Psychological Medicine, 2007, **37**, 883–891. © 2007 Cambridge University Press
doi:10.1017/S0033291707000074 First published online 19 February 2007 Printed in the United Kingdom

The long-term course of depressive disorders in the Lundby Study

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ABSTRACT

Background. The Lundby Study is a longitudinal cohort study on a geographically defined population consisting of 3563 subjects. Information about episodes of different disorders was collected during field investigations in 1947, 1957, 1972 and in 1997. Interviews were carried out about current health and past episodes since the last investigation; for all subjects information was also collected from registers, case-notes and key informants. This paper describes the course and outcome of 344 subjects who had their first onset of depression during the follow-up.

Method. In this study individuals who had experienced their first episode of depression were followed up. Their course was studied with regard to recurrence of depression related to duration of follow-up, transition to other psychiatric disorders including alcohol disorders, as well as incidence and risk factors of suicide.

Results. Median age at first onset of depression was around 35 years for individuals followed up for 30–49 years. The recurrence rate was about 40% and varied from 17% to 76% depending on length of follow-up. Transition to diagnoses other than depression was registered in 21% of the total sample, alcohol disorders in 7% and bipolar disorder in 2%. Five per cent committed suicide; male gender and severity of depression were significant risk factors.

Conclusion. The low rates of recurrence and suicide suggest a better prognosis for community samples than for in- and out-patient samples.

INTRODUCTION

Depressive disorders are common and recurrent diseases and knowledge about their course and outcome is essential for the clinician. Three major aspects of the natural history of psychopathology can be identified: onset, course and outcome (Eaton, 2002).

The age at onset of depressive disorder is difficult to assess and depends on the threshold for 'caseness'. In an out-patient study on the first major depressive episode, women had a lower mean age at onset (24·3 years) than men (26·5 years) (Marcus *et al.* 2005). In another study of a clinical cohort, unipolar patients had a later median age of onset (49 years) than bipolar patients (33 years) and women had an earlier age of onset than men (Angst & Preisig, 1995*a*).

The course of depressive disorders is often characterized by recurrences. Recurrences can occur after long healthy periods. For instance, 58% of a sample of 105 subjects who had remained well for 5 years experienced a recurrence of an affective disorder during the subsequent 10-year follow-up period (Mueller *et al.* 1999). In a study of subjects with unipolar major

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depression (both in- and out-patients), Solomon *et al.* (2000) reported that nearly two-thirds of the subjects suffered at least one recurrence during a 10-year follow-up period. However, about 70% of unipolar patients in a clinical cohort experienced recurrences within 2 years after an episode of depression (Angst & Preisig, 1995*b*).

Winokur (1997) proposed that major depressive disorder is aetiologically a heterogeneous syndrome and can be divided into an endogenous group and a group probably secondary to emotional instability. This heterogeneity can lead to different kinds of courses: a subject with emotional instability and depression may have a more favourable course than a subject with an 'endogenous' depression.

A review article describing the course of depressive disorders in the community and primary care found recurrence rates between 30% and 40%, suggesting a milder course of depression for those samples (van Weel-Baumgarten *et al.* 2000). On the contrary, a high recurrence rate of 67% was reported from a study of 70 predominantly in-patients with moderate to severe depression (Kennedy *et al.* 2003).

The introduction of new pharmacological treatments did not seem to have reduced the rate of recurrence for unipolar and bipolar in-patients during the period 1994–1999 (Kessing *et al.* 2004). Furthermore, the long-term outcome had not changed for severely depressed subjects (Kennedy *et al.* 2003).

Women seem to experience depression twice as often as men (Culbertson, 1997). A female to male ratio of 3:1 for depression has been reported (Klerman & Weissman, 1989). Current knowledge provides no evidence that there are differences between the genders with respect to the course of depressive disorder. Thus, Angst *et al.* (2003) found that there was no evidence of a gender difference in the recurrence risk for severe major depression. An analysis from the Baltimore epidemiologic catchment area (ECA) cohort showed that a gender difference existed for first incidence of depression but not for course variables such as recurrence and length of episodes (Eaton *et al.* 1997).

Another topic of interest is whether depression remains a stable diagnosis over time or a transition to other mental disorders takes place. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) study showed that the 15·2% of subjects with mood disorder underwent a co-morbid transition to anxiety disorder or substance use disorder (de Graaf *et al.* 2004). In addition, studies on clinical cohorts showed a high risk for subsequent development of bipolar disorder (Angst & Preisig, 1995*a*; Goldberg *et al.* 2001).

The most feared outcome of depressive disorders is suicide. The rate of suicide is higher in depressed individuals than in the general population (Schneider *et al.* 2001). In a study of hospitalized patients with affective disorder, where the patients were followed up for up to 38 years after hospitalization, the proportion of suicide was found to be 10·8% (Angst *et al.* 2002). Previously, the Lundby Study reported that about 1% of subjects had committed suicide over a 25-year observation period (1947–1972), half of them suffering from a depressive disorder (Hagnell *et al.* 1982).

The aim of this study was to describe the long-term course (1947–1997) of first incidence of depression from the Lundby cohort. In particular, we wanted to examine:

(1) age at onset of first depression in men and women;
(2) rate of recurrences in men and women;
(3) transition to other diagnoses;
(4) incidence and risk factors of suicides among depressed individuals.

Background

The aim of the Lundby Study was to investigate the distribution of personality traits and mental disorders and their inter-relations in a geographically defined population (Essen-Möller *et al.* 1956). The Lundby district comprises two adjoining parishes, Dalby and Bonderup, in the south of Sweden. The first field investigation was started in 1947 and included 2550 subjects registered as inhabitants in the Lundby area on 1 July. Ninety-nine per cent of the individuals were investigated by psychiatrists (Essen-Möller *et al.* 1956). In 1957, 1013 newcomers (511 men and 502 women) were added (Hagnell, 1966); one-third of these subjects were born in the area and two-thirds were immigrants. The living Lundby population in 1957 consisted of 3310

subjects with a median age of 34 years (range 0–96 years). Hagnell & Öjesjö (1994) performed a second follow-up of the subjects in 1972. A third follow-up was carried out in 1997–2001 (Nettelbladt *et al*. 2005). During the three follow-ups, all individuals were investigated, including subjects who had moved to other places in Sweden. Few subjects had emigrated from Sweden. Information about deceased subjects was also gathered from registers, hospital records and key informants. The total population in the Lundby Study was 3563, comprising 1823 men and 1740 women. After 1957, no new subjects were added to the study.

The attrition rate for the follow-ups in 1957 and 1972 were between 1% and 2% (Hagnell *et al*. 1990). The third follow-up had an attrition rate of 6% (Nettelbladt *et al*. 2005).

Sample

In the Lundby population of 3563 subjects, 436 subjects during the follow-up time had their first episode of depression, of at least medium degree of impairment according to the Lundby diagnostic system. Sixty-five of these subjects had suffered from other types of mental disorders, of at least medium degree of impairment, before their first depression and they were excluded from the present study. Twenty-seven subjects with alcohol problems before onset of the first depression episode were also excluded from the analyses. Furthermore, 43 subjects who had been suffering from depression before inclusion in the cohort were excluded. Thus, the remaining sample consisted of 344 subjects, 116 men and 228 women in the present study with first episode of depression during 1947–1997.

METHOD

In all investigations the fieldworkers were clinically experienced psychiatrists. The interviews in 1947, 1957 and 1972 were semi-structured and contained questions about sociodemographic background, somatic health, mental health, contact with medical services and life events that had taken place during the past period. The assessment of mental health also included alcohol problems. The subjects were asked about onset and termination of episodes of mental disorders. When it was impossible to obtain accurate information about onset and termination, an approximation was obtained according to defined principles (Hagnell *et al*. 1990). In 1997 some new questions were added, such as questions about present satisfaction with life and the social situation.

Before the interview an introductory letter was sent to all subjects. The interview usually took place in the subject's home or at their place of work. The majority of the interviews were face-to-face, and only 128 interviews were accomplished by telephone in the 1997 field investigation.

The investigators also had access to case-notes and several registers, including the Patient Register that contained information about all in-patient care in Sweden from 1972 to 1997 (The National Board of Health and Welfare, 2004). A local out-patient care register, the Dalby-Tierp Register, covering the Lundby district was also useful (Community Medicine Institution, 2004). Key informants who had good knowledge of the subjects provided additional information. The final evaluations of the clinical diagnoses were made after collection of all available information and a best-estimate diagnosis was agreed upon. In 1997 clinical diagnoses according to ICD-10 and DSM-IV were added (WHO, 1992). DSM-IV diagnoses were also added in retrospect to the subjects that had fallen ill in episodes of depression before 1972 (APA, 1994).

Diagnostic criteria

The Lundby Study started before the DSM system was in use and applied a simple and comprehensive diagnostic system adapted to fieldwork since 1957. The main groups of the Lundby diagnostic system are: depression, anxiety disorders, tiredness, mixed neurosis, schizophrenia, other psychoses, organic syndrome and dementia. The DSM diagnosis of bipolar disorder is found in the category of other psychoses. Cases that do not fit into other categories are assigned to the group mixed neurosis (a residual 'neurotic category'). Only one diagnosis per episode is registered because the system is hierarchical, with organic brain disorders and dementia taking precedence over psychotic disorders, which in turn over-ride neurotic disorders.

The Lundby diagnosis of depression has remained unchanged during the period. In

https://doi.org/10.1017/S0033291707000074 Published online by Cambridge University Press

Table 1. *DSM-IV diagnoses for 344 subjects diagnosed with depression 1947–1997*

Diagnoses	Men	Women	Total
Major depressive disorder 296·2	71	136	207
Depressive disorder NOS 311	27	53	80
Dysthymic disorder 300·4	1	3	4
Adjustment disorder with depressive mood 309·0	14	34	48
Mood disorder due to medical condition 293·83	3	2	5
Total	116	228	344

respect of depression two categories are possible: depression proper and depression plus other psychiatric symptoms. The main symptoms found in subjects diagnosed as suffering from depression proper were the following:

Lowered mood, depressive feelings, tendency to guilt feelings, gloomy outlook, reduced activity, lack of initiative, reduced self-esteem, lowered enjoyment of life and feeling of low vitality, anxiety and fear. Has more difficulty than usual, and is often unable to carry out his daily responsibilities. Sometimes retardation is present. The subject is often worse in the morning and better towards the evening. Often he has sleep disturbances and wakes up in the early morning. Loss of appetite and weight (Hagnell, 1966).

The Lundby diagnosis of depression plus other psychiatric symptoms indicates a lowered mood and a clear depression, but other symptoms such as anxiety and obsessive symptoms could also be prominent. However, even if there are other symptoms, the depressive symptomatology dominates. In this study these two diagnostic groups were combined together and called depression. Anxiety, tiredness and mixed neuroses were combined and termed 'neurotic disorder'.

Other psychoses was kept as a separate diagnostic category and organic disorders were grouped together with dementia. DSM-IV diagnoses are shown in Table 1 for 344 subjects diagnosed with depression during the period 1947–1997.

In order to be counted as a case of alcoholism, the following definition was used:

(*a*) alcohol dependence with a persistent pattern of withdrawal symptoms, craving and tremor (DSM-IV 303.90);

(*b*) alcohol abuse with a persistent pattern of heavy (excessive) drinking, frequent intoxications, and a tolerance change (DSM-IV 305.00).

Impairment

In a previous study three levels of impairment were used (Rorsman *et al.* 1990). Every depressive episode was rated according to the degree of impairment, which was rated as mild, medium and severe (Leighton *et al.* 1963). A mild degree of impairment corresponds to a Global Assessment of Functioning (GAF) score of 70–61. Medium impairment corresponds to a GAF score of 60–51 and severe impairment to a score of 50–31. Episodes of disorders with a mild degree of impairment were not counted for any diagnosis; hence impairment of medium degree was defined as the threshold for 'caseness', in accordance with proposals by Eaton *et al.* (1997).

Duration of episode

The onset and termination dates of all episodes were recorded. As it is often difficult to decide when an illness starts and ends, we tried to determine the month or the half-year when an episode began or ended. If the subject was on medication for a mental disorder, the subject was considered as not healthy and hence not at risk for recurrence.

Statistical methods

The subjects were categorized by gender and number of years of follow-up after their first onset of depression. We calculated 95% confidence intervals (CIs) for median time to recurrence of depression according to Gardner & Altman (2000). The probability of remaining free of recurrence during follow-up was illustrated for each gender by a Kaplan–Meier curve. Risk factors for suicide were determined by means of Cox regression analyses. Results were considered statistically significant for p values below 5%.

RESULTS

The distribution of age at onset of first depression according to duration of follow-up is shown in Table 2. Individuals who were followed up for a few years were in general older at

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Table 2. *Distribution of age at onset of first depression for men and women according to duration of follow-up (n = 344, 116 men and 228 women)*

Time of follow-up (years)	Men			Women		
	n	Median age	Range	*n*	Median age	Range
0–9	35	57	20–83	57	64	32–89
10–19	25	48	29–76	40	48·5	22–78
20–29	30	39	18–66	55	42	21–75
30–39	22	36	19–55	59	36	15–62
40–49	4	35	21–41	17	35	19–49

Table 3. *Percentage of men and women with recurrences according to duration of follow-up after onset of first depression (n = 344)*

Time of follow-up (years)	Men (% of subjects)	Women (% of subjects)
0–9	22·9 (8/35)	17·5 (10/57)
10–19	36·0 (9/25)	32·5 (13/40)
20–29	20·0 (6/30)	32·8 (16/55)
30–39	45·5 (10/22)	42·4 (25/59)
40–49	75 (3/4)	76·5 (13/17)
Total	31 (36/116)	34 (77/228)

start than those who could be followed up longer; thus the median age at onset was fairly high (around 60 years) for subjects who had been observed 0–9 years after first onset of depression. The median age at onset decreased with longer follow-up times until it stabilized at around 35 years for individuals who could be followed up for 30–49 years. Median number of total years of follow-up after onset was 18·2 years for men and 21·8 years for women.

The percentage of men and women with recurrences according to duration of follow-up after onset of first depression is shown in Table 3. The risk of recurrence increased with follow-up time. For those followed up for 30–39 years after onset of first depression, having a median age of 36 at onset, the proportion who had a recurrence was 46% for females and 42% for males. There was an increase to around 75% for those with 40–49 years of follow-up. The high recurrence rate for those observed for more than 30 years does not entirely depend on the long period of follow-up as 41% of the males and 37% of the females in this subsample had had a recurrence before the 30 years of follow-up.

We compared those who had been diagnosed with a depressive disorder before 1972 with those diagnosed after 1972. The proportion of the sample who had had a recurrence in the different time periods was evenly distributed. We found that 28% of the males and 24% of the females followed up for 20–29 years before 1972 had a recurrence and 22% of the men and 28% of the women had a recurrence after 1972. The median time to recurrence for another episode of depression of medium degree of impairment was 4·6 years (95% CI 1·9–8·3) for men and 3·6 years (95% CI 1·9–5·0) for women.

The Kaplan–Meier curve (Fig. 1) illustrates the probability of remaining free of recurrence during follow-up for the 344 subjects who had experienced a first episode of depression. The individuals began their period of follow-up at different calendar times and thus had a different duration of follow-up before a recurrence, from a few weeks up to 45 years. The cumulative probability of remaining free of recurrence is about 60%. Males and females had similar curves, illustrating that the course for the genders did not show substantial differences in this study.

Transition to other diagnosis after at least one episode of depression

Seven per cent of the total sample, 14% of the men (16/116) and 4% of the women (9/228), had been registered as cases of alcohol disorder after onset of their first depression. Approximately 8% men (9/116) had alcohol dependence and 6% (7/116) had alcohol abuse. About 2% of the women (5/228) were diagnosed as cases of alcohol dependence and 2% (4/228) as alcohol abuse. Six per cent of the men had experienced a diagnosis of neurotic disorder after an episode of depression. Twelve per cent of the women had experienced an episode of neurotic disorder, mostly anxiety disorders. The median time for receiving a neurotic diagnosis was longer for men (11·3 years) than for women (5·2 years).

Later in their course eight individuals had an episode of other psychoses, and of these, seven subjects had a DSM-IV diagnosis of bipolar disorder (type 1). One subject received a

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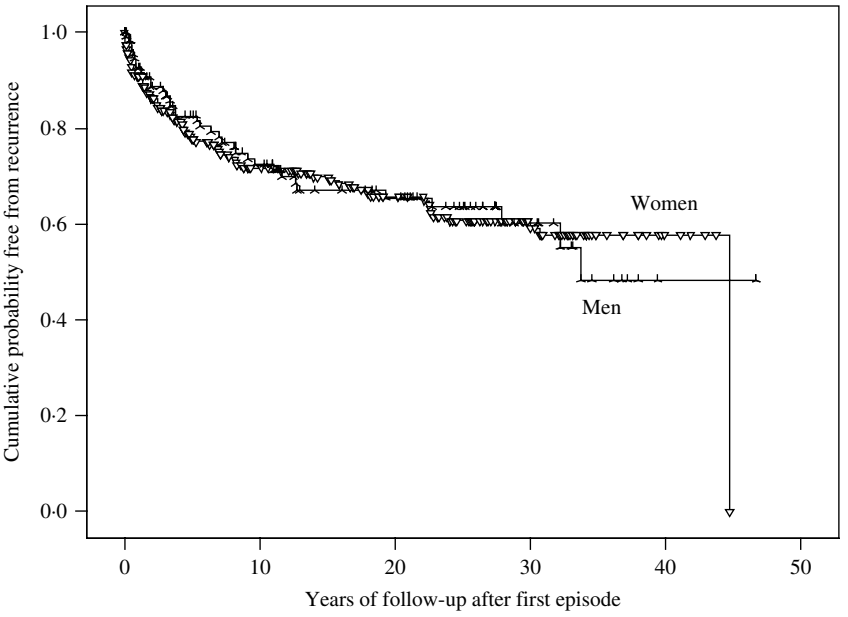

FIG. 1. Time to recurrence after first episode of depression. Cumulative probability represents the proportion free of recurrence.

diagnosis of psychotic disorder due to a medical condition. No subject was diagnosed with schizophrenia. The median follow-up time of 17 years to an episode of other psychoses was similar for the sexes.

Organic syndrome and dementia were combined together. Six per cent of the men and 10% of the women developed organic disorder or dementia. Of the few men who later in their course were diagnosed with organic disorder or dementia, none was followed up for more than 24 years and the median time to the diagnosis was 6·3 years. Women were followed up for longer time periods than men and the median time to diagnosis was 17·2 years.

Suicide

Five per cent of suicides (17/344) were registered. Ten per cent of the men (12/116) and 2% of the women (5/228) committed suicide. Eleven of the subjects who had committed suicide had only one episode of depression registered. Of the 17 suicides, 12 took place in connection with a registered episode of depression. The suicides occurred early in the course of depression; thus 10 of the male suicides took place within the follow-up period of 0–9 years. For the women, four suicides occurred within a 19-year follow-up period and one suicide occurred late in the course of illness. The age at onset of those who committed suicide ranged from 20 to 83 in the sample.

The following risk factors were considered for suicide: degree of impairment of depression, age at onset, alcohol disorder and gender (Table 4). Severe degree of impairment and male gender were found to be significant risk factors. Age at onset and alcohol disorders were not statistically significant risk factors for suicide in this sample.

DISCUSSION

Our results are based on a sample with different lengths of follow-up after onset of the first episode of depression. The sample is a community sample with subjects of varying ages. Sixty per cent of the depressions according to the Lundby system were major depressive disorders according to the DSM-IV system, whereas the rest could be classified as different subtypes of depressive disorder. Eighteen per cent of the individuals had been hospitalized at least once for psychiatric disorders. Subjects with previous diagnoses, such as, for example, anxiety syndromes, were withdrawn from the study because

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Table 4. *Risk factors for suicide* ($n=17$)

Risk factor	Hazard ratio (95% CI)	*p* value
Gender[a]	6·11 (2·07–18·00)	0·001
Age at onset (years)	1·02 (0·99–1·06)	0·160
Severe impairment[b]	4·49 (1·70–11·81)	0·002
Alcohol disorder[c]	0·54 (0·12–2·48)	0·427

CI, Confidence interval.
[a] Female gender (reference category).
[b] Medium degree of impairment (reference category).
[c] Subjects without alcohol disorder (reference category).

their course was not considered to be representative of the depressive disorder itself.

The high median age at onset may be caused by recall bias, as the first episode is sometimes forgotten or recognized much later in retrospect. In addition, subjects with mental disorder below the age 15 were all diagnosed as cases of 'child neuroses' and were not counted as cases of depression. These facts may have contributed to the rather high median age of onset for the subjects. However, those who were followed up for more than 30 years had a considerably lower median age at onset of around 35 years. Similarly, a median age of onset for mood disorders of around 30 years was found in the National Comorbidity Survey Replication (Kessler *et al*. 2005).

If a subject in old age had a first episode of depression, they might not live long enough to experience another episode. This could have led to the rather high proportion of single episodes. Of course, the fact that the sample was heterogeneous concerning the variety of diagnoses could also explain the high proportion of single episodes. The Lundby diagnosis of depression included adjustment disorder with depressed mood and probably this disorder could have a more favourable course, but they represented only a minor part of the sample at around 14%. In addition, our threshold for 'caseness' was high. Another possibility is that prophylactic treatment prevented recurrences for the subjects in our sample, so that fewer subjects were 'at risk' for recurrences. Episodes of depression could also have been forgotten because the period under study was long and there were few field investigations. However, more persistent cases should probably have been detected and all episodes of depression resulting in hospitalization were counted due to access to the Patient Register and hospital records.

The probability of remaining free of recurrence was about 60% in the whole sample. The proportion of subjects experiencing recurrence increased with the duration of the follow-up period. However, a substantial proportion of individuals who had been followed up for over 40 years had a recurrence before 30 years of follow-up.

As the recurrence rates were similar in the time periods before and after 1972, this result suggests that the course of depressive disorder had not changed markedly in the later period in the Lundby Study. More women than men were affected by depressive disorders, but the Kaplan–Meier curves for the different genders were similar. Angst *et al*. (2003) also found no evidence of a gender difference in the recurrence risk of severe major depressives.

Higher proportions of depressed women than men were later suffering from a neurotic disorder. Women were less stable in their diagnostic patterns. Of the total sample of 344 subjects with depression, a few became bipolar ($n=7$). Our observed frequency of transition to bipolar disorder was low compared to previous studies (Angst, 1996). The observed frequency of 'switching' to bipolar 1 was about 2% in our sample, which is about half that observed by Akiskal *et al*. (1995). However, most of the subjects in their study were in-patients (79·7%).

A proportion of the sample developed alcohol disorders during the follow-up time after their first onset of depression. There was a clear male dominance, with 13·8% of the men and only 3·9% of the women developing alcohol disorders. Although in clinical samples depression is the disorder most commonly associated with alcohol disorders, these findings show that depressive disorders may be a precursor of alcohol disorders.

An important finding in the present study is that only about 5% of the subjects committed suicide. In a sample with hospitalized individuals with depression, a suicide rate of 10% was reported after 42 years of follow-up (Brådvik & Berglund, 2001). An even higher rate (15%) was reported by Guze & Robins (1970). Our data may suggest a better prognosis for community samples, but because of the

variable lengths of follow-up, our calculated suicide rate may also underestimate the true risk. However, for both sexes, the observed suicides tended to occur early in the course of depression. The risk factors for suicide in this study were found to be male gender and severe degree of impairment of the first depressive episode.

To summarize, the course of depression in the Lundby cohort was variable and less severe than for in-patient samples. The recurrence rate of about 40% was dependent on age at onset and follow-up time. Few subjects in our sample became bipolar. Transition to other 'neurotic' diagnoses occurred in about 10%. The frequency of suicide was about 5%, which is less than for in-patient samples. More men than women committed suicide and developed alcohol disorders.

Limitations

For those subjects who had their first episode of depression before 1972, DSM-IV diagnoses were added in retrospect. The recall periods were of considerable length (10, 15 and 25 years), possibly introducing bias and resulting in an underestimation of episodes registered. The length of episodes of mental disorder could have been difficult to assess in retrospect. In addition, a limitation was that we had no information on whether the subjects had received treatment, although the finding that 18% of the sample had been admitted to psychiatric care suggests that most of the subjects had received antidepressive treatment. A possible limitation may be that cases with a previous history of depression were excluded from the study, which may favour the selection of subjects with late onset of depression with a better prognosis.

CONCLUSION

The low rates of recurrence and suicide suggest a better prognosis for community samples than for in- and out-patient samples. Significant risk factors for suicide were male gender and the degree of impairment of the first depressive episode. The diagnosis of depression was fairly stable for the subjects in the Lundby cohort, and only a few cases of first-onset depression became bipolar. More males than females developed alcohol disorders. Depressive disorder was a precursor of alcohol disorder in 14% of males.

ACKNOWLEDGEMENTS

This study was supported by the Swedish Council for Planning and Coordination of Research, the Swedish Council for Social Research, the Swedish Research Council, the Swedish Medical Research Council, the Medical Faculty, Lund University, the Principal Government of Scania, the Söderström-Königska Foundation, the Bror Gadelius Foundation, the Sjöbring Foundation, and the OM Persson Foundation.

DECLARATION OF INTEREST

Povl Munk-Jörgensen has received a non-conditional educational grant from Eli Lilly and Wyeth, the latter terminating in 2002. He has also received minor lecturing honorariums from Lundbeck, GlaxoSmithKline, AstraZeneca and Wyeth.

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