Course and cognitive outcome in major affective disorder

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1. THE THESIS IS BASED ON THE FOLLOWING PAPERS:

1. Kessing, L.V., Andersen, P.K., Mortensen, P.B. and Bolwig, T.G. (1998a) Recurrence in affective disorder I - a case register study. Br. J. Psychiatry 172, 23-28.
2. Kessing, L.V. (1998c) Recurrence in affective disorder II - effect of age and gender. Br. J. Psychiatry 172, 29-34.
3. Kessing, L.V., Andersen, P.K. and Mortensen, P.B. (1998b) Predictors of recurrence in affective disorder - a case register study. J. Affect. Disord. 49, 101-108.
4. Kessing, L.V. and Andersen, P.K. (1999) The effect of epi sodes in affective disoder - a case register study. J. Affect. Disord. 53, 225-231.
5. Kessing, L.V. (1999a) The effect of the first manic episode in affective disoder - a case register study. J. Affect. Disord. 53, 233-239.
6. Kessing, L.V. (1999b) The effect of comorbid alcoholism on recurrence in affective disoder - a case register study. J. Affect. Disord. 53, 49-55.
7. Kessing, L.V., Mortensen, P.B. and Bolwig, T.G. (1998c) Clinical definitions of sensitisation in affective disorder - a case register study of prevalence and prediction. J. Aff. Disord. 47, 31-39.
8. Kessing, L.V., Mortensen, P.B. and Bolwig, T.G. (1998d) Clinical consequences of sensitisation in affective disorder - a case register study. J. Affect. Disord. 47, 41-47.
9. Kessing, L.V., Olsen, E.W. and Andersen, P.K. (1999a) Recurrence in affective disorder - analyses with frailty models. Am. J. Epidemiol. 149, 404-411.
10. Kessing, L.V. and Mortensen, P.B. (1999) Recovery during the course of affective disorder - a case register study. Acta Psychiatr. Scand. 100, 279-287.
11. Kessing L.V. (1998d): Cognitive impairment in the euthymic phase of affective disorder. Psychol. Medicine 28, 1027-1038.
12. Kessing, L.V., Olsen, E.W. and Andersen, P.K. (1999b) Dementia in affective disorder - a case register study. Acta Psychiatr. Scand. 100, 176-185.

2. TERMINOLOGY

Major affective disorders: include "manic episode", "bipolar affective disorder", "depressive episode" and "recurrent depressive disorder" (ICD-10, F30-F33).
Unipolar disorder: includes "depressive episode" and "recurrent depressive disorder" (ICD-10, F32-F33).

Syndromal criteria: defined according to any of several criterion-based assessment systems.
Episode: a period of days, during which syndromal criteria for the disorder are met.
Remission: a period (following an episode) during which the patient no longer meets syndromal criteria for the disorder but continues to evidence more than minimal symptoms.
Recovery: a period (following remission) during which the patient is asymptomatic or has no more than minimal symptoms. Recovery here means recovery from episodes and not recovery from the illness per se.
Relapse: the return of an episode during remission (before recovery).
Recurrence: the appearance of a new episode during recovery.
Response: the point at which remission begins.
Euthymia: = recovery, the period of well-being.

Adapted definitions according to *Frank et al.* (1991) and *Kupfer and Frank* (1992).

3. INTRODUCTION

Knowledge of the course of major affective illness has clinical as well as theoretical importance. For the patient and clinician, estimations of the chances of recovery and the risk of recurrence are important in relation to the choice of acute and prophylactic treatment and in relation to the patient's potential plans for the future. From the theoretical point of view, longitudinal studies have had major implications during the last hundred years on the classification and understanding of psychiatric disorders. Regarding classification, *Kraepelin* (1921) was among the first to conduct systematic epidemiological studies within psychiatry and he based his dichotomy of schizophrenia and affective disorders on findings from these studies. Schizophrenia (Dementia praecox) was characterised by a gradually deteriorating course and affective disorder (Manisch-depressive Irresein) by recurrent affective episodes with periods of recovery. Many years later, *Robins and Guze* (1970) included "the longitudinal study" as one phase among the five phases they outlined for the diagnostic validation

of psychiatric illness. With regard to the understanding of psychiatric disorders, longitudinal studies may help to cast light on the pathophysiology of the disorders. Psychiatric illness may develop in the interplay between biological, psychological and social factors (*Engel*, 1977, 1997; *Goldberg and Huxley*, 1992). This may also be the case for major depression (unipolar affective disorder) and bipolar affective disorder. In this interplay, an essential question in the understanding of the pathophysiology of affective disorder is whether the individual is changed biologically by experiencing an affective episode or not. A biological change may be reflected in a changed risk of experiencing new episodes and changed chances of recovery from these episodes for the individual, and may possibly also be reflected in persisting cognitive dysfunction as an expression of brain function affected during a longer period. The present thesis focuses on the pattern of recovery and recurrence of episodes and the cognitive function during recovery.
The major aims of the thesis were to answer the following questions:

1. Does the risk of recurrence change during the course of illness in unipolar and bipolar affective disorder?
2. How do socio-demographic and illness-related variables affect the risk of recurrence during the course of unipolar and bipolar affective disorder?
3. Does the probability of recovery change during the course of illness in unipolar and bipolar affective disorder?
4. How do socio-demographic and illness-related variables affect the probability of recovery during the course of unipolar and bipolar affective disorder?
5. Is cognitive impairment or dementia related to affective disorder and does the impairment worsen with the number and frequency of affective episodes?

The thesis consists of reviews of the literature dealing with these five questions including results from the corresponding studies by the author designed to answer the questions - and subsequent discussions. Some other issues related to these five questions or to the course and outcome of affective disorders will be commented upon but not discussed in detail. Finally, clinical and theoretical implications and proposals for future research will be suggested.
The studies by the author were case register studies using data from the Danish Psychiatric Central Register supplemented with follow-up studies of subpopulations of patients selected from the register.
As the intention was to combine reviews of several research areas within affective disorder an extensive presentation has been necessary. The presentation will be divided into the following main-sections:

- a review of prior studies of recurrence during the course of affective disorder.
- a presentation of the design and results of studies of recurrence by the author followed by a discussion of the methodological advantages and disadvantages in relation to prior studies.
- a review of prior studies of recovery during the course of affective disorder and a discussion of methodological issues.
- a presentation of results of studies of recovery by the author.
- a review of prior studies of cognitive impairment and dementia in affective disorder and a discussion of methodological issues.
- a presentation of the design and results of studies of cognitive impairment and dementia in affective disorder by the author.
- overall conclusion, implications, and proposal for future research.

In 1921, *Kraepelin* (1921) described the heterogeneity of the course of affective disorders and later *Rennie* (1942) stated that "So many variations occur in the number of attacks, the length of attacks and the duration between attacks that it is impossible statistically to give any comprehensive statement of the course." Nevertheless, many studies have been devoted to describing the long-term course of affective disorder. The long-term course of illness can, in principle, be described by four components: the duration of episodes of illness, the severity of these episodes, the duration of intervals between episodes of illness, and the presence of psychiatric symptomatology during these intervals. In the following, reviews of studies concerning these issues are presented beginning with a review of changes in recurrence, followed by a review of changes in recovery and a short review of changes in the severity of episodes during the course of affective disorder. With regard to symptomatology in the periods between episodes, focus will be on the cognitive component of this symptomatology, which will be reviewed at the end of the thesis.

4. RECURRENCE DURING THE COURSE OF MAJOR AFFECTIVE DISORDER

4.1 A REVIEW OF THE LITERATURE.

Most of the studies published in the literature have only dealt scantly with the question of the changes in the risk of recurrence during the course of affective disorder. Only studies by *Kessing* (paper no. 2: *Kessing*, 1998c; paper no. 5, 6: *Kessing*, 1999a,b) and *Kessing and colleagues* (paper no. 1, 3, 7, 8: *Kessing et al*., 1998a,b,c,d; paper no. 4: *Kessing and Andersen*, 1999; paper no. 9: *Kessing et al*., 1999a) have specifically focused on the relation between recurrence and the episode number. Furthermore, it should be emphasised that the majority of studies included in the following review do not discriminate between relapse and recurrence.
Kraepelin (1921) was the first to conduct a longitudinal study of manic-depressive patients. During the last part of the 1800 century he followed prospectively 899 manic-depressive patients consecutively admitted to the University Psychiatric Clinic in Munich. He found that the free interval between episodes decreased with every new episode for patients with depressive or manic episodes exclusively, and for patients with combinations of depressive and manic episodes. Several studies, but not all, have subsequently replicated his original finding (Table 1). Some important studies will be further mentioned. Early retrospective studies from USA by *Swift* (1907) and *Mac Donald* (1918) replicated the finding. However, *Lewis* (1936) did not find that the intervals grew shorter with the number of episodes in a small sample of admitted depressive patients followed up to eight years. The study of *Slater* (1938) was the first study in which the length of intervals was analysed separately for groups of patients with different numbers of episodes. In this study of 105 manic-depressive patients, there was a tendency for the first interval to be the longest but there was no significant pattern of decrease or increase in the length of subsequent intervals (for details see p. 57). *Lundquist* (1945) noted that the interval between the first and the second interval

Table 1. *Studies with analyses of the relation between time to recurrence and number of episodes in affective disorder.*

Reference	Year	N	Observation period (years)	Survival analysis	Deteriorating course
Unipolar					
Swift	1907	12	up to 28	–	+
MacDonald	1918	100	not recorded	–	+
*Kraepelin**	1921	167	up to 44	–	+
Lewis	1936	61	up to 8	–	–
Watts	1956	529	up to 10	–	+
Perris	1966	200	2	–	–
*Van Scheyen**	1973	84	4-7	–	+
Grof	1973	594	up to 50	–	+
Taschev	1973	469	not recorded	–	+
Kolakowska	1975	60	1-6	–	+
Zis	1980	229	not recorded	–	+
*Angst**	1981	159	16	–	+
*Keller**	1982	52	1	+	+
*Keller**	1983a	141	1	+	+
Fukuda	1983	284	12	–	–
Gonzales	1985	113	1-3	–	+
Faravelli	1986	101	1	–	–
Kiloh	1988	145	15	–	+
Lee	1988	89	19	+	+
Lewinsohn	1988	1,130	70	+	+
*Coryell**	1991	396	6	–	–
*Maj**	1992	72	1.6 - 9.0	+	+
*Winokur**	1993	172	5	–	+
*Lavori**	1994	431	5	+	+
*Goldberg**	1995a	42	4.5	–	–
*Ramana**	1995	70	1.3	–	–
Kessing	1996	60	10+	–	+
*Flint**	1997	84	2	+	–
Kessing (no. 1)	1998	17,447	0-23	+	+
*Mueller**	1999	380	15	+	+
Bipolar					
Swift	1907	25	up to 28	–	+
MacDonald	1918	195	not recorded	–	+
*Kraepelin**	1921	238	up to 44	–	+
Perris	1966	97	2	–	–
Saran	1969	51	4	–	–
Grof	1973	393	up to 50	–	+
Taschev	1973	160	not recorded	–	+
*Winokur**	1975	30	2-20	–	–
Zis	1980	105	not recorded	–	+
*Angst**	1981	95	16	–	+
Fukuda	1983	100	12	–	–
Roy-Byrne	1985	46	not recorded	–	+
*Tohen**	1990	75	4	+	–
*Winokur**	1993	148	5	–	–
*Winokur**	1994	131	10	–	–
*Goldberg**	1995a	42	4.5	–	+
*Goldberg**	1995b	51	4.5	–	–
*Gitlin**	1995	82	4.3	+	+
Kessing (no. 1)	1998	2,903	0-23	+	+
Mixed sample					
Paskind	1930	633	up to 40	–	+
Slater	1938	105	not recorded	–	–
Lundquist	1945	319	up to 30	–	+
Bratfos	1968	207	6 on average	–	–
Lehman	1988	110	11	–	–
Berghöfer	1996	30	8.2 on average	–	–
*Van Londen**	1998a	56	3-5	+	+

Deteriorating course: decreasing time to recurrence with the number of episodes.
*) Recurrence assessed prospectively following patient's entry into the study.

was longer than between the following ones for older manic-depressive patients but that the intervals varied irregularly for younger patients. *Perris and d'Elia* (1966) did not find any association between the number of prior episodes and the risk of recurrence during a two-year follow-up of Swedish unipolar or bipolar patients. Similarly, *Bratfos and Haug* (1968) found no clear decrease in the length of intervals between episodes during the illness in a Norwegian sample. In contrast, *Groff et al*. (1973), *Angst et al*. (1973) and *Zis et al*. (1980) reported a progressive course of episodes from an international co-operative study including patients from Switzerland, Canada, Czechoslovakia, Denmark and Germany. Also *Taschev* (1973), who studied the course of depressive patients after their death in order to avoid incomplete follow-up, found a progressive course of episodes.

The Iowa 500 study was the first prospective study to include a systematic evaluation of the course and the use of operational diagnostic criteria (the Feighner criteria (*Feighner et al*., 1972). Unfortunately, the study does not deal thoroughly with the issue of recurrence during the course of illness. Nevertheless, *Winokur* (1975) reported from the study that a group of 30 bipolar patients who had episodes prior to an index admission were less likely to have episodes during 2-20 years of follow-up. This finding is in accordance with the finding in a study from *Saran* (1969). The data suggested that a group of bipolar patients suffer from a flurry of episodes which will then die out in the course of time and *Winokur* argued that "the bipolar process is one that "burns out" after a period of time."

Angst (1981) presented data from a large study in which episodes were assessed prospectively during 16 years from entry into the study. All patients diagnosed with affective psychosis (ICD-8, code 296) on hospital admissions to a psychiatric university clinic in Zurich during 1959 to 1963 were assessed three times at five-year intervals by telephone interview and by a letter to the doctors who were in charge of the patient. The prospective design made it possible to include milder depressive and hypomanic episodes. In further contrast to most earlier studies, which analysed the length of time from one episode to the other, calculations were based on the length of cycles. A cycle, defined as the time from the onset of an episode to the onset of the next episode, was recommended as it was argued that it is more reliable to assess the onset of an episode than the end, because of the suppression of symptoms in an episode by modern treatment. *Angst* (1981) found that the cycles became shorter and shorter during the course of unipolar and bipolar illness.

In subsequent studies with retrospective assessment of all episodes, a deteriorating course was found by *Gonzales et al*. (1985), *Lee and Murray* (1988) and *Kiloh et al*. (1988) but not by *Fukuda et al*. (1983), *Faravelli et al*. (1986) and *Lehman et al.* ((1988), Table 1).

The investigators from the National Institute of Mental Health (NIMH) - Clinical Research Branch Collaboratory Program on the Psychobiology of Depression, were the first to define diagnoses and episodes of illness according to standardised research diagnostic criteria (with the Schedule of Affective Disorders and Schizophrenia - Lifetime version (SADS-L, *Endicott and Spitzer*, 1978), the Longitudinal Interval Follow-up Evaluation (LIFE, *Keller et al*., 1987) and with the Research Diagnostic Criteria (RDC, *Spitzer et al*., 1985)). Recovery was defined as eight consecutive weeks with no more than one or two mild affective symptoms and recurrence was defined as re-occurrence of a full syndrome of mania or depression (according to RDC) following recovery. In- and out-patients from public and private psychiatric units in Boston, Chicago, Iowa City, New York and St Louis have been followed prospectively with evaluations performed every six months for the first five years and annually thereafter for now a total of 15 years.

The findings vary with the type of disorder and partly with the length of follow-up. For unipolar patients, the number of episodes prior to the entry into the study predicted a significantly increased risk of recurrence at the one-year follow-up (*Keller et al*., 1982, 1983a), the five-year follow-up, at which more patients were enrolled into the study (*Winokur et al*., 1993; *Lavori et al*.,

1994) and at the 15-year follow-up (*Mueller et al*., 1999). For bipolar patients, a decreasing length of intervals was found with every retrospectively assessed episode in an early report (*Roy-Byrne et al*., 1985) whereas no effect of prior episodes was found at the prospective five-year follow-up (*Winokur et al*., 1993) and cycles showed no systematic decrease in length during the ten-year follow-up (*Winokur et al*., 1994).
A recent prospective study by *Maj et al*. (1992) also found a progressive course of episodes in unipolar disorder, but a 4.5-year *(Goldberg et al*., 1995a), a 1-year (*Ramana et al*., 1995) and a 2-year (*Flint and Rifat*, 1997) prospective study did not. Similarly, in recent studies of bipolar disorder, a deteriorating pattern was reported in a 4.5-year prospective study from *Goldberg et al.* (1995a) but not in another (*Goldberg et al*., 1995b) and in a 4.3-year prospective study by *Gitlin et al*. (1995) but not in a 4-year prospective study by *Tohen et al*. (1990).
All the studies mentioned so far concern patients allocated from psychiatric hospitals or clinics. The NIMH studies also included studies of a nonclinical population of subjects who consisted of a mixed sample of first-degree relatives and spouses of patients included in the clinical studies, and of community comparison subjects (*Coryell et al*., 1991). The subjects had a history of depression(s) but were not depressed at the initial evaluation and were recontacted six years after the initial evaluation.
All together, analyses of recurrence have been computed in four studies of extramural samples. These studies have also given divergent results. *Paskind* (1930) and *Watts* (1956) found a decreasing length of intervals in studies of patients from a private psychiatric practice and a general practice, respectively. These findings were replicated in a community sample study (*Lewinsohn et al*., 1989) but not in the NIMH study of nonclinical subjects: among patients with primary major depressive disorder, subjects with multiple prior episodes did not have more episodes during the six-year follow-up than subjects with one prior episode (*Coryel et al*., 1991).
Finally, two case register studies have investigated changes in the rate of readmission with calendar time. *Symonds and Williams* (1981) illustrated that the rate of psychiatric readmissions with mania increased in England during a five-year period. Similarly, *Dickson and Kendell* (1986) found, with the use of the Edingburgh Psychiatric Case Register, that the rate of psychiatric readmissions with a diagnosis of depression and with a diagnosis of mania increased steadily from 1970 to 1981. Although it was not directly analysed, the association between recurrence and calendar time might reflect that the risk of readmission increased with the number of prior admissions.
Previous reviews have dealt with the outcome in affective disorder in general and not focused specifically on the issue of recurrence in relation to the episode number. *Cutler and Post* (1982), the *NIMH Consensus Development Conference* (1985) and *Goodwin & Jamison* (1990) have stated that cycle length tends to get shorter with each recurrence in affective disorder. However, two recent general reviews of the outcome of affective disorder question the pattern of recurrence in bipolar patients (*Coryell and Winokur*, 1992; *Solomon et al*., 1995).
The present review focused specifically on the relation between the risk of recurrence and the episode number. It can be concluded from studies, excluding those by the author, that the majority found a deteriorating course of episodes in unipolar and bipolar affective disorder. Several important studies did not find any change in the interval between episodes (Table 1) and two studies of bipolar patients found an ameliorating course of episodes (*Saran*, 1969; *Winokur*, 1975). There are numerous sources of error that explain the inconsistent results and it will be illustrated later that, when these sources are taken into account, prior studies do not provide substantial evidence to draw conclusions about the effect of episodes on the risk of recurrence in unipolar and bipolar disorders.
In the following, a summary of the results by the author will be presented. Subsequently, reasons for discrepancies between studies in the literature will be discussed and the advantages and disadvantages of studies by the author compared with prior studies will be presented. Finally, the sum of indications of a progressive course of episodes in unipolar and in bipolar affective disorder will be discussed.

4.2 RECURRENCE DURING THE COURSE OF MAJOR AFFECTIVE DISORDER. STUDIES BY THE AUTHOR

In a series of studies, *Kessing* (paper no. 2: *Kessing*, 1998c; paper no. 5, 6: *Kessing*, 1999a,b) and *Kessing and colleagues* (paper no. 1, 3, 7, 8: *Kessing et al*., 1998a,b,c,d; paper no. 4: *Kessing and Andersen*, 1999; paper no. 9: *Kessing et al*., 1999a) investigated the risk of recurrence during the course of unipolar and bipolar disorders. These studies focused specifically on the change in the risk of recurrence and on the change in predictors of recurrence with every new affective episode. Focus was thus on the episode effect.
The studies used the Danish Psychiatric Central Register of admissions as a study base.

The Danish Psychiatric Central Register

The systematic sampling of data on patients admitted to Danish mental hospitals was initiated in 1938. The electronic part of the register commenced in 1969 and since then the register has been nation-wide with registration of all psychiatric admissions in Denmark for the 5.1 million inhabitants (*Munk-Jørgensen & Mortensen*, 1997). The International Classification of Diseases, 8th Revision (*National Board of Health*, Denmark, 1971) has been used in Denmark from April 1, 1969 to December 31, 1993.
All inhabitants in Denmark have a unique person identification number (Civil Person Registration number, CPR-number) that can be logically checked for errors, so it can be established with great certainty if a patient has been admitted previously, irrespective of changes in name etc. Data of death can also be established with equal certainty as the same identification number is used across all public registration systems.
Information on treatment intervention is not available.

The diagnosis of manic-depressive psychosis

The diagnosis of manic-depressive psychosis (code 296) in ICD-8 (*WHO*, 1967, 1974) encompasses six subdiagnoses. In the studies by *Kessing* (paper no. 2: *Kessing*, 1998c; paper no. 5, 6: *Kessing*, 1999a,b) and *Kessing and colleagues* (paper no. 1, 3, 7, 8: *Kessing et al*., 1998a,b,c,d; paper no. 4: *Kessing and Andersen*, 1999; paper no. 9: *Kessing et al*., 1999a) patients were divided into those with unipolar disorder and those with bipolar affective disorder on the basis of the subdiagnoses, in the same way as previously done in studies from the Danish Psychiatric Central Register by *Weeke* (1984) and *Weeke and Væth* (1986). Patients were classified as having unipolar affective disorder (= depressive disorder or non-bipolar disorder) if they at their first discharge ever from psychiatric hospital got a diagnosis of manic-depressive psychosis, typus depressivus (code 296.19) or a diagnosis of melancholia involutiones (code 296.09) and as long as they had not been discharged with a diagnosis of psychosis manio-depressiva, typus manicus (code 296.19) or typus circularis (code 296.39).

Patients were classified as having bipolar affective disorder from the time of a discharge with a diagnosis of psychosis manio-depressiva, typus manicus (code 296.19) or typus circularis (code 296.39).

Validity of the diagnosis of manic-depressive psychosis and other data from the Danish Psychiatric Central Register

The ICD-8 diagnoses of affective disorder recorded in the Danish Psychiatric Central Register has been validated in two different studies by the author. In the first study, the diagnostic accordance, within the register, was estimated between manic-depressive ICD-8 diagnoses made in 1993 and affective ICD-10 diagnoses made in 1994 according to the register (*Kessing*, 1998a). Totally, 1,487 patients got a main diagnosis of manic-depressive psychosis during 1993 and were re-admitted during 1994. The vast majority of patients (84.0 %) who got a manic-depressive diagnosis according to ICD-8 also got a diagnosis of affective disorder according to ICD-10. In the second study, a random sample of 100 patients with a diagnosis of manic-depressive psychosis on their first admission to a psychiatric ward were selected from the register (*Kessing*, 1998b). Case notes from all over Denmark were reviewed for all 100 patients and diagnoses were made with the use of OPCRIT (*McGuffin et al*., 1991). Patients who were still alive were contacted and interviewed face to face or by telephone. Totally, 95 out of the 100 patients got an ICD-10 diagnosis of affective disorder computed with OPCRIT and confirmed at the interviews. Classification into depressive disorder (= unipolar disorder) and bipolar disorder made on the basis of the presence of a manic/circular episode in the register was correct in 94 % of the cases when compared with ICD-10 diagnoses made on the basis of case notes and interviews. Psychotic symptoms with hallucinations, delusions or thought disorders in at least one affective episode were described in the case notes and often confirmed at interview for 34 % of the affective patients.

On average, the age at first admission seemed to reflect quite well onset of the first severe affective episode, and the number of admissions for which there was an interval of more than eight weeks of discharge to the next admission seemed, on average, to reflect the number of severe affective episodes in a reasonable

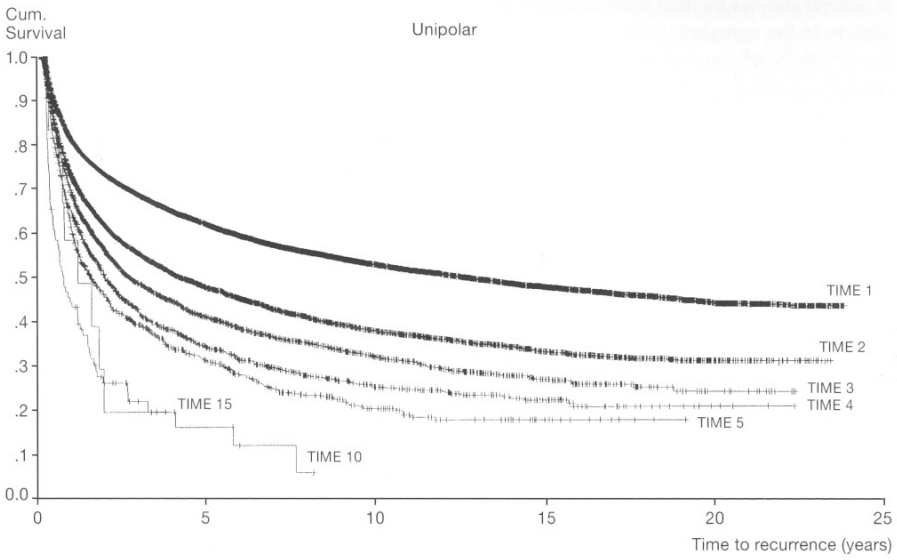


Fig. 1. *Recurrence at successive episodes in unipolar affective disorder (from* Kessing et al., *1998a. With permission from The British Journal of Psychiatry).*

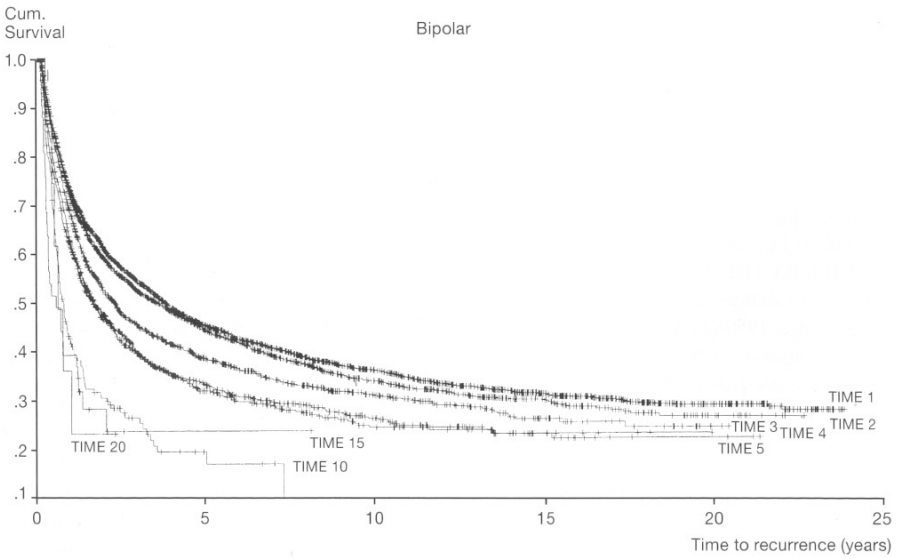


Fig. 2. *Recurrence at successive episodes in bipolar affective disorder (from* Kessing et al., *1998a. With permission from The British Journal of Psychiatry).*

way, as estimated from the case notes and the interviews (*Kessing*, 1998b; see 4.4 for more details and discussion).

Studies of recurrence

This part of the thesis is based on results published in:
paper no. 1: Kessing et al. (1998a)
paper no. 2: Kessing (1998c)
paper no. 3: Kessing et al. (1998b)

General introduction

The studies included all hospital admissions with primary affective disorder in Denmark during 1971-1993. Totally, 20,350 first-admission patients were discharged with a diagnosis of affective disorder. Among these, 17,447 patients presented with a depressive episode and 2,903 patients presented with a manic or circular episode. Throughout the studies, recurrence was defined as the appearance of a new episode according to *Frank et al*. (1991). Admission was taken as an expression of an affective episode. However, if readmission occurred within eight weeks of discharge, the admission periods of two admissions were added and counted as one episode so recurrence was defined as readmission, after having been discharged eight weeks. Data were analysed in a historical prospective way as survival analysis was used to estimate the rate of recurrence after successive episodes. Time to recurrence was censored if patients had their main diagnosis changed to organic psychosis (code 290-294) or schizophrenia (code 295) at later discharges, died, emigrated or had no more

The effect of episodes on recurrence

This part of the thesis is based on results published in:
paper no. 4: *Kessing and Andersen* (1999)

In this study, analyses of data were made in another way. Thus, the effect of the number of prior episodes on the rate of recurrence following the first discharge after 1984 was estimated. The rate of recurrence was on average 1.6 times greater for bipolar patients than for unipolar patients. Nevertheless, the effect of the number of episodes was greatest for unipolar patients. Thus, the rate of recurrence increased on average 15 % with every

Fig. 3. *Recurrence at successive episodes in unipolar affective disorder (including only episodes with affective diagnoses).*

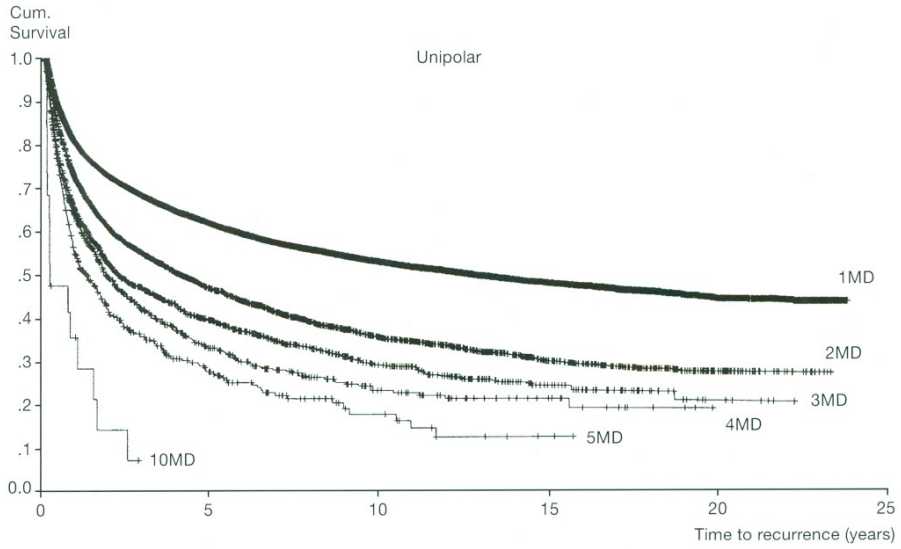
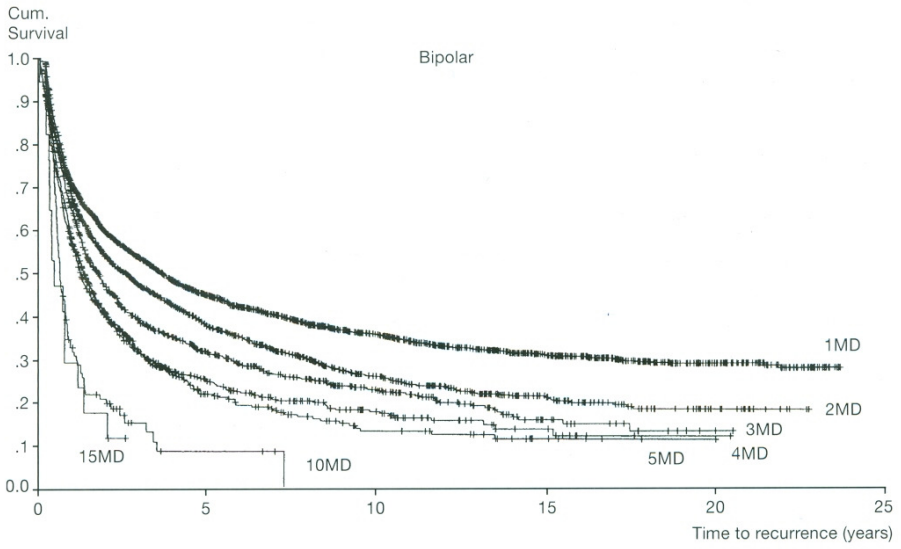


Fig. 4. *Recurrence at successive episodes in bipolar affective disorder (including only episodes with affective diagnoses).*



episode for unipolar patients and 9 % with every episode for bipolar patients, when adjusted for differences in age and gender. It was concluded that the risk of recurrence increases with every new episode in affective disorder and that the effect of episodes is greater for unipolar disorder than for bipolar disorder.

The effect of age and gender on recurrence
This part of the thesis is based on results published in:
paper no. 2: *Kessing* (1998c)
Analyses of the effect of gender on the risk of recurrence at successive episodes and adjusted for the effect of age (and calendar time) revealed that the effect was the same for unipolar and bipolar disorder. Female patients had greater risk of recurrence than male patients. Additionally, the effect was more pronounced at early episodes and declined at later episodes.
Analyses of the effect of age on the risk of recurrence at successive episodes and adjusted for differences in gender (and calendar time) showed that for unipolar men and for bipolar disorder in general, the risk of recurrence decreased with older age. For female unipolar patients, the risk of recurrence increased with older age after the first episode, while after later episodes, the risk of recurrence decreased with older age.
It was concluded that the episode number has to be taken into account when the effect of age, gender and type of disorder is estimated since the effect of age, gender and type of disorder changes with the number of episodes. Additionally, it was suggested that most studies probably include too few bipolar patients to demonstrate the relatively modest effect of gender. The findings need replication but may illustrate the complex effect of age and gender in affective disorder.

The effect of demographic variables and illness-related characteristics on recurrence
This part of the thesis is based on results published in:
paper no. 3: *Kessing et al*. (1998b)
Initially in the course of the illness, the type of disorder (unipolar / bipolar), gender, age and marital status together with the total duration of the illness predicted the risk of recurrence. Some variables had different predictive effect in the two types of illness. Later, especially the duration of the previous illness predicted the risk of recurrence.
It was concluded that initially in the course of affective disorder socio-demographic variables such as gender, age at onset and marital status act as risk factors for further recurrence. Later, however, the illness itself seems to follow its own rhythm regardless of prior predictors.

The effect of a manic episode on recurrence
This part of the thesis is based on results published in:
paper no. 5: *Kessing* (1999a)
Among the 17,447 patients who presented with depression on first admission, 762 patients presented with mania at later episodes (4.4 %).
For these 762 patients, younger age at onset was associated with increased risk of developing mania. Patients who had a late first manic episode (i.e. patients who have had a bipolar disorder for a short period) had the same rate of subsequent recurrence as patients with mania at first episode (i.e. patients who have had a bipolar disorder for a long period) and this rate was higher than the rate of recurrence for patients who remained depressive. Time since first manic episode had no importance in relation to the risk of subsequent recurrence.

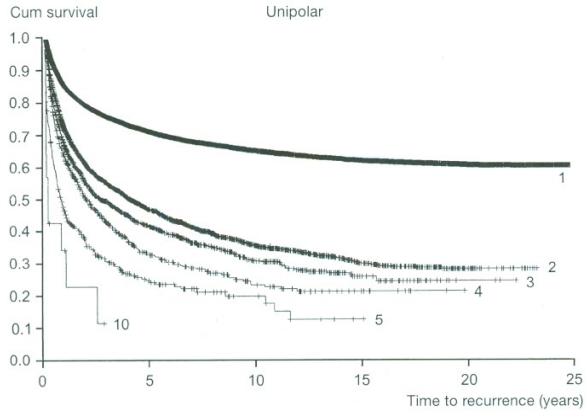


Fig. 5. *Recurrence at successive episodes in unipolar affective disorder (including only episodes with affective diagnoses and excluding known comorbidity).*

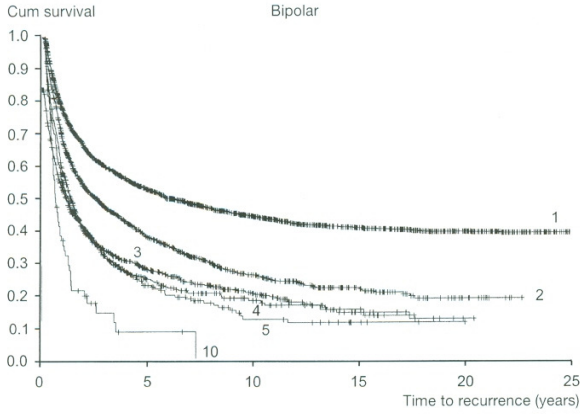


Fig. 6. *Recurrence at successive episodes in bipolar affective disorder (including only episodes with affective diagnoses and excluding known comorbidity).*

It was concluded that patients who present with depression and later develop mania carry the same risk of recurrence from onset as patients with initial bipolar disorder.

The effect of comorbid alcoholism on recurrence
This part of the thesis is based on results published in:
paper no. 6: *Kessing* (1999b)
Among the 20,350 patients included, 518 patients (2.6 %) had an auxiliary diagnosis of alcoholism. Patients with a current auxiliary diagnosis of alcoholism had increased rate of recurrence following the first three affective episodes but not following subsequent episodes compared with patients without auxiliary diagnoses. The effect of alcoholism declined with the number of episodes. In contrast, no effect was found of other auxiliary diagnoses on the rate of recurrence.
It was concluded that concurrent alcoholism increases the risk of recurrence of affective episodes during the initial course of unipolar and bipolar disorder but has no effect on recurrence later in the course of the illnesses. The study demonstrates the importance of taking the number of affective episodes into account in estimations of the effect of concurrent alcoholism on the risk of subsequent recurrence in affective disorder.

The effect of the individual frailty on recurrence
This part of the thesis is based on results published in:
paper no. 9: *Kessing et al*. (1999a)
In all previous studies, including the studies by *Kessing* (paper no. 2: *Kessing*, 1998c; paper no. 5, 6: *Kessing*, 1999a,b) and *Kessing and colleagues* (paper no. 1, 3, 7, 8: *Kessing et al*., 1998a,b,c,d; paper no. 4: *Kessing and Andersen*, 1999), estimation of recurrence has been affected by a selection. The statistical average course of the illness might have been dominated by the course of episodes of the most ill patients. That is, if patients with several episodes have a constant high risk of recurrence already from the first episode, these patients will increasingly affect the pattern with each subsequent episode because they will constitute a higher proportion of the remaining sample. Such a selection could explain nearly all the results which showed a progressive course of episodes (with two exceptions, see p. 59).
It is possible with the use of frailty models to take into account the individual liability to recurrence. The frailty reflects the individual degree of illness and thus contributes to the heterogeneity of the course of affective disorder. Re-analyses of data with such frailty models showed that for women with unipolar disorder (although less clear for older unipolar women) and for both women and men with bipolar disorder there was a substantial effect of episodes even when the effect of episodes was adjusted for the individual tendency toward recurrence. No effect of episodes but a large effect of the frailty parameter was found for unipolar men.
It was concluded that the risk of recurrence seems to increase with the number of episodes in bipolar affective disorder in general and for women with unipolar disorder. For unipolar men, no effect of episodes was found when the effect was adjusted for the frailty. The progressive course demonstrated for unipolar men in the study by *Kessing* (paper no. 2: 1998c) thus mainly seemed to be due to the frailty effect. Among unipolar men, some patients with many episodes demonstrated a high risk of recurrence already from the first episode and these frail patients (with a high frailty parameter) affected the analyses so a general progressive course was found.

Clinical consequences of recurrence
This part of the thesis is based on results published in:
paper no. 7: *Kessing et al*. (1998c)
paper no. 8: *Kessing et al*. (1998d)
The observation of progressive recurrence in affective disorder has been interpreted as a process of sensitisation. The clinical applicability of such a theoretical model was investigated using the Danish case register. The studies included 8,737 patients admitted to a psychiatric hospital at least twice.
Measures describing the initial course of admission episodes were defined in three different ways: 1) a short period between initial episodes 2) decreasing intervals between initial episodes or 3) a combination of 1) and 2).
Socio-demographic variables such as gender, age at onset and marital status differentiated between the three types of measures and the measures also demonstrated different effects in predicting the risk of further recurrence. In unipolar disorder, patients with a decreasing interval between episodes had the greatest risk of further recurrence, whereas for bipolar patients, a short period between episodes played a more important role than the sequence of episodes in itself.
The predictive effect of these measures of the initial course of episodes was investigated in relation to the subsequent risk of alcoholism, dementia, death and suicidal attempts / suicide.
A short period between initial episodes of the illness, reflecting a great intensity of illness, predicted increased risk of subsequent development of dementia, and for unipolar patients, decreased risk of subsequent alcoholism. A progressive course, with decreasing intervals between initial episodes of the illness, had no predictive effect. Similarly, no predictive effects on the risk of death or suicidal acts could be demonstrated with any measure of the initial course of episodes.

4.3 SOURCES FOR DISCREPANCIES BETWEEN STUDIES
The discrepancies between the studies in the estimated risk of recurrence and in the effect of predictors of recurrence may be explained by the inclusion of different patient populations, different study designs and by different ways of handling data in the studies. In the following, sources for the variance in the results will be reviewed with special emphasis on the studies by the author. "Studies by *Kessing*" without further specification refer to paper no. 2: *Kessing*, 1998 and paper no. 5, 6: *Kessing*, 1999a,b. "Studies by *Kessing and colleagues*" without further specification refer to paper no. 1, 3, 7, 8: *Kessing et al*., 1998a,b,c,d; paper no. 4: *Kessing and Andersen*, 1999 and paper no. 9: *Kessing et al*., 1999a.

Population
Selection bias
Studies in the literature present a selected picture of recurrence in affective disorder. First, all but two studies (*Lewinsohn et al*., 1989; *Coryell et al*., 1991) include only patients who sought treatment for active illness. However, most subjects with affective disorder do not seek or receive treatment (*Weisssmann et al*., 1981; *Bucholz and Dinwiddie*, 1989; *Dew et al*., 1988, 1991; *Lépine et al*., 1997; *Munk-Jørgensen et al*., 1997) and those who do are probably suffering from the more severe forms of disorder (*Dew et al*., 1988, 1991; *Coryell et al*., 1991, 1995). Second, patients were selected within specialised university centres (except in the studies by *Paskind* (1930) and *Watts* (1956), the two studies mentioned above and the studies by *Kessing* and *Kessing and colleagues* to which the more severe seriously ill patients and unusual cases are likely to be referred. All studies from university centres have included patients on the basis of consecutive admissions or treatment contacts and such patients will constitute, as described by *Cohen and Cohen* (1984), a sample of the more chronically ill patients who are admitted for long periods of time or who are repeatedly referred to psychiatric treatment. This sampling due to selective survival and chronicity increases the chances of finding a progressive course of episodes. Sampling due to selective survival and chronicity was avoided only in the studies by *Kessing* and *Kessing and colleagues* since in these studies, all first-admission patients who were discharged from all psychiatric departments in Denmark with a diagnosis of affective disorder during 23 years were included. Nevertheless, because of the study design, only episodes that led to hospitalisation were included in the study.
Third, all retrospective studies (except the study by *Taschev* (1973) and the studies by *Kessing* and *Kessing and colleagues* have analysed the course of episodes for living patients only, not including the course for patients who died during follow-up. Although suicide and suicidal acts have not been found to be increased in patients with a progressive course of episodes (*Kessing et al*., 1998d), a potential risk of underestimation of the rate of recurrence is implied when the course of dead patients is not included in the analyses.

Type of affective disorder
Bipolar I patients (i.e. patients with at least one manic episode) have in general been found to develop more episodes than unipolar patients (*Lundquist*, 1945; *Angst*, 1981; *Wolpert et al*., 1990; *Winokur et al*., 1993; *Kessing et al*., 1998ab). Thus, overall estimates of the rate of recurrence in a mixed (unipolar and bipolar) patient sample will vary as a function of the number of bipolar patients included (*Zis and Goodwin*, 1979). Similarly, as the risk of recurrence for bipolar II patients (i.e. patients with at least one hypomanic episode and without mania) is probably greater than the risk for unipolar patients (*Coryell et al*., 1989) estimations of the rate of recurrence are affected by the proportion of bipolar II patients included in the study. In the same way, the proportion of unipolar patients with depressive endogenous symptoms included in the study may affect the risk of recurrence, although a recent review found that the endogenous subtype was associated with increased risk of recurrence only in two out of the four studies dealing with the issue (*O'Leary*, 1996). The presence of psychotic features and a family history of affective disorder may also influence the course of illness (*Solomon et al*., 1992; *Winokur et al*., 1994; *Coryell et al*., 1996; *Flint and Rifat*, 1998). Finally, the inclusion or exclusion of patients with affective disorder secondary to other psychiatric illness may affect results. *Coryell et al*. (1991) found that the risk of recurrence increased with the number of prior episodes in patients with secondary affective disorder but not in patients with primary affective disorder.
In the studies by *Kessing* and *Kessing and colleagues* the risk of recurrence was estimated for patients with primary unipolar and bipolar disorder, separately.

Information bias
A potential source of bias in all prior studies is loss to follow-up due to simple drop-out of the study or to incomplete registration of death or migration. The effect of drop-out is difficult to estimate whereas incomplete registration of death and migration implies an underestimation of the risk of recurrence (*Mortensen*, 1995). It is thus most likely that loss to follow-up decreases the chances of finding a true progressive course of episodes. Most studies of recurrence in affective disorder do not present information about the proportion of patients who were lost during follow-up. Loss to follow-up has been found to vary from 19 % (*Angst*, 1981) to 26 % of the included patients (*Coryell*, 1991). In contrast, loss to follow-up was negligible in the studies by *Kessing* and *Kessing and colleagues* since the Danish case register covers all Danish treatment institutions and since registration of death and migration is virtually complete in Denmark (*Mortensen*, 1995).

Recall bias
The ideal of a purely prospective study is difficult to realise, as mentioned by *Angst* (1981), since in many instances patients have already suffered from several episodes before seeking treatment. In all the reviewed studies, the number of episodes that patients might have had before entry into the study was estimated retrospectively, often on the basis of information from interviews with patients and relatives. The validity of this retrospective information is dependent on the memory and the willingness of subjects to report memories. The reliability of the remembered number of episodes seems to be low (*Bromet et al*., 1986) and the recall of whether previous major affective episodes have occurred or not is quite unstable (*Bromet et al*., 1986; *Rice et al*., 1992; *Kendler et al*., 1993). Moreover, patients who are depressed at the index episode have been found to be more likely to report prior depressive episodes than patients in a phase between episodes (*Lewinsohn et al*., 1989). This implies a serious potential bias in the reviewed studies since patients were included into the studies on the basis of a current depressed (or manic) episode. The finding that the risk of recurrence increased with the number of prior episodes might thus be a result of this potential recall bias. This possibility is supported by the negative association found between the number of prior episodes and the risk of recurrence in the only study that included patients when they were in a phase between episodes (*Coryell et al*., 1991).
The studies by *Kessing* and *Kessing and colleagues* are unique in this way, since the dates of admission and discharge from hospitals were used to estimate recurrence of episodes. These "hard data" were collected routinely and independently of the study as a part of the official Danish health survey. The number and times of episodes are thus not affected by recall bias.

Confounders
Age and gender
Confounding may be caused by age-at-onset and by gender in estimations of recurrence during the course of illness in affective disorder, since the distribution of age and gender among patients changes with the number of episodes, and since the effect of age and gender on the risk of recurrence might also change with the number of episodes. The study by *Kessing* (1998c) investigated, as the only study, the rate of recurrence during the course of illness in different age and gender populations of patients with affective disorder.
Prior studies of the effect of age and gender on the risk of recurrence in affective disorder were also reviewed. It was concluded that in the majority of studies, female gender has been found to be associated with recurrence in unipolar disorder while no effect of gender has been found in bipolar disorder. The effect of age-at-onset was less clear. In both unipolar and bipolar disorder, younger age-at-onset and older age-at-onset have been shown to increase the risk of recurrence, while other studies have found no association at all.
Only *Kessing* (1998c) took the episode number into account in estimations of the effect of age, gender and type of disorder. The effect of gender and type of disorder on the risk of recurrence was found to decrease with the number of affective episodes while no persistent change was found in the effect of age-at-onset during the course of illness. In general, it is clear that the effect of predictors of recurrence depends on how many prior affective episodes the subjects in the sample have had.

Marital status
Marital status may confound results of recurrence during the course of illness in affective disorder since marital status changes with the number of episodes, and since the effect of marital status on the risk of recurrence may also change with the number of episodes (*Kessing et al*., 1998a).
Marital status has been found to be associated with recurrence in many epidemiological studies (*Winokur and Kadrmas*, 1988; *Sytema*, 1991; *Coryell et al*., 1991; *Mueller et al*., 1999) but not in all (*Keller et al*., 1983a). Thus, *Goodwin and Jamison* (1990, p. 175 - 176) concluded in a minor review that "it is plausible that being single or divorced does, in some populations, constitute a risk for bipolar illness" whereas *Angst* (1992) and *Kupfer and Frank* (1992) have concluded that marital status (together with many other socio-demographic variables) does not predict relapse or recurrence. *Kessing et al*. (1998b) found that unipolar and bipolar patients who had never been married had a greater risk of recur-

rence following the first hospitalised episode but not following subsequent episodes. Similarly, getting divorced or separated predicted increased risk of recurrence following the first episode whereas this event had no predictive effect on recurrence later during the course of illness. These findings emphasise the importance of taking the episode number into account in estimations of the effect of marital status (and probably also of other psychosocial events) on the risk of recurrence. Failure to account for previous affective episodes may be a major reason for discrepancies in results among studies of the effect of stressful life events on affective disorder. The results from the study by *Kessing* (1998c) and *Kessing et al*. (1998b) strongly support the conclusion in a major recent review by *Kessler* (1997) that "future work on the risk factors for depressive episodes needs to look separately at the predictors of onset and recurrence."

Comorbid alcoholism

Comorbid alcoholism may also confound results of recurrence during the course of illness in affective disorder since the frequency of comorbid alcoholism may change with the number of episodes, and since the effect of comorbid alcoholism on the risk of recurrence also may change with the number of episodes (Kessing, 1999b). Estimations of the risk of recurrence at successive episodes including only episodes with affective diagnoses and excluding known comorbidity (such as alcoholism) replicated the finding of a progressive course of episodes in unipolar and bipolar affective disorder (Figure 5 and 6).

Studies of the effect of comorbid alcoholism on the risk of recurrence have given contradictory results (see Kessing, 1999b) and a major reason seems to be that the number of episodes was not taken into account (Kessing, 1999b). According to the results from the study by Kessing (1999b) concurrent alcoholism increases the risk of recurrence of affective episodes during the initial course of unipolar and bipolar disorder but concurrent alcoholism has no effect on recurrence later in the course of the illnesses.

Other confounders

Other potential confounders of the effect of episodes and other predictors on the risk of recurrence, such as social class, school education, professional education, intelligence, race, etc., have not been systematically investigated in any study. It was not possible to adjust for these variables in the studies by *Kessing* and *Kessing and colleagues* since data on these variables are not available in the Danish Psychiatric Central Register. However, as stated by *Angst* (1992), *Kupfer and Frank* (1992) and *Mueller and Leon* (1996), studies have failed to demonstrate significant associations between relapse / recurrence and most of these variables.

The effect of comorbidity, such as anxiety disorders, personality disorders, physical disorders and substance abuse, on the risk of recurrence in affective disorders is poorly investigated. *Coryell et al*. (1991) found that depressive patients with comorbid alcoholism, phobic disorder or drug use disorder had increased risk of recurrence compared with patients with primary depression only, whereas no effect was found of comorbid panic disorder. *Kessing* (1999b) found that, except for comorbid alcoholism, comorbidity in general did not increase the risk of recurrence during the course of unipolar and bipolar affective disorder. The general finding seems to be that most comorbidity affects outcome (*Angst*, 1992, p. 9; *Merikangas et al*., 1996), such as rates of recovery / chronicity (*Weisssman et al*., 1978; *Hinrichsen and Hernandez*, 1993), disability (*Sartorius et al*., 1996) and suicidality (*Bronisch and Wittchen*, 1994), rather than recurrence.

Study design

All the reviewed studies had a "naturalistic" approach, i.e., patients may have received treatment and the treatment was at the discretion of the responsible clinician and not directed by the researcher.

Studies with prospective assessment of time to recurrence have the obvious advantage of a lower risk of missing mild to moderate episodes that patients might not notice, cannot remember or do not report, and consequently these may not be recorded by the researcher (*Haghighat*, 1996). Prospective assessment of data also has the advantage of allowing the use of standardised diagnostic criteria on new episodes and a more precise record of the date of start and end of episodes, and the duration and modality of any treatment used, as further described by *Haghighat* (1996). On the other hand, every prospective design includes the disadvantage of interfering with the longitudinal course of the illness. The researcher's repeated contacts with participants during several years of follow-up may affect the participants' attitude toward the illness and the treatment and thereby change compliance. Remitting questions about affective symptoms during longitudinally repeated mood ratings could increase the patients' recognition of early symptoms of recurrence of affective episodes resulting in early contact with the clinician responsible for treatment. Finally, the repeated contacts in themselves with the researcher, a professional health person, may stabilise the participants (*Esparon et al*., 1986). The finding that the course of episodes did not deteriorate in the 10-year prospective NIMH study of bipolar patients (*Winokur et al*., 1994) and in other studies with prospective assessment of recurrence (see Table 1) may eventually illustrate the influence of this long-lasting contact between researcher and patient.

Case registers present a way in which researchers can avoid any kind of contact or interference with the patient's life and course of illness. Thus, e.g. data from the Danish psychiatric case register are collected routinely and independently of researchers.

Number of subjects and duration of observation

Precision or statistical power is a central issue in every epidemiological study. The statistical power in studies of a predictor of outcome is affected by the sample size, the duration of observation and the magnitude of the relative risk associated with the predictor. As can be seen from Table 1, small sample size and short duration of observation suggest a small statistical power in several studies of recurrence. A small statistical power may explain some of the variability in studies of the effect of episodes (Table 1) and other predictors but not all the variability, since also studies with greater statistical power have different results. One of the major advantages in case register studies is the great precision which makes it possible to detect small effects of predictors (*Mortensen*, 1995). For example in the study by *Kessing* (1998c), female gender was associated with a 9 % (95 % CI: 5 - 14 %) to 13 % (95 % CI: 7 -20 %) increased risk of recurrence at initial episodes of bipolar affective disorder and it was concluded that most studies probably include too few bipolar patients to demonstrate this relatively modest effect of gender.

The effect of treatment on the course of episodes

As can be seen from Table 1, the majority of studies conducted before the introduction of ECT in the 1940s and antidepressants, lithium and neuroleptics during the 1950s found a progressive course of episodes.

All reviewed studies had a "naturalistic" approach, i.e., patients may have received treatment and the treatment was at the dis-

cretion of the responsible clinician and not directed by experimental protocol. It is not clear how treatment modifies the natural course of the illness in clinical practice. In the NIMH study, no association was found between treatment time or intensity (as indicated on a five-point scale) and mean cycle length in the ten-years of follow-up of bipolar patients (*Winokur et al*., 1994) or between treatment and the risk of recurrence in the 15-years follow-up of unipolar patients (*Mueller et al*., 1999). Thus, it appeared that treatment did not affect cycle lengths or the risk of recurrence. *Coryell et al*. (1991) found that the receipt of treatment was associated with significantly longer episodes and *Gitlin et al.* (1995) that treatment tended to be associated with increased risk of recurrence. These seeming paradoxes may be due to confounding of prognostic factors and treatment effects, as patients with more severe illness may be more prone to seek treatment than less ill patients (*Lavori et al*., 1994; *Mueller and Leon*, 1996). Or as expressed by *Keller et al*. (1983b), in naturalistic studies, "treatment itself becomes an outcome, because patient's state [is] likely to help determine the choice of treatment". In the studies *Kessing* and *Kessing and colleagues* it is not known whether patients were in treatment or not between episodes. However, in Denmark, patients with affective disorder who have had contact with a psychiatric hospital during the last decades have been widely exposed to medical treatment. In any case, possible treatment did not prevent a progressive course of episodes in unipolar or bipolar disorder.

Lithium

Randomised controlled trials

A review of the ten major double-blind studies comparing lithium prophylaxis of relapse / recurrence with placebo in bipolar patients concluded that the prophylactic effect of lithium is incontrovertible (*Goodwin and Jamison*, 1990, p. 686 - 687). This conclusion was later supported by other reviewers (*Guscott and Taylor*, 1994) but has recently been questioned for two main reasons (*Moncrieff*, 1997). The number of included patients in the studies was very low (from 6 to 52 patients) with one exception (*Prien et al*., 1973) and several of these studies used a discontinuation design that could increase the frequency of recurrence in the placebo group (see below).

Naturalistic studies

Several naturalistic studies have found a poor to modest effect of lithium prophylaxis on the risk of relapse / recurrence in affective disorder (*Marker and Mander*, 1989; *Aagaard and Vestergaard*, 1990; *Harrow et al*., 1990; *Koukopoulos et al*., 1995; *Maj et al*., 1998). As outlined by *Guscott and Taylor* (1994), a number of factors could explain the modest effectiveness of prophylactic treatment: 1) diagnostic shift to a non-affective disorder 2) tertiary-care (university hospital) referral bias resulting in selection of patients with a relatively poor response to conventional treatment 3) intermittent compliance causing relapse / recurrence, rebound manic episodes or lithium resistance (see below) 4) a change in the nature of the disorders toward increasingly recurrent and lithium-resistant illnesses (*Post*, 1986) 5) antidepressants inducing mania and cycle acceleration (*Goodwin and Jamison*, 1990 p. 586; *Altshuler et al*., 1995).

Among these factors, compliance by patient and provider is regarded as the most important by several authors (*Goodwin and Jamison*, 1990 p. 719; *Schou*, 1993; *Guscott and Taylor*, 1994; *Haywood et al*., 1995). The drop-out rate has been found to vary between 18 % and 66 % during the first years of lithium treatment (*Vestergaard and Schou*, 1988; *Maarbjerg et al*., 1988; *Guscott and Taylor*, 1994; *Berghöfer et al*., 1996; *Maj et al*., 1998; see also review by *Goodwin and Jamison*, 1990, p.752). Beyond the evident increasing risk of relapse / recurrence related to non-compliance itself, two other issues that are connected to non-compliance may affect the course of episodes. Firstly, sudden discontinuation of lithium may increase the risk of developing mania to a degree that exceeds what could be expected from the natural history of the illness (a kind of rebound phenomenon, *Suppes et al*., 1991; *Faedda et al*., 1993; *Baldessarini*, 1996). Secondly, reinstitution of lithium prophylaxis after discontinuation may be associated with nonresponse (*Post et al*., 1992; *Maj et al*., 1995).

It is basically not known how lithiumtherapy influences possible subsequent episodes. *Goodwin and Jamison* (1990, p. 690) have argued that the most consistent finding in the literature is that lithium is associated with a decrease in the intensity of subsequent episodes and that this decrease in intensity decreases both the estimated duration of episodes and the estimated frequency of episodes. This suggestion, however, conflicts with the finding that the severity of episodes increased during the course of illness in patients in prophylactic treatment with lithium and/or antidepressants (and in untreated patients) despite the observation that the risk of recurrence was lower among patients receiving prophylaxis (*Maj et al*., 1992).

It is not clear whether treatment with lithium can stop or weaken a potential progressive development of episodes since no study has assessed this question directly. However, according to analyses of a self-selected group of 247 bipolar patients taking lithium regularly for more than 15 years, this does not seem to be the case (*Maj et al*., 1998). The number of prior hospitalised episodes was the only variable among several socio-demographic and clinical features that was associated with increased recurrence. This finding, however, was not confirmed by a smaller study of 21 lithium-treated patients for whom the number of prior episodes did not predict recurrence during four years of follow-up (*Stefos et al*., 1996).

It is possible that late non-response to lithium could develop during the course of illness and in such a case it would influence the course of episodes in affective disorder. Thus, lithium maintenance treatment has been found effective in preventing relapse in patients with few previous episodes but not in patients with three or more episodes (*Gelenberg et al*., 1989) and earlier start on lithium has been found to predict greater clinical improvement (*Tondo et al*., 1998). Additionally, late non-response to lithium despite previous good response and despite continuous good compliance with treatment has been found in some studies (*Post et al*., 1993; *Koukopoulos et al*., 1995; *Maj et al*., 1996) but not in all (*Berghöfer et al*., 1996; *Coryell et al*., 1998a). In the NIMH study, analyses of the five-year outcome in bipolar patients showed that lithium prevented initial reappearance of episodes but not reappearance of episodes after eight months of recovery (*Coryell, et al*., 1997).

Three different explanations of this non-response phenomenon have been proposed: 1) loss of effect of lithium over time (development of tolerance) 2) progression of the underlying illness, remanifesting itself through an otherwise effective treatment modality (*Post and Weiss*, 1995) and 3) lithium is effective in the prevention of relapses but not in the prevention of recurrence (*Coryell, et al*., 1997). Results from the studies by *Maj et al*. (1996, 1998) suggest that the main determinant of late non-response was progression of the underlying illness. First, late non-responders had a significantly longer duration of illness and a

higher number of previous episodes and hospitalisations than patients with a stable response (*Maj et al*., 1996). Second, although prophylactic treatment with lithium decreased the risk of recurrence, a progressive course of episodes was still found (*Maj et al*., 1998).

In summary, it seems that treatment with lithium in naturalistic settings may moderate but not prevent the progressive course of episodes. The major reason for the modest effect seems to be a rebound phenomenon related to intermittent compliance.

Mood stabiliser combinations

Very few studies of recurrence have been conducted within this area. In bipolar patients, a combination treatment of lithium and imipramine did not seem to reduce the risk of recurrence more than lithium alone (*Kane et al*., 1981; *Prien et al*., 1984). Similarly in unipolar patients, the combined treatment of lithium and imipramine provided no advantage over imipramine alone (*Prien et al*., 1984). Additional treatment with either carbamazepine (*Kishimoto*, 1992; *Denicoff et al*., 1997) or valproate (*Solomon et al*., 1997a) with lithium has been found to decrease the risk of recurrence in bipolar patients whereas the addition of neuroleptics has demonstrated no effect (*Esparon et al*., 1986).

Antidepressants

It is well documented from randomised controlled studies that prophylactic treatment with antidepressants reduces the risk of recurrence in recurrent depressive disorder (*Frank et al*., 1990, *Kupfer et al*., 1992; *Montgomery and Montgomery*, 1992). Few controlled studies have investigated the interaction between previous episodes, antidepressant treatment and subsequent risk of recurrence. *Frank et al*., (1990) found that the number of previous episodes was not associated with survival time to recurrence, once treatment was taken into account. The authors argue that a reason for this could have been the uniformity of the sample (at least three prior episodes and with the immediately previous episode being no more than 2.5 years earlier than entry into the study). A similar result was found in another non-naturalistic study of elderly depressive patients (*Flindt and Rifat*, 1997).
Naturalistic clinical studies of the effect of antidepressants on the risk of recurrence have seldom been presented in the literature. In the study by *Maj et al*. (1992) prophylactic treatment with tricyclic antidepressants and / or lithium decreased the risk of recurrence but did not stop a progressive course of episodes.

It has been suggested that antidepressants may induce mania and cycle acceleration in some patients (*Goodwin and Jamison*, 1990 p. 586; *Altshuler et al*., 1995) and in this way account partly for the progressive course found in bipolar patients in several of the studies reviewed. However, this is hardly a satisfactory explanation since it does not explain the course for unipolar patients and since the effect of episodes seems to be greater in unipolar than in bipolar patients (*Kessing and Andersen*, 1999).
On the other hand, a possible explanation for a progressive course in unipolar patients could be, as with lithium, intermittent compliance with antidepressant treatment. Sudden discontinuation of antidepressants might induce reappearence of depressive symptoms. However, as these symptoms have usually been found to be of mild severity (*Lejoyeux and Adès*, 1997), recurrence due to intermittent compliance does not explain the progression of severe affective episodes.
The reasons for reduced compliance with maintenance treatment, whether due to side-effects of drugs, poor medical guidelines, denial of being ill or other psychological mechanisms are not sufficiently illuminated. In this connection, it remains to be systematically investigated whether the recently introduced selective serotonin reuptake inhibitors (SSRI) may improve the longitudinal course in naturalistic studies because of fewer and less severe side-effects than other drugs. The SSRI's have been used in Denmark since 1987, but so far the progression of the illness has not been changed for the hospitalised proportion of patients with major affective disorders according to the studies by the author (*Kessing et al*, 1998a; *Kessing*, 1998c).

Electroconvulsive therapy (ECT)

In early studies, patients given unmodified ECT without anaesthesia and muscle relaxation had the same risk of recurrence as patients given no ECT (*Ziskind*, et al., 1945; *Huston and Locher*, 1948). Surprisingly, later studies of unmodified ECT in unipolar and bipolar patients, respectively, showed significant increases in subsequent episodes in patients treated with ECT compared with patients who were not given ECT (*Winokur and Kadrmas*, 1988; *Wesner and Winokur*, 1989). Notably, there were no differences between the two groups in the number of episodes or hospitalisations prior to the index episode.
The only long-term study in a modern treatment setting found no effect of modified ECT on the number of episodes following eight weeks of remission during five years of follow-up compared with the effect of medical treatment (*Winokur et al*., 1990). However, the number of subsequent hospitalisations was significantly greater in the ECT-treated unipolar and in the ECT-treated bipolar group of patients than in non-ECT-treated patients.
In summary, ECT does not seem to decrease the risk of subsequent recurrence or to prevent a progressive course of episodes in affective disorder. On the contrary, there may be a tendency towards an increased risk of recurrence following ECT. This finding, however, is possibly caused by a selection of patients with the most severe episodes for the ECT groups.

Psychotherapy

Interpersonal psychotherapy (IPT) has been found to reduce the risk of recurrence during a three-year follow-up compared with a placebo intervention, but IPT in combination with antidepressant treatment did not reduce the risk of recurrence more than antidepressant treatment and consultation at a medication clinic (*Frank et al*., 1990). In some trials, cognitive therapy has been found more effective in preventing relapse than antidepressants alone (*Gloaguen et al*., 1998), although this finding may be due to methodological factors (Jørgensen et al., 1998). The effect of other types of psychotherapy on the long-term risk of recurrence in affective disorder has not been investigated (*Jørgensen et al*., 1998).

Conclusion

Although the interaction between treatment and recurrence is not thoroughly investigated, it seems reasonable to conclude that the combined effect of treatment in naturalistic settings seems to moderate the progressive course of episodes but not to prevent it. A major reason for the modest effect seems to be non-compliance with maintenance treatment possibly combined with a kind of rebound phenomenon related to intermittent compliance, as sudden discontinuation of treatment with lithium or antidepressants may induce relapse or recurrence. On the other hand, it is not likely that the rebound phenomenon or other mechanisms related to treatment account for the progression of episodes during the course of illness, as a progressive course was

also found in the majority of studies from the era before the introduction of treatment in the 1940s and 1950s.
Another possible explanation for the modest effect of treatment is that treatment may have been initiated too late to stop the evolving process of the illness. It is not possible to explore this hypothesis further from studies in the literature.

Handling of data

Diagnostic consistency

The diagnostic consistency or stability is a measure of the degree to which a diagnosis remains the same at repeated assessments of a patient (patient group) over long periods of time. The assessors as well as the patient's illness may vary from one diagnostic time point to another. Additionally the diagnostic system may change during a follow-up period of a study. In Denmark, the same diagnostic system, the International Classification of Diseases, 8th Revision (ICD-8; *WHO*, 1967) has been used since 1967 until the introduction of ICD-10 (*WHO*, 1992) on January 1 1994. Thus, ICD-9 (*WHO*, 1978) has never been used in Denmark.
It is well known that only a proportion of patients get the same diagnosis at inclusion into a study and at follow-up. In the Iowa-500 study, 80 % of patients who were diagnosed with unipolar disorder and 76 % of patients diagnosed with bipolar disorder continued to have the same diagnosis according to the Feighner criteria during a 30- to 40-year follow-up period (*Tsuang et al*., 1981). In the NIMH study, 78 % of patients diagnosed with major depressive disorder on a lifetime basis according to Schedule for Affective Disorders and Schizophrenia - Lifeterm version got this diagnosis throughout 15 years of follow-up (*Mueller et al*., 1999). Similarly, in the NIMH nonclinical study, 74 % of patients diagnosed with major depressive disorder also got this diagnosis six years later (*Rice et al*., 1992). In the 19-year study by *Lee and Murray* (1988) and in a 25-year follow-up study (*Marneros et al*., 1991), 80 % of patients originally diagnosed with unipolar disorder according to ICD-9 and 94 % of patients diagnosed with melancholia according to DSM-III continued to have affective diagnoses. Nevertheless, the diagnostic consistency of the sample is described in only a few studies of recurrence (*Winokur*, 1975 (the Iowa-500 study); *Lee and Murray*, 1988; *Rice et al*., 1992; *Kessing et al*., 1998a; *Mueller et al*., 1999). In the study by *Kessing et al*. (1998a), 1.6 % of the total sample of 20,350 patients diagnosed with manic-depressive psychosis according to ICD-8 (WHO, 1967) at first admission had their diagnosis changed to schizophrenia, and 4.0 % of the patients had their diagnosis changed to organic psychosis during follow-up ranging from 1 day to 23 years. Approximately 65 % of unipolar patients and 85 % of bipolar patients got a diagnosis of manic-depressive psychosis at later hospitalised episodes. Notably, the studies by *Kessing*, and *Kessing and colleagues* are the only studies that include the diagnostic inconsistency in analyses of recurrence. It is not possible to tell from reports from other studies how patients who had their diagnosis changed at later assessments have been handled in the analyses. Probably, these patients have been excluded from analyses and it is impossible to estimate how such an exclusion affected the rate of recurrence since this would depend on the diagnostic composition of the excluded patients.

Definition of episodes and recurrence of episodes

Early studies (Table 1) and some later studies (*Kiloh et al*., 1988; *Lee and Murray*, 1988; *Goldberg et al*., 1995a,b; *Kessing et al*., 1998a) used periods of psychiatric hospitalisations as expression of affective episodes. Other studies have included episodes between admissions too. Some studies included mild depressive and / or hypomanic episodes (*Watts*, 1956; *Perris and dÈlia*, 1966; *Van Scheyen*, 1973; *Angst*, 1981; *Keller et al*., 1982, 1983; *Lewinsohn et al*., 1989) whereas a number of studies did not define episodes or recurrence of episodes precisely or did not discriminate between relapse and recurrence (e.g. early studies and *Zis et al*., 1980; *Angst*, 1981; *Fukuda et al*., 1983; *Gonzales et al*., 1985, *Lehman et al*., 1988; *Winokur and Kadrmas*, 1988; *Van Londen et al*., 1998a). In the recent NIMH studies and in other recent studies (*Tohen et al*., 1990; *Maj et al*., 1992; *Gitlin et al*., 1995; *Ramana et al*., 1995; *Flindt and Rifat*, 1997) episodes were defined as a full syndrome of mania or depression according to the Research Diagnostic Criteria (RDC) or other standardised measures. Recovery was defined as a period (often eight consecutive weeks) with no more than one or two mild affective symptoms and recurrence was defined as re-occurrence of a full syndrome of mania or depression (according to RDC) following recovery.
In the studies by *Kessing* and *Kessing and colleagues*, an episode was defined as the time from the date of admission to the date of discharge. However, if readmission occurred within eight weeks of discharge, the admission periods of two admissions were added and counted as one episode. Remission was defined as the period of the first eight weeks after discharge and recurrence of a new episode as readmission after these first eight weeks. These definitions thus follow the generally accepted conceptualisation of the NIMH Consensus Development Conference Statement (1985) and of *Frank et al*. (1991) and also the guidelines of DSM-IV (*American Psychiatric Association*, 1994) and ICD-10 (*WHO*, 1992), according to which, episodes have to be separated by at least eight consecutive weeks without significant mood disturbance to be considered as two episodes.
In general no specific pattern is revealed. Some studies which include mild episodes and some which include more severe episodes find a progressive course of episodes while other do not. Analogously, some studies which focus on relapse and some studies focusing on recurrence do and do not find a progressive course of episodes.

Pre-index episodes

Reliable information about episodes preceding the index episode may be difficult to obtain, and some investigators have excluded preindex episodes from analyses of recurrence (*Zis and Goodwin*, 1979). For example in the 10-year NIMH study of bipolar patients, the mean duration of illness was 11 years at intake into the study, and only 10 % of the sample of patients were included from their first affective episode (*Turvey et al*., 1999). In register data of admissions too, it is difficult to be sure whether the first recorded admission in fact represents the first admission. In the studies by *Kessing* and *Kessing and colleagues*, validation of register data showed that 2 patients out of 100 had actually been admitted before the first admission recorded in the register (*Kessing*, 1998b).

Relapse versus recurrence

As mentioned earlier a majority of studies do not discriminate between relapse and recurrence in estimations of the course of episodes in affective disorder.
Within register data of admissions, it seems that relapse can be expressed fairly accurately as readmission within eight weeks following discharge and recurrence as readmission after being discharged eight weeks (*Kessing*, 1998b). It should be emphasised that the cut-off of eight weeks used in ICD-10 and DSM-IV is chosen more on the basis of clinical experience than on the basis of research. Nevertheless, only a very few episodes were falsely

classified as relapse and as recurrence, respectively, with the use of this cut-off point (*Kessing*, 1998b). So for practical reasons and in large-scale studies, it seems reasonable to look at time only and not at the severity of affective symptoms in the distinction between relapse and recurrence.

Interval length versus cycle length

It has been argued that modern treatment suppresses symptoms in an episode, but the episode will still be active, and thus that it is more reliable to assess the onset of an episode than the end (*Angst et al*, 1973; *Winokur et al*, 1994). Consequently, it is presumed that it is more reliable to include cycle lengths rather than interval lengths in analyses of the course of episodes in affective disorders. (A cycle length is defined as the interval from onset of one episode to onset of the next. An interval length is defined as the interval between the end of one episode and the beginning of the next). However, as argued by *Kessing et al*. (1998a), with the extensive modern out-patient treatment, the onset will often be less abrupt and symptoms will be suppressed both at the beginning and at the end of an episode, which is why the interval length is likely to be as reliable a measure as the cycle length. Nevertheless, cycle length cannot be used in analyses of time to relapse and time to recurrence, since cycle lengths provide a combined measure of relapse (into previous episodes) and recurrence (into new episodes).

Statistical analyses

"Slater's fallacy"

Slater (1938) was the first to draw attention to an error in previous analyses of the length of intervals between successive episodes. He demonstrated that totally the average length of intervals decreased with every episode in a sample of 105 manic-depressive patients but that this association disappeared when analyses were made for sub-categories of patients grouped according to the number of episodes. The reason is that within a given observation period, patients with many episodes will have shorter intervals between episodes and in calculations of the average length of successive intervals these patients will occur in more intervals than patients with fewer episodes. Patients with many episodes will therefore dominate the calculations resulting in an average shortening of intervals with the number of episodes.

To avoid this error in retrospective analyses, patients with a given number of episodes have to be analysed in a separate group (*Haghighat*, 1996). *Slater's* paper, written in German, did not attract much attention among Scandinavian and Anglo-Saxon authors and the error in the analyses, as pointed out by *Haghighat* (1996), has continued to occur in all subsequent retrospective analyses and studies. However, two exceptions emerge; in the international co-operative study reported by *Grof et al*. (1973) and *Angst et al*. (1973) and in re-analyses of the Zürich study, the length of cycles still decreased with increasing number of episodes when data were analysed within strata of patients with a similar number of episodes (*Angst and Preisig*, 1995).

Survival analyses

Longitudinal studies often provide incomplete sets of observations (censored data) as some patients do not experience the event of interest before the end of the study period, some patients die, and some patients are lost to follow-up due to simple drop-out, incomplete registration of death, emigration, homelessness, etc. The time these patients have been under risk of experiencing the event, the censored time, is not included in analyses without survival statistics (e.g. *Kaplan and Meier*, 1958). In analyses of the course of affective disorder, the risk of recurrence will be incorrectly estimated without survival analyses, with a tendency to overestimate the risk of recurrence. With the use of survival analyses, the cumulative probability of recurrence can be estimated as a function of time at risk (*Lavori et al*., 1984; *Willett and Singer*, 1994).

If focus is on studies using survival statistics in analyses (Table 2), four studies out of five found a progressive course of episodes in unipolar disorder (the studies of *Keller et al*., 1982, 1983; *Lavori et al.*, 1994 and *Mueller et al*., 1999 all relate to the NIMH study), whereas one study found (*Gitlin et al*., 1995) and one study failed to find a progressive course in bipolar disorder (*Tohen et al*., 1990). One study including mixed unipolar and bipolar patients found a progressive course of episodes (*Van Londen et al*., 1998a).

Table 2. *Studies with analyses of the effect of the number of episodes on time to recurrence in affective disorder. Survival analyses used.*

Reference	Year	N	Observation period (years)	Deteriorating course
Unipolar				
*Keller**	1982	52	1	+
*Keller**	1983a	141	1	+
Lee	1988	89	19	+
Lewinsohn	1988	1,130	70	+
*Maj**	1992	72	1.6-9.0	+
*Lavori**	1994	431	5	+
*Flint**	1997	84	2	–
*Mueller**	1999	380	15	+
Bipolar				
*Tohen**	1990	5	4	–
*Gitlin**	1995	82	4.3	+
Mixed				
*Van Londen**	1998a	56	3-5	+

Deteriorating course: decreasing time to recurrence with the number of episodes.
*) Recurrence assessed prospectively following patient's entry into the study.

Regarding the studies of unipolar disorder, *Keller et al*. (1982, 1983) and *Maj et al*. (1992) found that patients with three or more depressive episodes had a greater rate of recurrence than patients with fewer prior episodes. *Lee and Murray* (1988) found that the rate of readmission was greater for patients who had previously been admitted twice than for patients admitted once only. *Lavori et al.* (1994) included episodes as a continuous measure and *Mueller et al*. (1999) categorised the number of episodes into 0, 1, 2, > 3 episodes and both groups found that the number of prior episodes was associated with increased rate of recurrence. In analysis of four community samples, *Lewinsohn et al*. (1988) showed that, for men and for women, the annual hazard rate of developing a minor or major depressive episode according to RDC criteria increased successively for patients with no prior episode, to patients with one prior episode and to patients with two prior episodes. Elderly patients were included in the study according to a single interview and episodes were assessed retrospectively. It is a major drawback that, because of the study design, the risk of recurrence had to be estimated in survival analyses of patients who were selected on the basis of age so that patients who died before this age were not included. Censoring due to death was not possible since patients were included on the basis of the interview.

Finally, *Flindt and Rifat* (1997) found no significant predictive effect of the number of previous episodes in a Cox's regression

analysis of the risk of recurrence in elderly patients on full-dose antidepressant medication for two years.
Regarding bipolar disorder, *Tohen et al*. (1990) found no difference in the rate of recurrence in Cox regression analyses for patients with more than one prior episode compared with patients with one prior episode only. Similarly, *Stefos et al*. (1996) found no effect of the number of previous episodes in a small study of 21 patients followed for four years. In contrast, *Gitlin et al*. (1995) found that patients with more previous episodes relapsed earlier than patients with fewer previous episodes defined according to the median number of episodes.
It should be noted that survival analysis has only been used in the NIMH studies of unipolar patients (*Keller et al*., 1982, 1983; *Lavori et al*., 1994; *Mueller et al*., 1999) and unfortunately not in the NIMH studies of bipolar patients.
Estimations with survival analyses partly compensate for "Slater's fallacy" as time under risk is included. Patients are considered at risk for an event and patients can be included and can leave the study at different times. However, patients with many episodes from onset of the illness might still affect the estimation of the average risk for recurrence.

Table 3. *Interval in years between episodes in relation to the total number of episodes (medians).*

Total number of episodes	Interval 1	Interval 2	Interval 3	Interval 4	Interval 9	Interval 14
≥2	1.33					
≥3	1.13	1.09				
≥4	1.05	0.99	0.93			
≥5	0.99	0.91	0.81	0.91		
≥10	0.86	0.78	0.71	0.67	0.48	
≥15	0.75	0.87	0.56	0.64	0.36	0.76

From *Kessing et al.*, 1998a. With permission from The British Journal of Psychiatry.

Frailty analyses
As mentioned, survival analyses partly compensate for "Slater's fallacy". Estimations with frailty analyses compensate for another component of the "fallacy". Although *Slater* (1938) does not comment on this in his paper, his analyses show that some patients from onset of the illness have a great tendency toward recurrence. This is similarly demonstrated in the study by *Kessing et al*. (1998a) in which the risk of recurrence was predicted partly by an episode effect and partly by an individual tendency toward recurrence. As shown in Table 3, the duration of intervals between episodes decreases horizontally reflecting the episode effect and vertically reflecting the individual tendency toward recurrence.
This individual tendency toward recurrence can explain the finding of a progressive course of episodes in all previous studies of recurrence. In every study sample, a subset of subjects from the sample have a great tendency toward recurrence from the beginning of the illness and this subsample will then affect the statistical estimations of the whole sample. The individual tendency toward recurrence can, however, be incorporated in the statistical analyses. Thus in frailty analyses, a frailty factor, reflecting the individual frailty toward recurrence, is included (*Clayton and Cuzick*, 1985; *Hougaard et al*.,1992; *Andersen et al*., 1993).
Re-analyses of data from the with the use of frailty models demonstrated an episode effect in bipolar affective disorder in general and for women with unipolar disorder (*Kessing et al*., 1999a). For unipolar men, no effect of episodes was found when the effect was adjusted for the frailty. It is not possible to compare this latter result with findings in the literature since no other study has investigated the risk of recurrence specifically for unipolar men.

The NIMH studies
Finally, the NIMH studies will be discussed in more detail as these studies provide some major advantages with the inclusion of a large population of patients followed prospectively with rigorous definitions and assessment of episodes and recurrence during 15 years. In the five- and 10-year follow-up of bipolar patients, no effect of prior episodes on the risk of subsequent recurrence was found (*Winokur et al*., 1993, 1994). The 15-year report of bipolar patients does unfortunately not include analyses of the episode effect on the risk of recurrence, but it is stated that cycling per se did not predict a poor 15-year outcome defined as the presence of symptoms of major depressive disorder, mania or scizoaffective disorder througout the 15th year of follow-up (*Coryell et al*., 1998b). It is a major drawback that these studies only included patients who already at the index episode had a progressed illness. At intake into the study, the mean duration of illness was 11 years and only 10 % of the sample of patients were included from their first affective episode (*Turvey et al*., 1999). As the authors point out, it is possible that patients' cycle lengths may have shortened before entry into the study. Another major problem is that 29 % of the patients were lost to follow-up (*Turvey et al*., 1999) and, as earlier described, this may further imply an underestimation of the risk of recurrence. A third possibility, as previously mentioned, is that the prolonged participation in a prospective study in itself helped to stabilise the patients so they avoided developing full-blown affective episodes. Finally, the NIMH studies are hampered by selection bias due to tertiary study centres and by not using survival statistics and correction for diagnostic instability in the analyses.
The one-, five- and 15-year report of unipolar patients revealed an episode effect on the risk of recurrence (*Keller et al*., 1982, 1983a; *Winokur et al*., 1993; *Lavori et al*., 1994; *Mueller et al*., 1999). In a 10-year report, the rate of recurrence, following recovery from the first to the fifth prospectively observed episode, was illustrated graphically in the same way as done in the study by *Kessing et al*. (1998a), confirming that the rate of recurrence increased with each subsequent episode (*Keller and Boland*, 1998). In contrast, an episode effect was not found during six-year follow-up in the NIMH study of nonclinical subjects (*Coryell et al*., 1991). In general, the findings for unipolar disorder may be the result of some of the above mentioned drawbacks combined with the consequences of Slaters' fallacy.

Summary
A progressive course of episodes may have been falsely demonstrated in previous studies. First, most previous studies are affected by serious selection and recall bias and all previous studies are influenced by information bias (loss to follow-up) presumably increasing the probability of showing a progressive course of episodes. Second, only a minority of studies use survival statistics in the analyses and by not doing so the chances of falsely demonstrating a progressive course of episodes increase greatly. Third, no study uses frailty analyses in estimations of the course of episodes.
On the other hand, low statistical power due to small samples and short follow-ups in some studies may have lessened the possibility of showing a result with a progressive course of episodes as may have the researcher's interaction with the life of the participants in the prospective studies.

Furthermore, several drawbacks in the studies may have affected the results in unpredictable ways. Several studies are weakened by lack of definitions of relapse versus recurrence. Confounders such as gender, age, marital status, comorbidity, etc. were not considered. Finally, no study corrected for diagnostic instability in the analyses.
The sum of drawbacks and pitfalls affect the results of previous studies in unpredictable ways and makes it hazardous to draw conclusions about the effect of prior episodes on the subsequent course of unipolar and bipolar disorder.
In summary, previous studies do not provide enough evidence to draw conclusions about the effect of episodes on the risk of recurrence in affective disorder. The issue is not thoroughly investigated and no prior study has focused specifically on the effect of episodes on the risk of recurrence.
Finally, it can be concluded from the studies by *Kessing* (1998c, 1999a,b) and *Kessing et al.* (1998b) that the episode number has to be taken into account in analyses of the effect of a number of different predictors on the risk of recurrence in affective disorder. These predictors include age, gender, marital status and changes in marital status, type of disorder, comorbidity with alcoholism, and other clinical variables. It is most likely that this statement can also be generalised to be valid for analysis of the predictive effect of any other variable, whatever the origin (socio-demographic variables, psychosocial or biological stressors or events, comorbidity or clinical variables of any kind, or treatment interventions). The importance of considering the effect of prior episodes has also been emphasised by *Kessler and Magee* (1994) who presented examples of how the inclusion of the episode number in statistical analyses in various studies changed the results. Unfortunately, little or no attention has been paid to the episode effect in studies of predictors of recurrence (as emphasised in the studies by *Kessing*, 1998c; *Kessing* 1999a,b; *Kessing et al*., 1998b) and this may invalidate conclusions drawn from prior studies about the associations of these variables and the risk of recurrence in affective disorders.

Advantages of the present Danish studies
Points 1 - 3 relate to the advantages of the Danish Psychiatric Central Register in particular, points 4 - 5 to advantages of case registers in general and points 6 - 11 relate to advantages of the analyses used.

1. Inclusion of all psychiatric admissions in a whole country.
2. Inclusion of a large number of patients and a long duration of observation (high statistical power).
3. Complete registration with very low loss to follow-up.
4. No research interaction with the course of the patients' illness.
5. No recall bias in estimations of affective episodes.
6. Distinction between relapse and recurrence in analyses.
7. Adjustments for diagnostic inconsistency in analyses.
8. Historical prospective analyses with the use of survival statistics.
9. Inclusion of supplementary analyses with frailty models.
10. Inclusion of supplementary analyses of the confounding effect of age, gender, marital status and comorbid alcoholism.
11. Analysis of the effect of predictors of recurrence at successive episodes.

Further advantages relate to characteristics of the Danish population and Danish psychiatry.

1. The Danish population is ethnically and socially homogeneous.
2. The migration rate is low in Denmark.
3. Psychiatric care is well developed in Denmark.
4. Treatment in Denmark is free of charge.
5. No private psychiatric in-patient facilities exist.

Points 3 - 5 imply that the results in the studies are not biased by socio-economic differences.
Studies such as those presented in the present thesis cannot be conducted elsewhere since the Danish Psychiatric Central Register at the moment is the only data source of its kind in the world (*Munk-Jørgensen and Mortensen*, 1997).

Disadvantages of the present Danish studies
The disadvantages relate to the use of register data of admissions.

1. Clinical and not research diagnoses are used.
2. Inclusion of hospitalised patients only.
3. Inclusion of hospitalised episodes only.
4. Treatment unknown.
5. Potential confounders, other than those mentioned in point no. 10, are not investigated since they are not recorded in the Danish Psychiatric Central Register.

In conclusion, the present Danish studies have some major advantages compared with previous studies of recurrence in the literature in being representative for patients hospitalised for affective disorder and in inclusion of comprehensive analyses.

4.4 DISCUSSION

Among the disadvantages mentioned above, points no. 1 - 3 will be further discussed.

The validity of diagnoses (point no. 1)
Psychiatric diagnoses are defined according to arbitrary symptom clusters and provide no clear boundary between psychopathology and normality (*Tucker*, 1998; *Frances*, 1998). Regarding depression, there is clinical continuity between minor and major depressive disorders with no inherent nosological threshold for major depression (*Kessler et al*., 1997; *Kendler and Gardner*, 1998). It has been discussed whether current research diagnostic criteria according to ICD-10 and various versions of DSM-III to DSM-IV are too broad, since the 12-month prevalence of DSM-III mental and addictive disorder has been estimated to be about 29 % of the population in the two largest recent epidemiological studies (the Epidemiological Catchment Area (ECA) study and in the National Comorbidity survey (NCS); *Regier et al*., 1998). In these studies, the 12-month prevalence of affective disorder was 10.1 % (ECA) and 11.1 % (NCS) and 12-month prevalence of a major depressive episode was 6.4 % (ECA) and 10.1 % (NCS). The high rates have cast doubt upon the clinical significance of some of the diagnoses including the diagnosis of a major depressive episode and the diagnosis of affective disorders in general (*Regier et al*., 1998). *Regier and colleagues* (1998) argue that it is reasonable to hypothesise that some mental syndromes, in particular among the affective and anxiety disorders, represent transient homeostatic responses to internal or external stimuli that do not represent true psychopathological disorders. The authors further suggest that the validity of the ICD-10 and DSM-IV diagnoses would improve if the symptom threshold was defined according to the duration of the symptom and the consequences of the symptom, such as impairment or disability.
It has further been discussed whether hospitalisations were identifying more meaningful episodes than are found by the occur-

rence of a syndrome made up of symptoms (*Winokur et al*., 1990). This may be illustrated in the NIMH study in which the rate of unipolar affective disorder in relatives to patients with affective disorder was found to be significantly different across research centres using the RDC and SADS-L (*Coryell et al*., 1981). As one used more restrictive criteria, i.e. going from research diagnostic criteria only to research diagnostic criteria plus psychiatric hospitalisation, all centres had equal rates. This is further illustrated by the observation that the frequency of psychiatric hospitalisation among relatives to patients has been found to be much higher than the morbidity among relatives according to an interview (*Winokur*, 1983). In this way, results from the two family studies suggest that hospitalisation appears to increase the validity of the affective diagnosis.

In any case, it is likely that hospitalised patients with affective disorder are patients with the core illness while patients from the community may have milder forms of the illness. The studies by *Kessing* and *Kessing and colleagues*, based on hospitalised samples, support this suggestion. In a random subsample of patients included in the studies, patients were found to present with moderate to severe affective illness and more than 70 % of the patients presented with a somatic syndrome, psychotic symptoms or with bipolar affective disorder (*Kessing*, 1998b).

Finally, it should be mentioned that the validity of auxiliary diagnoses, such as alcoholism, not is investigated and that it may very well be low.

Hospitalised patients and episodes (points no. 2 and 3)

It should be emphasised that the studies by the author (like the majority of other studies) represent a very selected group of patients with affective disorders. As previously mentioned, most subjects with affective disorder do not seek or receive treatment (*Weisssmann et al*., 1981; *Bucholz and Dinwiddie*, 1989; *Dew et al*., 1988, 1991; *Lépine et al*., 1997; *Munk-Jørgensen et al*., 1997) and those who do seek treatment pass several "filters" on their pathway from community to psychiatric hospitals, leaving a selected group for admission (*Goldberg and Huxley*, 1992; *Huxley*, 1996). It seems probable that the hospitalised patients suffer from the more severe forms of the disorders (*Dew et al*., 1988, 1991; *Coryell et al*., 1991, 1995; *Goldberg and Huxley*, 1992, p.11-12; *Kessing*, 1998b).

It may further be argued that the number of hospitalisations is a gross measure of the number of episodes (*Roy-Byrne et al*., 1985; *Winokur et al*., 1994). The association between the number of psychiatric hospitalisations and the number of affective episodes varies between studies. In analyses of a subsample of the five-year NIMH study, the correlation of hospitalisations and episodes was only 0.31 for unipolar patients and 0.54 for bipolar patients (*Winokur et al*., 1990). In the two studies by Kessing investigating this issue (*Kessing,* 1998d; *Kessing*, 1998b), the correlation of hospitalisations and episodes was 0.64 and 0.66, respectively, for unipolar patients and 0.66 and 0.73, respectively, for bipolar patients ($P < 0.01$). The higher correlations in the studies by *Kessing* than in the NIMH studies presumably reflects two relationships. 1. Data in the NIMH study are partly assessed prospectively, increasing the number of estimated episodes which do not lead to admission. 2. Data in the NIMH study relate to university centres only, whereas data in the studies by *Kessing* and *Kessing and colleagues* relate to all hospitals in Denmark, increasing the proportion of episodes that lead to admission.

The (relatively) low correlations between the number of episodes and the number of hospitalisations indicate that a number of episodes in patients do not lead to admission. In summary, it seems reasonable to assume that hospitalisation occurs in the more serious patient cases and at the more severe affective episodes.

Hospitalisation as an expression of affective episodes

It may further be argued that hospitalisation may also occur for other reasons than for mood episodes (*Burgess et al*., 1991; *Kent and Yellowlees*, 1994). However, patients presented with mood disturbances due to relapse or recurrence at the vast majority of hospitalisations whereas admission seldom occurred in the neutral phase in relation to social events or comorbidity alone (*Kessing*, 1998b).

The probability of hospitalisation presumably also depends on the structure, the resources and the view of the health system, and on the community, specifically the family and friends of the patients (*Holmes and Solomon*, 1981; *Winokur et al*., 1990).

It may be argued that the rate of readmission depends on the level of "continuity of care" and the effectiveness of community care. Two studies have investigated this matter. *Fisher et al*. (1992) compared the rate of readmission in 5 regions in Massachusetts, USA. One of the regions differed clearly from the others in a higher funding of community facilities and a lower funding of inpatient care. *Sytema and Burges* (1999) compared the risk of readmission in Groningen (Netherlands) and Victoria (Australia). The mental health care system was more community based in Victoria with a higher level of "continuity of care". Both studies found that the risk of readmission was equal in areas with high and low community facilities and that the rate of readmission was unaffected by aftercare contact after discharge. The studies conclude that "the risk of readmission is predominantly bound by attributes of mental illness" (*Sytema and Burges*, 1999) and that the pattern of readmission "have more to do with the clinical course of serious mental disorders than with the nature of the services patients recieve" (*Fisher et al*., 1992). It should be emphasised that the impact of the service system not has been investigated specifically for patients with affective disorder.

Only a few studies have investigated the complex interaction between social factors, the severity of psychiatric disorders and the propability of hospitalisation. In general, the severity of the disorder has been found to be the most important factor predicting hospitalisation. Thus, in a study predicting "revolving door" patients, rehospitalisation was not related to family problems, housing problems or financial problems (*Haywood et al*., 1995). In another study, social disability and the severity of clinical disorder were both predictive of psychiatric hospitalisation, but the effect of social disability disappeared when controlling for the severity of the disorder in a discriminant analysis (*Hurry et al*., 1987). In a study investigating the screening procedure for treatment and hospitalisation at a Danish community psychiatric service, psychopathology was similarly found to be of greater significance than social strain (*Søgaard and Søndergaard*, 1996). Regarding patients with affective disorder specifically, hospitalisation has not been found to be associated with lack of social support in older patients with major depression (*Callahan and Wolinsky*, 1995). It seems that patients seek treatment for major depressive disorder primarily on the basis of the number, the severity, and the duration of affective episodes (*Dew et al*., 1988, 1991; *Coryell et al*., 1995).

It seems reasonable to conclude that in large scale studies with inclusion of many patients, psychiatric admissions seem to be a good measure, on average, of moderate to severe affective episodes.

The threshold for admission

It may be argued that the threshold for admission might decrease with every admission for the individual patient, as the patients themselves, the relatives and the mental health personnel more easily expect hospitalisation (*Decker and Stubblebine*, 1972; *Sheridan and Teplin*, 1981; *Saarento et al*., 1994) resulting in a progressive course of admissions not necessarily reflecting a progressive course of affective episodes. This does not seem to be the case within the major affective disorders in Denmark during 1971 -1993 because of to two circumstances. First, the threshold for admission was found to increase with time and it became increasingly difficult to be readmitted in the period (*Kessing et al*., 1998b) as the number of available psychiatric in-patient beds in Denmark declined dramatically during the 23 years the patients were followed (*Søgaard et al*., 1992; *Munk-Jørgensen et al*., 1993; *Kessing et al*., 1998b). Second, if the threshold for admission should decrease with every admission, it would imply that patients during their illness were admitted for less severe affective episodes. However, although difficult to estimate retrospectively, it was the impression from information from case reports, patients and relatives in the validation study by *Kessing* (1998b) that the severity of hospitalised episodes did not decrease during the illness. This impression further gains support from an ongoing prospective clinical evaluation undertaken at the Department of Psychiatry, Rigshospitalet, Denmark. Various clinicians diagnosed all patients with depressive episodes according to ICD-10 (WHO, 1992) and rated the patients with Hamilton Depression Scale, 17 items (*Hamilton*, 1960) at successive admissions and discharges in a period from 1995 to 1999. Additionally, depressive symptoms was recorded by self-rating with the 21-item Beck Depression Inventory (BDI; *Beck et al*. 1961). It should be noted that the data were collected by other doctors independently by the author of the present thesis and analysed by a statistician who was unaware of the purpose of the analysis. As can be seen from Table 4, these preliminary data confirm that, on average, the threshold for admission does not decrease during the course of illness.
In fact, the severity of episodes generally seems to increase during illness (*Lewinsohn et al*., 1988; *Maj et al*., 1992).
Additionally, the data in Table 4 confirm that the vast majority of patients were admitted to hospital with moderate to severe depressive episodes and discharged with only minor depressive symptoms. All patients scored more than seven on the Hamilton Depression Scale and 82.5 % of the patients scored more than 14, on admission. On discharge, 65 % of the patients scored seven or below, and 93.4 % of the patients scored below 14.

4.5 CONCLUSION

The studies by *Kessing* and *Kessing and colleagues* investigated the question of recurrence during the course of unipolar and bipolar major affective disorder in a new and more comprehensive way than previous studies. From the present studies, it can with reasonable certainty be concluded that, on average, the risk of recurrence increases with the number of episodes for patients hospitalised with unipolar and bipolar affective disorder. Whether this is also the case for patients with less severe affective disorders without contact to psychiatric hospitals remains unproven. For unipolar men, the relation is mainly due to a subgroup of patients who have a great liability to recurrence from the beginning of the illness while the remaining unipolar men do not present with a progressive course of episodes.

Table 4. *Hamilton and BDI scores (mean (SD)) at successive admissions and discharges for patients admitted with depression.*

	Admission/discharge			
	1 N=167	2 N=32	3 N=5	4 N=2
Admission				
Hamilton	20.2 (6.1)	20.1 (7.9)	18.4 (5.3)	24.0 (0.0)
BDI	17.4 (8.2)	17.6 (8.5)	20.0 (6.9)	30.0 (0.0)
Discharge				
Hamilton	6.3 (5.0)	6.8 (4.5)	7.8 (5.6)	3.0 (–)
BDI	7.0 (5.8)	8.6 (7.2)	3.0 (2.7)	–

5. RECOVERY DURING THE COURSE OF MAJOR AFFECTIVE DISORDERS

5.1 A REVIEW OF THE LITERATURE

Studies of the duration of successive episodes in affective disorder have given inconsistent results. The duration of episodes has been found to increase, to decrease and to be stable during the course of both unipolar and bipolar disorder in studies in which the duration of successive episodes have been compared (Table 5).

Table 5. *Studies with analyses of the duration of successive episodes in affective disorder.*

Reference	Year	N	Observation period (years)	Survival analysis	Duration of episodes
Unipolar					
Swift	1907	12	up to 28	–	+
Macdonald	1918	100	not indicated	–	+
Lewis	1936	61	up to 8	–	+
Rennie	1942	142	>24	–	+
Taschev	1973	469	up to death	–	+
Grof	1979	594	up to 50	–	0
*Angst**	1981	159	16	–	–
*Coryell**	1989	442	5	+	0
*Maj**	1992	72	1.7-9.0	–	0
*Coryell**	1994	605	6	+	0
*Solomon**	1997b	258	10	+	0
*Eaton**	1997	114	12-15	–	–
Bipolar					
Swift	1907	25	up to 28	–	+
Macdonald	1918	195	not indicated	–	+
Rennie	1942	66	>24	–	+
Taschev	1973	160	up to death	–	+
Grof	1979	393	up to 50	–	0
*Angst**	1981	159	16	–	–
Roy-Byrne	1985	46	not indicated	–	0
*Coryell**	1989	53	5	+	0
Mixed unipolar and bipolar					
*Kraepelin**	1921	899	up to 44	–	+
Paskind	1930	633	up to 40	–	–
Pollock	1931	3,247	up to 11	–	0
Port	1945	141	10-15	–	–
Lundquist	1945	319	up to 30	–	–
Bratfos	1968	207	6 on average	–	+
Lehman	1988	110	11	–	0
Berghöfer	1996	30	>10	–	–

Duration of episodes:
+: increasing time to recovery with the number of episodes.
–: decreasing time to recovery with the number of episodes.
0: unchanged time to recovery with the number of episodes.
*) Episodes estimated prospectively following patient's entry into the study.

Table 6. *Studies with analyses of the effect of the number of prior episodes on time to recovery from a prospectively observed episode in unipolar affective disorder.*

Reference	Year	N	Observation period (years)*	Survival analysis	Effect
Weissman	1978	150	1.7-4.0	–	no effect
Keller	1986	101	0.5-2.0	+	no effect
Sargeant	1990	423	1.0	–	+ effect
Keitner	1992	70	1.0	–	no effect
Hinrichsen	1993	127	1.0	–	no effect
Ramana	1995	70	1.3	+	no effect
Kendler	1997	235	3.0	+	no effect

*) Time to recovery is estimated prospectively but the number of episodes is estimated retrospectively.

Other studies, in which the issue was investigated by the use of regression analyses, have found that the number of previous episodes in unipolar disorder does not predict the rate of recovery of a prospectively observed depressive episode with the exception of one study ((*Sargeant et al*., 1990), Table 6). Finally, some studies have found significantly more previous episodes in both unipolar (*Scott et al*., 1988) and bipolar patients (W*inokur et al*., 1993) with a chronic course than in non-chronically ill patients.

The inconsistencies are reflected in major publications. *Kaplan and Sadock* (1989, p.893) stated in their Textbook of Psychiatry from 1989 that the duration of episodes tends to increase with successive episodes, especially for the unipolar patients, while *Goodwin & Jamison* (1990, p.138) in their extensive survey of manic-depressive disorder from 1990 concluded that several studies have found episodes generally to lengthen with the progression of the illness whereas more comprehensive studies actually find episode duration to be stable through the course of the illness. In fact the issue has never been substantially reviewed and no conclusion has been drawn in recent years, during which time textbooks have avoided the issue (*Kaplan and Sadock*, 1994, 1996).

Several methodological problems involved in longitudinal studies may explain the discrepancies and the finding of a constant or a decreasing duration of episodes during the course of illness in particular might be a consequence of various epidemiological drawbacks. First, as in the studies of recurrence, various degrees of selection bias may have affected the results. Thus, patients were selected within specialised university centres (except in two studies (*Eaton et al*., 1997; *Kendler et al*., 1997)) to which the most severe and unusual cases are most likely to be referred. Furthermore, the number of patients included may not have been large enough to cover the heterogeneity found in the course of affective disorder (*Kessing et al*., 1999a). Second, the failure to find an effect of episodes might be due to a type 2 error as the number of patients may not have been large enough to provide a significant effect of the number of episodes (studies listed in Table 6). Third, different lengths of follow-up may have played a role. Short lengths of follow-up may have increased the proportion of short episodes among patients included in the studies while longer episodes may not have been included. In particular, the observation period must be of sufficient length to encompass several episodes. Fourth, as pointed out by *Goodwin & Jamison* (1990, p.139), these results may have been affected by confounders such as age (and perhaps gender). The relation between the duration of episodes and the number of episodes has not been investigated in different age- and gender-specified samples. Fifth, as with analyses of recurrence (see prior sections), analyses without survival statistics may result in a finding of a constant or a decreasing duration of episodes during the course of illness as a consequence of Slaters' fallacy.

As can be seen from Table 5, analyses of recovery from successive episodes with survival statistics have been provided in one study only: the study from the National Institute of Mental Health (NIMH), USA (*Coryell et al*., 1989, 1994; *Solomon et al*., 1997). In a five-year follow-up report, a total of 53 bipolar I patients had the same survival time to recovery from the first prospectively assessed episode as from the second one (*Coryell et al*., 1989). In the six-year follow-up of 605 unipolar patients, survival times to recovery were similar in the two prospectively observed mood episodes (*Coryell et al*., 1994). In the latest ten-year follow-up report, survival times to recovery from the five prospectively observed mood episodes were found to be uniform in 258 unipolar patients (*Solomon et al*., 1997b). No information was provided regarding time to recovery from episodes prior to the index episode or following the five observed episodes, since these episodes extended beyond the observation period. Three studies of unipolar patients used survival analyses in Cox regression models and found no effect of the number of prior episodes on the chances of recovery from a prospectively assessed episode (*Keller et al*., 1986; *Ramana et al*., 1995; *Kendler et al*., 1997; Table 6).

5.2 RECOVERY DURING THE COURSE OF MAJOR AFFECTIVE DISORDER. STUDIES BY THE AUTHOR

This part of the thesis is based on results published in:
paper no. 10: *Kessing and Mortensen* (1999).

The design and the analyses in these studies were similar to those in the studies of recurrence. The Danish Psychiatric Central Register was used to identify all hospital admissions for patients with primary affective disorder in Denmark during 1971-1993. The rate of recovery was estimated with survival analyses at successive episodes. A total of 9,174 patients with recurrent episodes were followed from their first admission. The rate of recovery did not change with the number of episodes in unipolar or in bipolar disorder (Figures 7 and 8). Additionally, the rate of recovery was constant across episodes regardless of the combination of age, gender and type of disorder (Figures 9 to 16). Initially in the course of illness, the rate was a little higher for bipolar than for unipolar patients but later in the course of the illness the rate of recovery was the same for the two disorders. A lower rate of recovery was predicted by younger age and longer prior episodes. No consistent effect across episodes was found for gender, and marital status was without importance.

It was concluded that the duration of episodes in modern treatment settings is constant across episodes irrespective of age, gender and type of disorder.

5.3 DISCUSSION

The study by *Kessing and Mortensen* (1999) replicated the findings from the prospective NIMH study of recovery in patients with affective disorder (*Coryell et al*., 1989, 1994; *Solomon et al*., 1997b). The 6-year NIMH study also involved a nonclinical sample of 826 subjects consisting of relatives, controls and spouses (*Coryell et al*., 1994). No increasing duration of episodes was found in this nonclinical sample just as it has not been found in studies from the general population (*Kendler et al*., 1997; *Eaton et al*., 1997).

Several studies indicate that it is likely that a substantial proportion of patients experience milder symptoms between affective episodes (*Keitner et al*., 1992; *Hinrichsen*, 1992; *Paykel et al*., 1995; *Hawley et al*., 1997; *Cornwall and Scott*, 1997; *Judd et al*.,

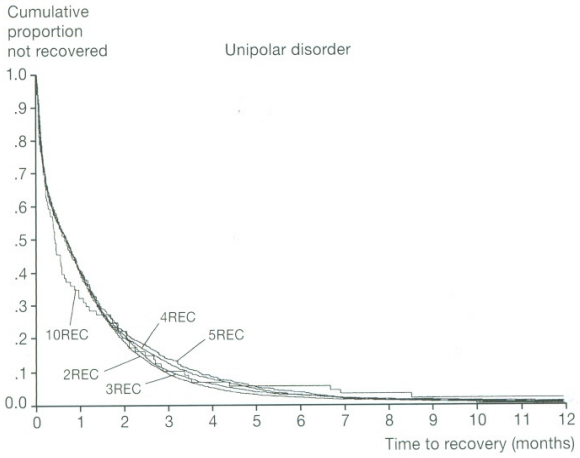


Fig. 7. *Time to recovery from successive episodes in unipolar affective disorder (from* Kessing and Mortensen, *1999. With permission from Acta Psychiatrica Scandinavica).*

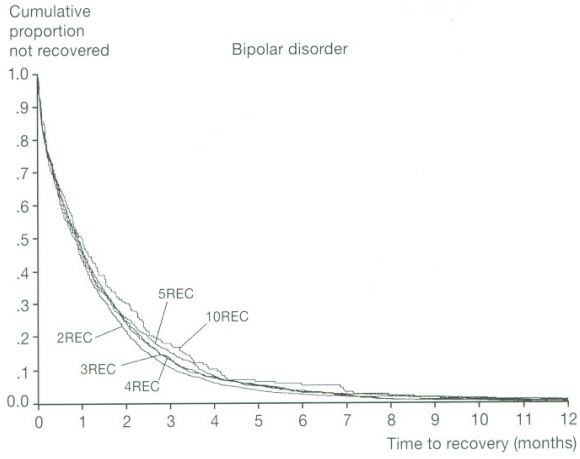


Fig. 8. *Time to recovery from successive episodes in bipolar affective disorder (from* Kessing and Mortensen, *1999. With permission from Acta Psychiatrica Scandinavica).*

1998). However, it has not been investigated whether the prevalence of this partial remission changes during the illness. The cognitive component of the symptomatology between episodes is in focus later in the present thesis.
Advantages and disadvantages of the study by *Kessing and Mortensen* (1999) compared with prior studies are the same as for the studies of recurrence reviewed above and will not be commented upon further.
It seems to be a general finding that the duration of episodes does not progress during the course of the illness in unipolar or in bipolar affective disorder in modern treatment settings. It should be emphasised that in these studies, patients were treated under "naturalistic" conditions, i.e. under normal clinical or daily life conditions and treatment was not under the control of the investigators.

The effect of treatment on the duration of successive episodes
As can be seen from Table 5, it is striking that the majority of studies conducted before the introduction of ECT in the 1940s and antidepressants, lithium and neuroleptics during the 1950s found that the duration of episodes in affective disorder increased during the illness (Table 5). In contrast, such a deteriorating course was found in only one study of patients in the treatment era (*Sargeant et al*., 1990), and in this study, time to recovery was only increased when patients with 10 or more episodes were compared with patients with fewer episodes (Tables 5 and 6; in the studies by *Bratfos* (1968) and *Tashev* (1973) most patients had their initial episodes in the pre-treatment era).
It is broadly accepted that treatment reduces the length of mood episodes (*Kaplan and Sadock*, 1996, p171) and that episodes lasted longer before the introduction of effective treatment than after (*Winokur and Tsuang*, 1996, p.24). It is not known, however, how treatment affects the duration of successive episodes.
For ethical reasons it is not possible to conduct a controlled study of effective treatment versus placebo, so the only way to study this question is to compare studies before and after the introduction of effective treatment.
However, several methodological problems are involved in such a comparison. First, are diagnoses comparable? There were no systematic diagnostic criteria at the beginning of this century, but, as pointed out by *Winokur & Tsuang* (1996), Kraepelin's description of manic-depressive insanity was well known, and furthermore, a reassessment of Kraepelin's cases has revealed a high degree of concordance with ICD-9 (*Jablensky et al*., 1993). Second, are episodes comparable? Although nearly all studies were based on patients from psychiatric clinics or hospitals, recovery was mainly defined as discharge from hospital in the pre-treatment studies whereas recovery in later studies was defined as a period, often eight weeks, with minimal affective symptoms. In the present study, a combination of the two definitions was used, as recovery was defined as discharge from hospital without a subsequent admission within eight weeks. So interestingly, the present study represents a link across history on the question of recovery. Data were admissions data as in the early studies, definition of recovery was a combination of the definition in early and more recent studies and analyses were survival statistics as in the NIMH studies. But the result was the same as in the NIMH study. No increasing duration of successive episodes was found.
Third, do different analyses then account for the different results? This does not seem to be the case, since in the more recent studies, analyses with and without survival statistics provide similar results.
Finally, is there any other support for the hypothesis that treatment decreases the duration of successive episodes? Only two studies have systematically investigated this matter. In open-trial studies, the same treatment, tricyclic antidepressants and interpersonal psychotherapy, was given across depressive episodes and it was found that time to remission for the subsequent episode was reduced compared with the index episode (*Kupfer et al*., 1989; *Reynolds III et al*., 1994). Some evidence for the effect of treatment is further provided from naturalistic studies of patients in lithium treatment in which a shortening of episodes has been found over a 10-year treatment period (*Berghöfer et al*., 1996).
Finally, although results regarding the effect of ECT on successive episodes not are available, ECT has been found to reduce the duration of episodes in general (*Ziskind et al*., 1945; *Huston and Locher*, 1948; *Olfson et al*., 1998).
An alternative explanation could be that the course of affective disorder has ameliorated during this century. However, no data or study supports this explanation, so it is most likely that the difference in the course of episodes before and after 1945 is due to the effect of treatment.

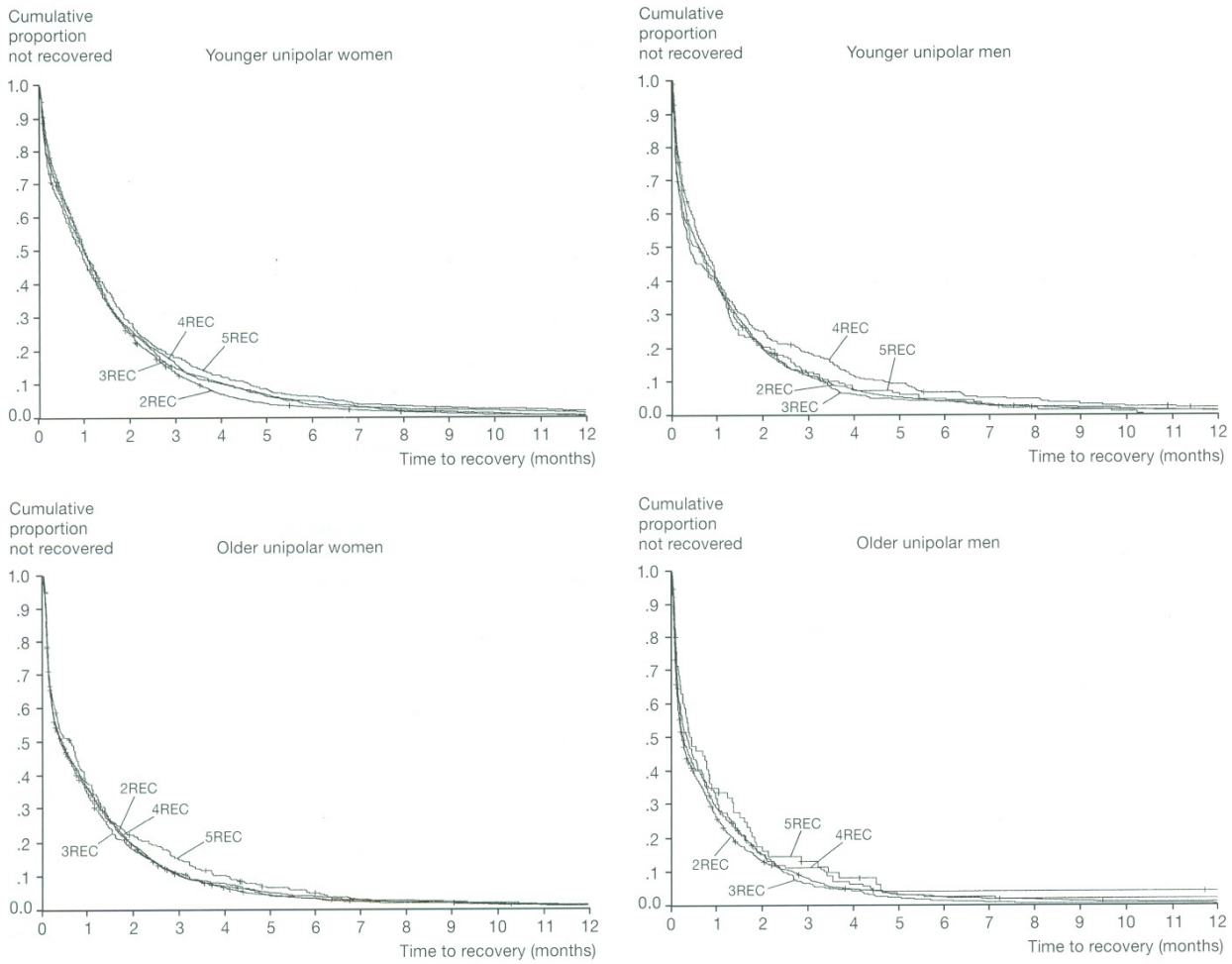


Fig. 9-12. *Time to recovery from successive episodes in unipolar affective disorder.*

5.4 CONCLUSION

It seems reasonable to conclude from the present study and from a review of prior studies that, for untreated unipolar and bipolar disorders, the duration of episodes increases as the illnesses progress and that treatment can stop the deteriorating course.

6. SEVERITY OF EPISODES DURING THE COURSE OF MAJOR AFFECTIVE DISORDER

Several studies have found that the risk of subsequent relapse or recurrence is greater for patients with symptomatically severe episodes (*Gonzales et al*., 1985; *Coryell et al*., 1991; *Ramana et al*., 1995; *Staner et al*., 1997). However, few studies have investi gated the severity of successive episodes during the course of the illness. Two naturalistic studies revealed that the severity of symptoms seemed to increase with increasing number of episodes in unipolar disorder (*Lewinsohn et al*., 1988; *Maj et al*., 1992). This finding is partly contradicted by a study in which a highly selected subsample of mixed unipolar and bipolar patients, who adhered to lithium treatment during more than 10 years, showed decreased severity of manic episodes during follow-up whereas no longitudinal change was found in the severity of depressive episodes (*Berghöfer et al*., 1996).

The severity of episodes is not recorded in the studies by the author.

Conclusion

The issue has been only superficially investigated and especially was not systematically investigated in the era before active treatment. However, it appears from preliminary naturalistic studies that the symptomatic severity of affective episodes increases with every new episode and that rigorous treatment may stop this deterioration. It is thus most likely, although not certain, that the severity of episodes also increases progressively in untreated patients.

7. LIFE EVENTS AND COURSE OF EPISODES

Studies of life events are complicated by a number of methodological problems about defining and measuring life events, and the design of the studies (see *Monroe and Simons*, 1991; *Mazure and Druss* (1995); *Hammen*, 1995; *Kessler*, 1997). It goes beyond the scope of the present thesis to deal more thoroughly with the issue.

Only a minority of studies of the impact of stressful life events pay attention to the number of prior affective episodes in the patient sample. Nevertheless, two reviews conclude that these studies

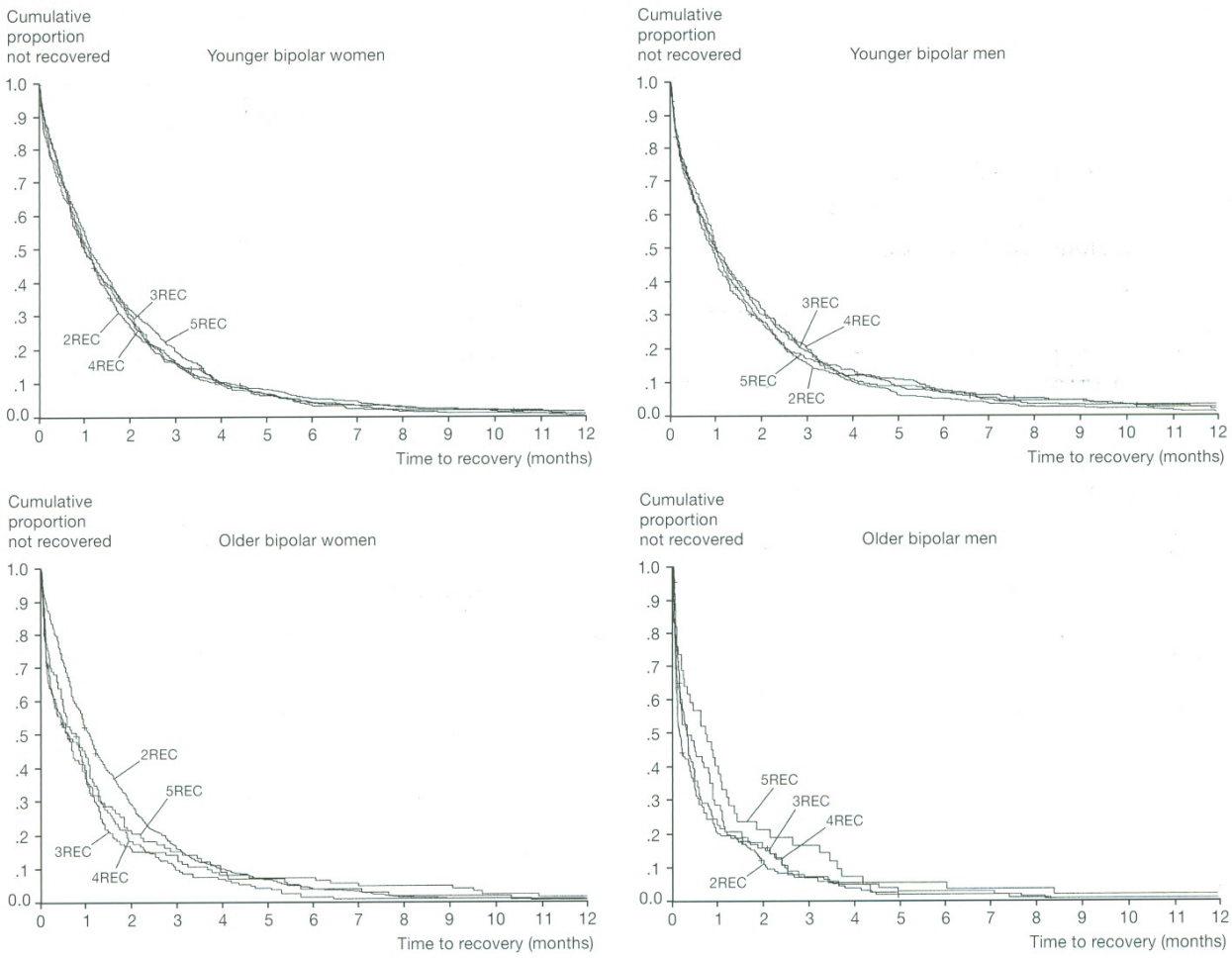


Fig. 13-16. *Time to recovery from successive episodes in bipolar affective disorder.*

demonstrate that more psychosocial stressors are involved in the first episode than in subsequent episodes of major affective disorder (*Goodwin and Jamison*, 1990, pp. 142-146; *Post*, 1992). However, as noted by *Mazure and Druss* (1995), this relation has not been found in all studies of unipolar disorder (*Perris*, 1984; *Bidzinska*, 1984) and bipolar disorder (*Bidzinska*, 1984; *Ellicott et al*., 1990; *Hammen and Gitlin*, 1997).

It has been objected that, in the primary retrospective studies of precipitating events, patients are more likely to search for stressors prior to onset of the illness, whereas once the illness is accepted less attention is paid to stressors (*Goodwin and Jamison*, 1990, p. 143; *Johnson and Roberts*, 1995).

Studies with prospective rigorous assessment of stressors are few and include a short follow-up period only (up to three years, *Ellicott et al*., 1990; *Pardoen et al*., 1996; *Paykel et al*., 1996; *Monroe et al*., 1996; *Hammen and Gitlin*, 1997). Thus, no study encompasses appropriate long follow-up time to compare the presence of prospectively assessed life events before early episodes and before later episodes (*Hammen and Gitlin*, 1997). Such long-term prospective studies may be difficult to perform in a valid way since they may be hampered by selective drop-out as patients with increased prevalence of life events seem to have an increased tendency to drop-out of the study. (*Monroe and McQuaid*, 1994; *Monroe et al*., 1996). Thus, it is possible that stress precipitates recurrence and it is possible that stress increases drop-out from the study. If the latter association is prominent, then the former would not be detectable (*Monroe and McQuaid*, 1994, p. 67).

In this regard, register data offer some remarkable advantages. Recall bias is completely avoided since data are "hard facts" collected routinely and independently of researchers. Selective drop-out is for practical reasons not relevant in Danish register studies as the Danish Psychiatric Central Register covers all inpatient facilities in Denmark. Also, there is no reason to believe that patients with increased prevalence of life events who have once been psychiatrically hospitalised are less likely to be readmitted. Psychosocial stress is not measured in register studies; instead marital status is routinely recorded and changes herein can be used as expressions of major life events and stress. It should be mentioned, that in the Danish Psychiatric Central Register, data of marital status has not been validated and that the date of a change in marital status is not precisely recorded. Thus, marital status may have changed even long before the discharge date at which the event was first recorded.

The studies by *Kessing* (1998c) and *Kessing et al*. (1998b) showed that initially in the course of unipolar and bipolar illness, the type of disorder (unipolar / bipolar) and socio-demographic variables such as sex, partly age and marital status predicted recurrence

whereas these variables had no effect later in the course of the illnesses. Patients who had never been married had greater risk of recurrence after the first and the second episode but not after subsequent episodes, and divorced / separated patients had greater risk of recurrence after the first episode but not after subsequent episodes. It should be mentioned that further analyses, taking the individual liability to recurrence into account, confirmed that the effect of the type of disorder, age at first admission, and never engaging in marriage decreased during the course of illness but revealed no differences in the effect of gender and in the effect of a recent divorce between early and later episodes (*Kessing et al*., 2000).

Conclusion

Studies of life events are hampered by serious methodological problems (Kessler, 1997) and the impact of psycho-social stressors on the risk of recurrence during the course of illness has not been thoroughly investigated. A majority of studies, including studies by the author, suggest that early episodes are more often associated with prior life stressors than later episodes. This putative association, however, has to be investigated more thoroughly and in detail in prospective (or historical prospective) long-term studies.

8. COGNITIVE IMPAIRMENT AND DEMENTIA IN MAJOR AFFECTIVE DISORDERS

8.1 A REVIEW OF THE LITERATURE

Cognitive impairment

A majority of studies have found memory impairment in depressed patients (for a meta-analysis of studies see *Burt et al*. 1995) but only a few studies have investigated cognition in the euthymic phase of affective disorder. A review of such studies by *Kessing* (1998d) revealed diverging results, although most studies found cognitive dysfunction in one or more neuropsychological tasks. It was concluded that the diverging results can be largely explained by the inclusion of small selected samples of patients and controls, the lack of correction of various degrees of subclinical psychopathology and the use of over-specialised tests (*Kessing*, 1998d). The design and results of quite recent studies have not changed these conclusions (Table 7).

Table 7. *Recent controlled cross-sectional studies of cognitive function in euthymic state of affective disorder.*

Reference	Year	N patients/controls	Mean age of mood patients	Cognitive dysfunction in affective disorder
Unipolar patients				
Paradiso	1997	20/19	56	Visual-motor sequencing. Executive function. Immediate memory and attention.
Dahabra	1998	23/15	67	Digit symbol substitution. Immediate and delayed story recall. Visual pattern recognition. Sample matching. Paired-associate conditioned learning.
Bipolar patients				
Paradiso	1997	11/19	57	*No* difference in visual-motor sequencing, executive function or immediate memory and attention.
Gorp	1998	25/22	52	California Verbal Learning Test. *No* difference in: test of nonverbal memory, Stroop color and Word Test, Wisconsin Card Sorting Test, Trail Making Test, etc.
Ferrier	1999	41/20	44	Trail Making Test. Digits backward. Contolled Oral Word. Association. *No* difference in: tests of attention, working and memory.

Cognitive impairment and course of illness

Only a very few studies have investigated the relation between cognitive impairment in the euthymic phase and the prior course of affective illness.

In a study of 60 elderly unipolar patients, cognitive impairment correlated with the number of prior psychiatric admissions and the number of prior affective episodes and less with the duration of the illness (*Kessing et al*., 1996). Current or previous treatment or differences in social characteristics could not explain the dysfunction. This result is in accordance with the finding in a study of 26 euthymic patients with recurrent affective disorder among whom patients with impaired cognitive functioning had had more hospitalisation episodes than patients with normal cognitive functioning (*Tham et al*., 1997). Similarly, in a recent study, analyses of 13 bipolar patients showed that cognitive impairment in the euthymic phase correlated positively with the number of prior manic episodes and negatively with the duration of lifetime depressive and manic episodes (*Gorp et al*., 1998). In contrast, in an other recent study (*Ferrier et al*., 1999), no difference was found in cognitive function between 21 bipolar patients with good outcome (< 2 affective episodes in the last five years) and 20 bipolar patients with bad outcome (> 3 episodes in the last two years).

Few studies have investigated other cognitive associations with recurrence in affective disorder. However, the number of prior depressive episodes has been found to correlate with response latencies in test performance (*Beats et al*, 1996).

Dementia

The relation between affective disorder and dementia has been investigated in three different kinds of longitudinal studies: 1) studies of patients with affective disorder, 2) studies of patients with Alzheimer's disease (or other dementia) and 3) studies of community samples.

1. Studies of dementia in affective disorder

Prior studies that have found cognitive dysfunction in the euthymic phase of affective disorder have assessed the impairment to be subclinical or mild. The relation to more severe dementia is not clear, since clinically demented patients have often been excluded in advance in an attempt to avoid inclusion of Alzheimer's patients and other patients with dementia secondary to distinct neurological disorders. This fallacy has recently been pointed out by *King and Caine* (1996, pp. 211-212), who, alternatively, proposed a broader inclusion of patients followed longitudinally.

Studies of the development of dementia in affective disorder are complicated by several epidemiological problems. First of all, only a small proportion of patients with affective disorder may develop dementia and several years may elapse from the first affective episode before dementia develops. Second, it is difficult to find a suitably large control group without affective disorder. The

conduct of prospective studies within this area is thus time consuming and expensive.

Controlled studies

Only one study has compared estimations of the risk of developing dementia for patients with affective disorder and subjects without (*Jacoby et al*., 1981). In a follow-up of a minimum of one year, 41 depressed patients failed to reach the level of 50 age-matched controls on the Mental Test Score although a significant improvement was found for patients on a number of other scales (Table 8). The cognitive impairment was related to persisting depression but correction for depressive level was not done.

Uncontrolled studies

Several uncontrolled studies have shown that some patients with reversible dementia during a depressive index episode (also called depressive pseudodementia) develop dementia at follow-up. In a two-year follow-up study of 16 patients with mixed symptoms of depression and dementia, 8 showed cognitive improvement and 8 showed deterioration (*Reynolds III et al*., 1986). In a study of 44 elderly, successfully treated, unipolar patients, followed with tests every six months for 4 to 18 years, 89 % developed dementia of the Alzheimer type (*Kral and Emery*, 1989). Similarly, 32 % of 25 elderly bipolar patients followed for 5 - 7 years experienced a decline to below a score of 24 on the MMSE (*Dhingra and Rabins*, 1991).

Some investigators have more specifically compared cognitive outcome in longitudinal studies of patients with and patients without reversible dementia during a depressive index episode (Table 9). In three studies, no significant overall difference was found at follow-up between patients with and patients without reversible cognitive dysfunction although, in all studies, a greater number of patients in the dysfunctional group developed dementia or persisting cognitive impairment after initial recovery (*Rabins et al*., 1984; *Pearlson et al*., 1989; *Stoudemire et al*., 1991, 1993, 1995). Only one study, the study of *Alexopoulos et al*. (1993), used survival statistics in the analyses. In this study, patients with reversible cognitive dysfunction at the index episode had 4.7 times increased risk of developing irreversible dementia, defined according to DSM-III-R, following recovery from the depressive symptoms.

2. Depression in Alzheimer's disease

The possibility of an association between affective disorder and dementia gains further support from research on Alzheimer's disease. *Jorm and colleagues* (1991) pooled data from 11 case-control studies of Alzheimer patients and found an association between a history of depression and late-onset Alzheimer's disease. No associations with antidepressant treatment or major life events were demonstrated. Recently, the association between previous depression and Alzheimer's disease has been confirmed in some studies (*Speck et al*., 1995; *Steffens et al*., 1997) but not in all (*Mendez et al*., 1992; *The Candian Study of Health and Aging*, 1994).

3. Depression and dementia in community studies

A number of prospective community studies have investigated the longitudinal association between depressive and cognitive symptomatology. Three studies have not found that depressive symptoms at baseline predicted dementia or cognitive deterioration at follow-up of community samples of elderly persons (*Bickel and Cooper* (1994); *Dufouil et al*. (1996); *Henderson et al*. (1997)). In contrast, *Devanand and colleagues* (1996) found that depressive mood at baseline was associated with increased risk of incident dementia in a prospective community study, with one to five-year follow-up and annual systematic assessments of depression and cognition. Similarly, this relation was found in a four-year follow-up community study (*Schmand et al*., 1997) but the relation disappeared when adjusted for the effect of subjective memory complaints and objective cognitive performance at baseline. An association between a history of depression and increased risk of developing Alzheimer's disease was also found in a Danish follow-up study and the number of depressions correlated to the severity of cognitive impairment (*Andersen*, 1997).

Table 8. *Long-term follow-up studies of cognitive outcome in patients with affective disorder.*

Reference	Year	N patients/controls	Mean age of patients	Follow-up period	Cognitive dysfunction at follow-up
Jacoby	1981	41/50	72	>1 year	Improvement on: Geriatric Mental State Schedule. Digit copying. Digit Symbol Substitution – but not in Mental Test Score. Explained by persisting depression.

Table 9. *Long-term follow-up studies of cognitive outcome in patients with reversible cognitive dysfunction and patients without cognitive dysfunction during depressive index episode in unipolar affective disorder.*

Reference	Year	N + dysfunction/ – dysfunction	Mean age of patients	Follow-up period	Cognitive dysfunction at follow-up
Rabins	1984	14/16	?	2.0	MMSE No difference between groups. Two from the dysfunction group remained depressive and demented.
Pearlson	1989	11 / 9	72	2.0	MMSE No difference between groups. One from the dysfunction group developed dementia.
Stoudemire	1991 1993 1995	35/20	72	0.5 and 1.2 and 4.0	Mattis Dementia Rating Scale (MDRS). The non-dysfunction group remained stable. The dysfunction group improved during follow-up although cognition was still impaired (MDR<130).
Alexopoulos	1993	23/34	74	2.8	MMSE Patients with dysfunction had 4.7 times increased risk of developing dementia.

Similarly, a "dose effect" was found in a prospective community study of nondemented women (*Yaffe et al*., 1999). A higher number of depressive symptoms at baseline was associated with increased risk of cognitive deterioration and greater odds of having a diagnosis of dementia at follow-up four years later. Mixed results were found in a 12 years follow-up study of an elderly community sample (*Bassuk et al*., 1998). An elevated level of depressive symptoms was associated with increased risk of incident cognitive decline but only among persons with moderate cognitive impairment. In a 8-year prospective community study (*Chen et al*., 1999), depressive symptoms appeared to be early

manifistations, rather than predictors, of Alzheimers disease. Depressive symptoms were assessed prospectively and a history of depression before entry into the study was not included.
As the study by *Speck et al*. (1995) and a recent study by *Pálsson et al*. (1999) suggest, it seems that depression may act as a predictor of dementia particularly when there is a large interval between onset of depression and onset of dementia (10 years or more between the onset of depression and the onset of dementia).
In general, community studies may be criticised for only including a small number of persons with mild depressions and for not using diagnostic instruments for depression or dementia resulting in analyses which may have washed out a true association between the disorders (*Meyers and Bruce*, 1998; *Chen et al*., 1999).

APOE genotypes in affective disorder
The ε4 allele of apolipoprotein E has been found to be associated with late-onset sporadic and familial Alzheimer's disease as the APOE-ε4 allele frequency has been estimated to be approximately three times greater than the frequency in controls (*Strittmatter et al*, 1993; *Corder et al*, 1993; *Saunders et al*, 1993; *Corder et al*, 1994).
According to prior studies, the role of APOE genotypes in affective disorder is unclear. It is not clear whether APOE-ε4 allele is more frequent in patients with affective disorder than in subjects without and it is not clear whether cognitive impairment in affective disorder is associated with the APOE genotype (*Kessing and Jørgensen*, 1999).

Conclusion
A majority of small studies of affective disorders, flawed by the mentioned drawbacks, suggest that cognitive impairment is more frequent in patients with affective disorder than in subjects without affective disorder, and that a subgroup of patients with affective disorder might have increased risk of developing frank dementia. A putative association between affective disorder and dementia gains support from the majority of studies of Alzheimer's disease and partly from community studies, as it appears that depression is a risk factor for developing Alzheimer's disease and dementia. However, the literature lacks a representative study of patients with affective disorder and controls, with assessment of cognitive function with general neuropsychological measures and with adjustment for subclinical psychopathology in the analyses. Additionally, a longitudinal study comparing the risk of developing dementia in large samples of patients with affective disorder and controls is needed.

8.2 STUDIES OF COGNITIVE IMPAIRMENT AND DEMENTIA BY THE AUTHOR
The studies consist of a controlled cohort study presented in two papers and in two case register studies.

A controlled cohort study
This part of the thesis is based on results published in:
paper no. 11: *Kessing* (1998d)

The study was designed as a controlled cohort study, with the Danish psychiatric case register of admissions used to identify patients and the Danish civil register to identify controls. Patients who were hospitalised between 19 and 25 years ago with an affective diagnosis and who at interviews fulfilled criteria for a primary affective unipolar or bipolar disorder, according to ICD-10, were compared with age- and gender-matched controls without affective disorder. The samples of patients and controls included in the study seemed to be representative samples of patients with moderate to severe affective disorder and of gender- and age-matched controls in general. Interviews and assessment of the cognitive function were made in the euthymic phase of the disorder with five different measures: the Cambridge Cognitive Examination (CAMCOG; *Roth et al*., 1986; *Huppert et al*., 1995), the Mattis Dementia Rating Scale (MDRS; *Mattis*, 1976), the Gottfries-Bråne-Steen Dementia Rating Scale (GBS; *Gottfries et al*., 1982), the Mini Mental Status Examination (MMSE; *Folstein*, 1975) and the Global Deterioration Scale (GDS; *Reisberg et al*., 1988).
In all, 118 unipolar patients, 28 bipolar patients and 58 controls were included.
Analyses were adjusted for differences in the level of education and for subclinical depressive and anxiety symptoms. Patients with recurrent episodes were significantly more impaired than patients with a single episode and more impaired than controls, and within the patient group the number of prior episodes was associated with cognitive outcome when adjusted for the effect of age. The observed cognitive impairment had in every case developed during the course of the affective disorder. There was no difference in the severity of the dysfunction between unipolar and bipolar patients. A total of 16.2 % of unipolar and 14.3 % of bipolar patients with recurrent affective disorder and aged 40 years or older presented with dementia (MMSE < 24). In contrast, only 4.0 % of patients with a single episode and 3.4 % of controls without affective disorder scored in the demented range of MMSE.
It was concluded that the prevalence of cognitive impairment seems to be increased in out-patients with unipolar and bipolar affective disorder compared with subjects without mental illness and that the severity of impairment seems to be associated with the number of affective episodes.

APOE genotype
The ε4 allele of apolipoprotein E has been found to be associated with late-onset sporadic and familial Alzheimer's disease. Among the subjects described in the study by *Kessing* (1998d), blood tests were available for 106 unipolar patients, 21 bipolar patients and 46 controls (*Kessing and Jørgensen*, 1999). The frequency of APOE-ε4 allele was approximately the same in unipolar patients (0.189) and in bipolar patients (0.167). No significant overall difference was found between the frequency of APOE-ε4 allele in patients (0.185) and controls (0.131) and the frequency of APOE-ε4 allele did not correlate with cognitive impairment. It was not possible to identify subgroups of patients with an increased frequency of APOE-ε4 allele as no association was found with gender, age at onset, the number of affective episodes, the presence of psychotic features or the prevalence of familial affective disorder.
It was concluded that it seems that cognitive impairment in affective disorder is attributable to other pathways than the APOE genotype.

A controlled case register study
This part of the thesis is based on results published in:
paper no. 12: *Kessing et al*. (1999b)

In the Danish Psychiatric Central Register of admissions, 3,363 patients with unipolar and 518 patients with bipolar affective

disorder and 1,024 schizophrenic and 8,946 neurotic patients were identified and the rate of readmission with a diagnosis of dementia was estimated during 24 years of follow-up. Additionally, the rates were compared with the rates for admission to psychiatric hospitals with a discharge diagnosis of dementia for the total Danish population.
For unipolar and especially for bipolar patients, the risk of getting a diagnosis of dementia was greater than the risk for patients with neurosis and greater than the risk for the gender- and age-matched groups of the Danish population. The increased risk for patients with affective disorder may partly be a consequence of the greater frequency of admissions.
It was concluded that patients with unipolar and bipolar affective disorder have an increased risk of hospitalisation with dementia.

A case register study
This part of the thesis is based on results published in:
paper no. 8: *Kessing et al*. (1998d)
This study has been described in section 4.2.

A short period between initial episodes of unipolar and bipolar disorder, reflecting a great intensity of illness, predicted increased risk of subsequent development of dementia. A progressive course, with decreasing intervals between initial episodes of the illness, had no predictive effect. It was concluded that among patients hospitalised for the major affective disorders, increased frequency of affective episodes seems to be associated with increased risk of developing dementia.

Conclusion
The risk of developing cognitive impairment seems to be increased for patients with unipolar affective disorder and for patients with bipolar affective disorder. The risk is not related to any particular APOE-genotype but seems to increase with the number and frequency of affective episodes. It should be emphasised that the causality between the number of affective episodes and the presence of cognitive impairment is still uncertain because of the retrospective design of the hitherto conducted studies. Thus, the results need replication in prospective studies with assessment of cognitive function in the euthymic phases following successive affective episodes.

9. COGNITIVE FUNCTION IN AFFECTIVE DISORDER AND BRAIN IMAGING
Soares and Mann (1997) have recently reviewed the literature and found that in five (*Dewan et al*., 1988, *Pearlson et al*., 1989; *Rothschild et al*., 1989; *Abas et al*., 1990; *Coffman et al*., 1990) of six (*Andreasen et al*., 1990) controlled studies, cognitive impairment in depressed patients was associated with global brain atrophy on structural brain imaging. Similarly, extensive white matter lesions on magnetic resonance imaging (MRI) have been found to be related to cognitive impairment (*Steingart et al*., 1986, 1987; *Junque et al*., 1990; *Dupont et al*., 1990, 1995; *Lesser et al*., 1996, *Hickie et al*., 1995, 1997), but not in all studies (*O'Brien et al*., 1996). Consequently, *Soares and Mann* (1997) concluded, in agreement with *Videbech* (1997) in another recent review of structural neuroimaging studies, that cognitive impairment in affective disorders appears to be related to global atrophy, extensive white matter lesions and perhaps localised lesions in the frontal lobe and in the basal ganglia.
In the study by *Dupont et al*. (1990), bipolar patients with white matter hyperintensities had a history of more hospitalisations and appeared more cognitively impaired than patients without MRI abnormalities. However, no association between the number of previous depressive episodes and white matter hyperintensities were found in another study of bipolar patients (*Altshuler et al*., 1995) and in a study with a mixed sample of unipolar and bipolar patients (*O'Brien et al*., 1996).
It should be emphasised that in these studies, cognitive function was assessed and brain imaging performed while most patients were suffering an affective episode. In contrast, one study evaluated recovered unipolar patients and found more hippocampal changes (volume loss) in patients than in controls (*Sheline et al*., 1996). Furthermore, hippocampal changes was associated with the total duration of major depression whereas the relation to the number of episodes and to cognitive function was not investigated.
Only a few functional brain imaging studies of patients with affective disorder and cognitive impairment have been presented and with contradictory results (reviewed by *Kennedy et al*., 1997).

10. COGNITIVE FUNCTION IN AFFECTIVE DISORDER AND NEUROLOGICAL FACTORS
Cognitive impairment has been found to be associated with tardive dyskinesia and the dyskenesia was related to the number of prior episodes and not to the duration or dosage of treatment (*Wolf et al*., 1983; *Waddington and Youssef*, 1988; *Waddington et al*., 1989).
Additionally, some investigators have demonstrated soft neurological signs such as changed reflexes and dystonia in affective disorders (*Goodwin and Jamison*, 1990, pp. 507-508; *Nizamie et al*., 1994; *Sobin and Sackeim*, 1997); however, no study has related these signs to cognitive function.

11. OVERALL CONCLUSIONS
Patients hospitalised for unipolar and bipolar affective disorders have on average a progressive course with increasing risk of recurrence with every new episode and most likely increasing duration and severity of untreated episodes. However, a subgroup of unipolar men have a great liability to recurrence from the beginning of the illness and the remaining unipolar men do not present with a progressive course of episodes.
Initially, the two types of disorders follow markedly different courses, but later in the course of the illness the risk of recurrence is the same for the two disorders.
Initially in the course of affective disorders, socio-demographic variables such as gender, age at onset and marital status seem to act as risk factors for further recurrence. Later, however, the illness itself seems to follow its own rhythm regardless of prior predictors. Thus, the long-term course of the illnesses seems to be determined by two factors mainly: the individual liability to recurrence and the episode effect, i.e. the frequency of affective episodes per se. The effect of episodes seems to persist during the long-term course with no tendency to abate.
Unipolar and bipolar affective disorders seem associated with increased risk of developing cognitive impairment and dementia. The risk is not related to any particular APOE-genotype but seems to increase with the number and the frequency of affective episodes. The thesis thus supports previous evidence suggesting that the course of affective illness is associated with changes in the brain.
Treatment as practised in modern treatment settings seems to prevent the progression in duration of episodes but not the progression in frequency and, most probably, not the progression in severity of episodes and cognitive impaiment.

12. IMPLICATIONS

The thesis has some methodological implications for epidemiological studies and some clinical as well as theoretical implications for affective disorders.

Methodological implications

Some major methodological implications are mentioned below.

The thesis

- presented arguments for the potential of register data in analyses of longitudinal psychiatric disorders, exemplified by affective disorder.
- showed that analyses of the effect of various predictors on the risk of recurrence in affective disorder have to consider the effect of the number of prior affective episodes.
- indicated that also drug trials and other experimental studies should consider the effect of prior affective episodes in the analyses or even better randomize patients into treatment groups with an equal number of prior affective episodes.
- showed that it is practically possible with the use of frailty models to provide a measure of the heterogeneity in vulnerability to recurrence in affective disorder.

Clinical implications

The progressive deteriorating course of unipolar and bipolar affective disorders underlines the need for early intervention. However, it seems that treatment, as practised in modern settings, may stop the progression in the duration of episodes but not the progression in the frequency or severity of episodes. It is not known whether treatment might prevent the progression of cognitive impairment seen in some patients. Treatment thus seems to reduce the severity of affective symptoms but not to affect the liability to illness. Three possibilities may be considered to explain these relationships. First, treatment may be initialised too late to stop the evolving process of the illness. Second, intermittent compliance may accelerate the process of the illness. The third possibility is, however, that accessible treatment basically does not affect the illness process.

It is an important challenge for research in the future to investigate whether early and sustained maintenance therapy can stop and prevent the progression of the illnesses and, at the same time, to discover new treatment principles in affective disorders.

Theoretical implications

The course of affective disorder may in some ways reflect the illness process itself.

In general, the thesis showed that unipolar and bipolar affective disorder seem to be progressive in nature and that persistent changes in cognition seem to develop during the illnesses. It has been suggested that episodes come in bursts or clusters and also that the tendency toward recurrence might decrease following years of illness and that the illness process might die out or "burn" out following a number of episodes (*Winokur*, 1975). The thesis did not support these theories, as the risk of recurrence was shown to persist for decades (at least 23 years), and as the rate of recurrence on average was found to continue to increase with every episode (investigated up to the 15th episode). However, it is not possible to exclude the possibility that the illness process might "burn" out in a subgroup of patients. Such a subgroup could include the proportion of unipolar men who did not show a progressive course of illness (*Kessing et al*., 1999a). This possibility is so far not supported by brain imaging studies as more abnormalities have not been found in unipolar men as compared to unipolar women.

The thesis shows that the course of illness seems to be determined by a combination of the individual liability to recurrence and the episode effect. After the onset of the illness the individual liability to recurrence is modified by the illness process itself, creating a time-dependent total risk of recurrence of new episodes of illness.

The individual effect

The individual liability to recurrence reflects the premorbid probability of illness for the individual and in statistical terms corresponds to the frailty parameter and in medical terms to the diathesis.

The basic premise in the diathesis-stress theories is that stress activates a diathesis, transforming the potential of predisposition into the presence of psychopathology and onset of the illness (*Monroe and Simons*, 1991). The theory has only rarely been tested in relation to affective disorders. One exception is a twin study in which genetic liability was found to interact with the presence of stressful life events in precipitating the onset of depressive episodes (*Kendler et al*., 1995). As illustrated in the present thesis, the liability to recurrence following onset of the illness also depends on factors related to the individual. Some individuals develop a severe course of illness and others do not. It has not, at present, been investigated whether, or to what degree, the liability to recurrence is genetically influenced (*Jamison and Goodwin*, 1990 pp. 585; *Sharma et al*., 1997). The present thesis suggests, however, that it might be reasonable to integrate the episode effect into the diathesis-stress theories of affective disorder.

The episode effect

The progressive course of unipolar and bipolar disorder may fundamentally be a consequence of aging, a consequence of psychosocial interactions, or a consequence of psychosocio-biological interactions.

1. A consequence of aging.

It is possible that episode recurrence may simply be a function of age as mentioned by *Segal et al*. (1996). The developmental changes in the brain related to increasing age may lead to an overall decrease in neurotransmitter receptor levels (*Volkov et al*., 1998) or other changes in the neurotransmitter system (*Salzman*, 1992, pp. 41-59) and thereby make depression more likely (*Salzman*, 1992, pp. 41-59). Findings, as referred in the present thesis, argue against this hypothesis. First, in general, the rate of recovery from episodes increases (*Kessing and Mortensen*, 1999) with older age, and the risk of recurrence decreases (*Kessing*, 1998c; *Kessing et al*., 1998b). Second, young patients with affective disorder also present with a progressive course of episodes (*Kessing*, 1998c).

2. A consequence of psychosocial interactions.

Psychosocial theories of depression focus on the interaction between the individual subject and the environment. At one end of the spectrum, some theories of social psychology emphasise the importance of the environment, as a decrease in pleasant events or an increase in unpleasant events is assumed to lead to dysphoria, which is seen as the key manifestation of depression (*Lewinsohn et al*., 1985). In this context, episode recurrence may be seen as a function of decreasing social and environmental support associated with a chronic and debilitating affective disor-

der, so patients become depressed following ever lower magnitude stressors (*Lewinsohn et al*., 1985; *Monroe and Simons*, 1991). In this model, the patient and the diathesis of the patient basically remain the same but the environmental stress increases. At the other end of the spectrum of psychosocial theories, behavioural and cognitive theories stress the importance of the individual. In behavioural theory settings (negative reinforcement or learned helplessness), an individual's learned noncontingency between behaviour related to environmental stimuli, and outcome, may lead to behavioural helplessness and depression (*Seligman and Maier*, 1967; *Seligman et al*., 1968). In cognitive science settings, depressive relapse or recurrence is due to activation of negative patterns of information processing that distort the individual's experience with the environment in a negative manner (*Beck*, 1971). *Hammen* (1991) has proposed that depressed individuals generate stressful conditions for themselves, which lead to recurrence ("the stress generation hypothesis"). The hypothesis implicates that patients with a history of many episodes should generate more dependent life events (i.e., events that are due to behaviour or characteristics of the depressed individuals themselves) than patients with fewer episodes. The issue is scantily investigated and no clear support has been provided for the hypothesis (*Harkness et al*., 1999).
In general, psychosocial theories put little weight on the presence and importance of the illness itself. The increasing risk of recurrence with every episode is seen to be caused primarily by the progressively decreasing psychological condition of the individual and / or by progressively decreasing social and environmental support. Growing evidence, as referred to in the present thesis, emphasises that at least a proportion of patients with major affective disorders display persisting cerebral correlates as reflected in persisting cognitive impairment and brain imaging abnormalities and it seems that these correlates develop during the course of the illness. Therefore, the illness itself has to be included as an evolving factor in the models of affective disorders.

3. A consequence of psychosocio-biological interactions.
Only one coherent model of the pathophysiology of affective disorder has taken its starting point in the long-term course of the illness, which is assumed to be determined by an interaction between biological events in the brain (due to the illness itself) and psychosocial events in the environment:

Kindling and sensitisation as a conceptual model for affective disorder
Robert Post and others have proposed that the paradigm of kindling and sensitisation might be a concept of the development of the course of episodes in affective disorder in a non-homologous model (*Post and Ballenger*, 1981; *Post et al*., 1986; *Post*, 1992; *Weisss and Post*, 1994; *Post and Weisss*, 1989, 1995, 1997). According to these theories, biochemical and anatomical substrates underlying affective disorders evolve over time as a function of prior episodes. It is suggested that repeated affective episodes may change gene expression and thereby neuropeptides and transmitters in the hippocampus and elsewhere in the limbic system (*Post*, 1992; *Post and Weisss*, 1997; *Duman et al*., 1997). Initially, psychosocial stress may precipitate the development of affective episodes, while later in the course of illness episodes develop more autonomously. As emphasised by *Post and Weisss* (1989, 1995), the models are non-homologous as affective disorder is not a seizure disorder like epilepsy in any clinical sense of the term. The inducing principles, neurophysiological processes and the behaviours induced in the animal kindling models are, at best, only rough analogies to those observed in affective disorder (*Post and Weiss*, 1988). However, kindling provides a conceptual model of how psychopathology may develop during the long-term course of affective disorders.

Kindling and sensitisation
Kindling is an experimental model of epilepsy and possibly also a general model of plasticity in the brain (*Cain*, 1992). The phenomenon of kindling was first described by *Graham Goddard* (*Goddard*, 1967; *Goddard et al*., 1969). It is now well established that repeated electrical or pharmacological stimulation of selective brain locations in the hippocampus, the amygdala and elsewhere in the limbic system and related structures can eventually lead to the appearance of convulsive activity in rats and other animals that are initially unresponsive to the stimulation. At the endstage of kindling, spontaneous epileptiform events may develop in the absence of exogenous stimulation (*Racine and McIntyre*, 1986; *Racine et al*., 1989; *Cain*, 1992). The kindling process seems to induce synaptic remodeling and neuronal degeneration (*Woldbye et al*., 1996) and involve permanent synaptic remodeling, possibly involving altered mRNA function and consequently altered gene expression (*Bailey and Kandel*, 1993; *Post and Weiss*, 1995, 1997; *Ghaemi et al*., 1999). The brain has become sensitised to the original stimulus but also to other stimuli as a cross-sensitisation may occur (*Post and Weiss*, 1989; *Hemmingsen*, 1989; *Glenthøj et al*., 1993). Kindling is thus the process by which sensitisation of the brain occurs and has been found ubiquitous across every vertebrate species tested (*Racine et al*., 1989). The term sensitisation has also been defined more broadly as the result of any neuronal process in which repetitive exposure to a stimulus results in increased response (*Kalivas and Barnes*, 1988, preface). By this definition, the phenomena of sensitisation and kindling may represent a general model of plasticity in the brain (*Antelman*, 1988; *Cain*, 1992).

The kindling process is progressive in nature. The first epileptiform afterdischarge is short in duration with relatively weak propagation to anatomically related sites. With repeated stimulation, the discharges increase in amplitude, duration and frequency and propagate throughout the brain (*Racine*, 1972a,b; *Racine et al*.,1989; *Cain*, 1992).

Kindling and memory
Some authors emphasise that kindling may be implicated in learning and memory (*Majkowski*, 1989) and *Goddard* originally studied the effect on learning of electrical and pharmacological stimulation of the amygdala (*Goddard and Douglas*, 1975). Similarly, the concept of sensitisation has its origin in learning theories (where it is viewed as the counterpart process to habituation in non-associative learning, *Rankin et al*., 1988). It seems from several animal studies that kindling is associated with a long-lasting decrease in learning and memory consolidation in the absence of any brain lesion (passive avoidance learning, predatory behaviour, reactivity to tail pinch, bar pressing, acquisition of taste and odour aversions, and the avoidance condition reflex (*Majkowski*, 1989; *Cain*, 1992; *Gilbert et al*., 1996; *Becker et al*., 1997).
In fact, memory has been defined broadly as the neuronal plasticity consisting of relatively long-lasting neuronal alterations, induced by the interaction between the brain and environmental stimulation (*Majkowski*, 1989). In this way, the definition of memory resembles the broad definition of sensitisation presented above.

Kindling and other non-convulsive behaviour

It is clear that electrical and pharmacological kindling can lead to changes in a variety of non-convulsive behaviours between seizures and even before the development of a generalised convulsion (*Cain*, 1992). In addition to changes in learning and memory, changes in sleep, spontaneous motor behaviour, and emotional state (reviewed in *Ebert and Koch*, 1996) are also related to kindling (*Racine et al*., 1989; *Mellanby and Sundstrom*, 1989; *Cain*, 1992).

Similarities between the process of kindling and the course of affective disorder

From the present thesis, it can be concluded that the course of episodes in affective disorder resembles the process of kindling in several aspects. 1) The episode effect is central in both conditions: the severity, duration and frequency of episodes seem to increase with the number of prior episodes during the course of affective illness just as during the process of kindling. 2) The threshold for developing an episode in affective disorder seems to decrease during the course of illness just as the threshold for developing seizures or behavioural changes during the kindling process. 3) Some patients with affective disorder develop cognitive impairment analogous to the memory impairment induced by kindling. Furthermore, although only preliminarily investigated, studies by the author (*Kessing et al*., 1996; *Kessing*, 1998d; *Kessing et al*., 1998d; *Kessing et al*., 1999b) and other studies (*Tham et al*., 1997;. *Gorp et al*., 1998) show that the number and the frequency of affective episodes seems to be associated with cognitive impairment.

Several other aspects common to kindling and affective disorders have been pointed out such as the increasingly rapid onset of seizures / affective episodes during the course of illness; the increasing complexity of seizures / affective episodes; the prevalence of psychosensory features (clinical phenomena hypothesised to reflect temporolimbic sensitisation, *Atre-Vaidya and Taylor*, 1997); and the response to treatment during the course of affective disorder (*Weiss and Post*, 1994; *Post and Weiss*, 1995, 1997; *Swann et al*., 1999). It is beyond the scope of the present thesis to deal with these issues.

Sensitisation in mammals

It is not possible to study sensitisation experimentally in humans. However, sensitisation has been experimentally induced in rhesus monkeys as sensitisation to separation from their mothers or from peers (*Suomi et al*., 1970, 1978; *Suomi*, 1997). Each subsequent separation elicited a greater intensity of depression-related behaviour. The animals stayed sensitised for years: following reunion, sensitised animals reacted with increased intensity of depression-related behaviour on a new separation years later, compared with animals who had never experienced separation. Sensitisation has also been induced by other stressors than separation (*Suomi*, 1997).

Sensitisation and possible neuropathology in affective disorder

It seems that affective disorder is pathophysiologically connected with organicity in some way since cognitive impairment in affective disorder is associated with brain imaging abnormalities. *Altshuler* (1993) has suggested the possibility that episodes of manias and depressions cause damage to brain tissue. Although the association between the course of episodes and cognitive impairment requires replication, it might further be speculatively hypothesised that a sensitisation mechanism in the brain results in recurrent episodes and cognitive impairment in affective patients (*Kessing et al*., 1996).

Sensitisation may possibly occur in various neurobiological systems. A sensitised system can be defined as one that is primed to respond more vigorously to the same or similar challenge (*Yehuda et al*., 1996). One illustrative theoretical example of a sensitised system in affective disorder could be the hypothalamic-pituitary-adrenal (HPA) axis which is known to be involved in the secretion of glucocorticoid and the experience of stress. The activity of glucocorticoid is regulated by pituitary and hypothalamic sites, but also via the limbic system, particularly the hippocampus (*Jacobson et Sapolsky*, 1991). A host of observations associate major affective disorder with stress and abnormalities in the HPA system. Cortisol has consistently been found to be elevated in a proportion of patients with affective disorder (*Goodwin and Jamison*, 1990, pp. 448-451; *Rubin et al*., 1996) and dysregulation of the HPA axis has been found to persist following remission and predict relapse (*Ribeiro et al*., 1993; *Paykel*, 1995; *Yehuda et al*., 1996; *Vieta et al*., 1997; *Lauer et al*., 1998; *Zobel et al*., 1999). Rhesus monkeys sensitised to separation from their mothers show increased cortisol compared with monkeys reared without intervention (*Higley et al*., 1992). Rats exposed to stress (*Watanabe et al*., 1992) or to repeated injections of glucocorticoid (*Sapolsky et al*., 1985, 1986; *Sapolsky and McEven*, 1988; *Wooley et al*., 1990) have been found to develop hippocampal neuronal loss. Analogously, humans exposed to combat-related stress (*Bremner et al*., 1995; *Gurvits et al*., 1996), adults exposed to childhood abuse (*Bremner et al*., 1997) and patients with recurrent affective disorder have been found to develop atrophy of the hippocampus (*Sheline et al*., 1997). Elevated plasma cortisol has been found to be associated with memory impairment in acutely depressed patients with affective disorder (*Rubinow et al*., 1984; *Wauthy et al*., 1991; *Bemelmans et al*., 1996; V*an Londen et al*., 1998b). Finally, elevated cortisol has been found to predict atrophy of the hippocampus and memory deficits in healthy humans without affective disorders (*Lupien et al*., 1998; *Newcomer et al*., 1999). It may be hypothesised from these studies that damage to the hippocampus might change the feedback regulation of the HPA axis resulting in dysregulation of the HPA system and increased vulnerability to psychosocial stress and to subsequent affective episodes (*Sheline et al*., 1997). In this way, each affective episode may result in brain damage which increases the risk of recurrence (and cognitive impairment) which again causes brain damage, etc. Thus, this hypothesis reflects a sensitised HPA system. Finally, it should be mentioned that the development of hippocampal glucocorticoid receptors is partially dependent on the serotonergic system, so the HPA neuroendocrine system and the serotonergic neurotransmitter system are mutually connected (*Mitchell et al*., 1990a, 1990b). However, still purely theoretically, sensitisation may occur in other neurobiological systems (*Post and Weiss*, 1997).

The theories of kindling and sensitisation in relation to other theories

In behavioural and cognitive science settings, depressive relapse or recurrence is due to activation of negative patterns of information processing (*Beck*, 1971). In contrast to these theories, the illness itself plays a major role in the theories of kindling and sensitisation, as affective episodes may themselves function as a kind of stress that increases the risk of further recurrence. In this way, the kindling and sensitisation theories constitute an integrative model of a triangle of interactions between the environment, the subject and the illness (Figure 17).

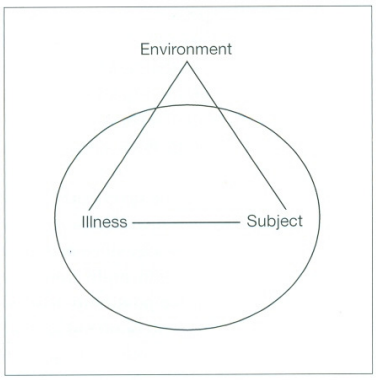


Fig. 17. Interactions between environment, subject and illness.

In the fully kindled condition, the changes induced in brain function are irreversible in contrast to what is believed about "knowledge structures" in the behavioural / cognitive models. Apart from these conceptual disagreements, the behavioural / cognitive models and the sensitisation and kindling model of affective disorder are compatible. Negative patterns of information processing might thus be activated more easily and on the basis of increasingly minimal clues the more they have been activated previously (*Segal et al*., 1996).

It has been suggested that recurrent affective disorder is basically a neurodevelopmental (*Nasrallah*, 1991, *van Os et al*., 1997) or, conversely, a neurodegenerative illness (*Merriam*, 1995) characterised by an increasing incapacity in the patients to maintain a stable affective state. These theories imply that affective episodes develop as a function of time, in contrast to the kindling and sensitisation theory, which emphasises that recurrence develop as a function of prior episodes.

Conclusion

Among the few existing hypotheses or models taking their starting point in the long-term course of affective disorder, the sensitisation and kindling model seems to be the one that, for the time being, best find support from epidemiological data. The present thesis of course provides no evidence for the validity of such a model but only evidence for the validity of some of the epidemiological data which constitute the premises for applying the kindling and sensitisation theory to affective disorder. Analyses of longitudinal data, as presented in the present thesis, emphasise the importance of the individual diathesis in this model. While the similarities between the kindling and sensitisation process and the course of major affective disorder might seem appealing, it has to be emphasised that the sensitisation and kindling model alone, at best, might be a conceptual framework for further investigations of the pathophysiology of affective disorder. The basic element in this framework is that the number of prior affective episodes has to be considered in analyses of the course of unipolar and bipolar affective disorders, because the course seems to evolve in a dynamic interaction between a genetically determined diathesis, psychosocial and biological stressors and the number of prior affective episodes. Episodes may thus act as a kind of primer in the brain increasing the sensibility to stressors and thus the risk of new affective episodes in such a way that the cerebral substrate underlying the disorders constantly changes. The present thesis suggest that this mechanism may either not occur in unipolar men or be compensated for by other factors.

Notably, it is possible that an episode effect is involved in other psychiatric disorders and a sensitisation process has similarly been proposed to be involved in alcoholism (*Hemmingsen*, 1989), anxiety and obessive-compulsive disorders (*Post and Weiss*, 1998) and in schizophrenia (*Glenthøj and Hemmingsen*, 1997). The sensitisation phenomenon remains, however, to be elucidated in man in general and in patients with psychiatric and affective disorders in particular.

13. SUGGESTIONS FOR FUTURE EPIDEMIOLOGICAL RESEARCH

The paradigm of sensitisation and kindling implies that affective illness may be an evolving process with evolving changes in neuropsychology, neurochemistry and neuroanatomy. Such changes are presumably more central to the process underlying the illness when found in the euthymic phase than are those seen during affective episodes (*Goodwin and Jamison*, 1990, p. 486). Persistent changes found in the euthymic phase may thus reflect traits that are associated with the underlying vulnerability to illness. Nevertheless, research has mainly focused on the illness state (*Goodwin and Jamison*, 1990, p. 488; *Flory et al*., 1998). On the background of the present thesis, epidemiological research within the following areas of affective disorders may be suggested:

Neuro-psychological, -chemical, and -anatomical aspects of the episode effect

The episode effect, which is central in the paradigm of sensitisation and kindling, could be further investigated in prospective studies of patients with first affective episodes followed longitudinally with assessment of stressful events, cognitive and neurological function, neurochemical and brain imaging changes - in the euthymic phases between affective episodes. More specifically, it would be interesting to investigate the role of HPA axis activation in the interplay between stressors in the euthymic phase, the risk of subsequent recurrence of affective episodes, cognitive function following recovery from such episodes and eventually changes in brain imaging in a prospective study of successive affective episodes.

Genetic aspects of the episode effect

Studies (including case register studies) of similarities and dissimilarities in the course of illness in patients who are blood relations in general and in patients who are twins in particular.

Aspects of the effect of psychosocial stressors on the course of illness

Prospective long-term studies or case register studies of the impact of psychosocial stressors on the risk of recurrence and the chances of recovery during the course of unipolar and bipolar affective disorder.

Treatment intervention and the episode effect

One ethically acceptable way to elucidate whether treatment might reduce or stop the episode effect may be a randomised controlled clinical study with assessment of the severity of episodes, time to recovery and time to recurrence following early intervention (after first or second affective episode) with prophylactic treatment and therapy compared with later intervention.

Finally, the results of the thesis suggests that future studies of the course of affective disorder should pay attention to the episode effect in the design of the studies and in analyses of the data, and that frailty models should be used to estimate the individual

heterogeneity in affective disorder as well as in other disorders with an episodic course.

14. SUMMARY

Knowledge of the course and outcome of major affective illness has clinical as well as theoretical implications. In understanding the pathophysiology of the major affective disorders, an essential question in the interplay between biological, psychological and social factors is whether the individual is changed biologically by experiencing an affective episode or not. A biological change may be reflected in a changed risk of experiencing new episodes and changed chances of recovery from these episodes for the individual, and may possibly also be reflected in persisting altered cognitive function as an expression of brain function affected during a longer period.

Previous studies of the course of affective episodes are flawed by a number of drawbacks such as various definitions of recovery and recurrence, various kinds of bias and confounders, low statistical power, and statistical analyses conducted without survival models and without paying attention to diagnostic instability or the individual heterogeneity of the course of episodes. Totally, these drawbacks and pitfalls affect the results of previous studies in unpredictable ways and make it hazardous to draw conclusions about the effect of prior affective episodes on the subsequent course of unipolar and bipolar disorder.

The present thesis avoided most of these pitfalls or adjusted for them in analyses of hospital data from the Danish Psychiatric Central Register, collected nationwide from 1971 to 1993. Hospitalisation was used as an expression of an affective episode. On average, a progressive course with increasing risk of recurrence with every new episode was found for unipolar and bipolar affective disorders. Initially, the two types of disorders followed markedly different courses, but later in the course of the illness the risk of recurrence was the same for the two disorders. However, analyses with frailty models revealed that for unipolar men, this progressive course was due to a subgroup of patients who had a great liability to recurrence from the beginning of the illness, whereas the remainder of the unipolar men did not have a progressive course of episodes.

Initially in the course of affective disorders, socio-demographic variables such as gender, age at onset, and marital status and comorbidity with alcoholism acted as risk factors for further recurrence. Later, however, particularly variables related to the previous course of illness played a role.

The chances of recovery from an episode were found not to change during the course of unipolar or bipolar disorder. In contrast, a review of studies from the era before active treatment revealed that the duration of untreated episodes seemed to increase during the course of illness.

Further case register studies and a clinical follow-up study by the author showed in accordance with previous studies that unipolar and bipolar affective disorders seem to be associated with increased risk of developing cognitive impairment and dementia and that the risk seems to increase with the number and the frequency of affective episodes.

Overall, the thesis illustrates 1) that case register studies can supplement prospective clinical studies in longitudinal research of major affective disorders. 2) the importance of taking the number of episodes into account in the analyses of data. 3) that affective episodes persistently increase the liability to illness for the individual, and that a cerebral component seems to bee present in some patients with major affective disorder. 4) that the treatment methods used so far seem to prevent the progression in the duration of affective episodes but not the progression in the frequency of episodes. It seems that, among the existing pathophysiological models, the sensitisation and kindling paradigm is the one that fits these epidemiological data best.

Studies for future epidemiological research on the course of affective disorder are suggested.

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