinal development of these brain abnormalities remains to be investigated; thus, future prospective longitudinal studies with brain imaging following successive affective episodes might cast further light on the episode effect in affective disorders.

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