Depression in the Lundby Study 1947-1997 Incidence, course and risk-factors

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To Sven, Nils, Siri and Ylva

“It ain’t over till it’s over”, Lawrence Peter “Yogi” Berra

Contents

Abbreviations

ECA	Epidemiological Catchment Area Study
CIDI	Composite International Diagnostic Interview
DIS	Diagnostic Interview Schedule
DPAX	Depression and Anxiety Schedule
DSM-IV	Diagnostic and Statistical Manual of Mental disorders, Fourth Edition, Washington DC, 1994
ICD-10	The ICD-10. Classification of Mental and Behavioural Disorders, WHO, Geneva, 1993
NCS	National Comorbidity Survey
NEMESIS	Netherlands Mental Health Survey and Incidence Study
PSE	Present State Examination
SCAN	Schedules for Clinical Assessments in Neuropsychiatry
UKKI	Prospective study on a population from Uusikapunki and Kemijärvi
ODIN	European Outcomes of Depression International Outcome Study

Original papers

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I Nettelbladt P, Bogren M, Mattisson C, Öjesjö L, Hagnell O, Hofvendahl E, Toråker P, Bhugra D. **Does it make sense to do repeated surveys? - the Lundby Study, 1947-1997.**
Acta Psychiatrica Scandinavica, 2005, 111, 1-9.

II Mattisson C, Bogren M, Nettelbladt P, Munk-Jörgensen P, Bhugra D. **First incidence depression in the Lundby Study: A comparison of the two time periods 1947-1972 and 1972-1997.** Journal of Affective Disorders, 2005, 87, 151-160.

III Mattisson C, Bogren M, Horstmann V, Munk-Jörgensen P, Nettelbladt P. **The long-term course of depressive disorders in the Lundby Study.** Psychological Medicine, 2007, 37, 883-891.

IV Mattisson C, Bogren M, Horstmann V, Munk-Jörgensen P, Tambs K, Nettelbladt P. **Risk factors for depressive disorders a - 50 year prospective clinical follow-up in the Lundby Study.** Journal of Affective Disorders, 2008. In press.

Introduction

Depressive disorders have tormented human beings for ages, and melancholia was already described by Hippocrates (460-370 BC). He described melancholia (black bile) as a disease with a range of psychiatric symptoms. Aretaeus of Cappadocia who lived in Alexandria in the 1st century was influenced by Hippocrates and was the first to link mania and melancholy (Angst and Marneros, 2001). In England, Robert Burton wrote an extensive book of affective illness in 1621, and categorized various forms of melancholy. Freud suggested that melancholia was caused by an object-loss which is withdrawn from consciousness, resulting in repressed hostility and aggression directed towards the self (Freud, 1917).

A moving picture of a depression that plagued the Swedish poet Tegnér was given in his poem "Spleen". He described vividly in the poem that his heart was bitten by a malignant elf and that the world turned into a place of misery. Another heartbreaking description of a severe depression and its cure was given by William Styron in his book Darkness Visible (Styron, 1991). The author describes depressed individuals as having "their minds turned agonizingly inward", but he also describes his way to recovery and health.

The word depression was introduced in the 19th century by the German psychiatrist Wilhelm Griesinger and Emil Kraepelin continued to use the term (Kraepelin, 1921). Kiloh and Garside (1963) argued that the group of depressive states consists of two separate entities, the neurotic depression and the endogenous depression. In addition, they emphasized that those patients diagnosed as suffering from endogenous depression had a significantly better response to antidepressive drugs. These two entities were lumped together in the 1980 DSM-III version, although psychotic and/or melancholic features could be specified (American Psychiatric Association, 1980).

In the recent terminology according to DSM-IV, the depressive syndrome is included in "mood disorders". The depressive syndrome comprises several criteria as depressed mood, loss of interest and pleasure, weight loss, psychomotor retardation, loss of energy, diminished ability to think and guilt-feelings. Often the subject has recurrent thoughts of death and suicidal ideation. These symptoms should persist over a period of at least weeks and the subjects habitual functioning should be impaired.

The concept of major depression popularized in DSM-III, has recently been criticized as over-inclusive naming bereavement-related sadness as major depression (Wakefield et al., 2008). Some researchers have proposed a return to the concept of two depressions, melancholic and non-melancholic illness (Shorter, 2007). Shorter discusses the doctrine of the two depressions and its origins, and points out that endogenous depression traditionally served as a

synonym for melancholia, whereas neurotic/reactive depression was a heterogeneous condition mixed up with anxiety and character disorder. The Lundby diagnosis of depression resembles the melancholic category of depression (Hagnell et al., 1994).

The Lundby Study is considered as a classic epidemiologic study of common psychiatric disorders. The study, launched in 1947, contains a fragment of Swedish psychiatric history and many individuals' life courses. The Lundby Study covers a period of fifty years. The oldest subject in the study was born in 1854 and the youngest in 1957. During the study period the society has undergone rapid change in the labour market, sex roles, urbanisation and progress in health care. After the first field-investigation in 1947, follow-ups were carried out in 1957, 1972 and in 1997. The study with its long period of follow-up and repeated surveys illustrates several methodological problems. Nevertheless, the Lundby Study offers an opportunity to study depressive disorders over time between 1947-1997 with respect to incidence, course and risk-factors.

Background

Short introduction in epidemiology

Epidemiological studies can provide valuable information about health status in defined populations. Studies of the public health could assess the extent of "unmet need" for care (Burke, 2002). If the information is of good quality, it is a solid ground for health planners to estimate the need for health services (Lopez, 2005). The well-known Global Burden of Disease Study highlighted the public health significance of depressive disorders on a worldwide level (Üstun et al., 2004). The investigators reported depression as the fourth leading cause of disease burden accounting for 3.7% of total disability adjusted life years in the world in 1990.

Epidemiological studies could be cross-sectional or longitudinal. Cross-sectional studies could estimate prevalence which is the proportion of a group of people possessing an outcome or disease at a given point in time (Fletcher et al., 1996). Prevalence is affected by the average duration of disease and captures mostly chronic cases in the community. Also, prevalence depends on curability and mortality.

In a longitudinal study a cohort is followed over time giving possibilities for calculating incidence. An incidence rate refers to new cases of disease during a specific time period occurring in a cohort initially free of the disease (Fletcher et al., 1996). The risk period is the time period during which cases of the disease are identified in a cohort (Susser et al., 2006). Individuals are "at risk"

until they either receive the disease, are lost to follow-up, die or the study-period ends. The time "at risk" is called person-time and may be measured in any unit of time, for instance person-years. The incidence rate is an estimate of the probability or risk of contracting an illness. Estimations of prevalence and incidence are needed, but often have to be complimented with data on impairment and disability, since diagnostic criteria are limited as guidance to the need for treatment (Spitzer, 1998). Longitudinal studies are resource-intensive and complicated to do, but can yield several outcomes and information about probable risk factors. By identifying risk factors, intervention and prevention could be targeted against disorders.

There are many methodological difficulties inherent in longitudinal studies. Longitudinal studies demand endurance of the research team and administrative support. Also, multiple generations must collaborate, since a lifetime can be too short to cover a longitudinal project with a long time-span (Isohanni, 2001). During the research process the different teams will face problems with tracing of subjects, attrition, interrater-reliability, validity of diagnosis, changing diagnostic systems and different sources of bias, such as recall bias. Also, a condition for succeeding in longitudinal research is access to registers of good quality.

The Stirling County Study from Canada (Leighton et al., 1963) and the Lundby Study are early ground-breaking epidemiological studies investigating mental disorders. The Stirling County Study contains several important aspect of epidemiology as search for etiological components of psychiatric disorders, a description of the panorama of mental disorders in the community and the socio-cultural environment. Both studies are longitudinal studies with long periods of follow-up, but have small samples compared to newer studies (Murphy et al., 2000 a). Both studies with their long history in the epidemiological field illustrate a lot of difficulties in doing repeated surveys, but also methods to deal with them.

Incidence studies

Incidence studies could give indications of secular changes in the rate of diseases. Secular effects of rates of depression can be divided into age effects, period effects and cohort effects. Age effects refer to age-specific stages in life during which subjects are more prone to fall ill. Period effects refer to variations in rates of illness associated with a specific time period. Cohort effect refers usually to changes in rates of illness among groups of people born in the same year or decade. These temporal changes may occur separately or interact with one another (Horwath et al., 2002). Usually, studies distinguish between first incidence episode and the following episodes, since probably the first one is more causative than the following episodes (Tsuang, 2004).

There are at least six studies that give incidence estimates of depression. (Table 1). The Epidemiological Catchment Area study (**ECA study**) which used DSM-III diagnoses at base-line is based on samples from five geographically defined areas of the US and included 13,538 subjects aged 18-65+ at baseline (Eaton et al., 1989). The follow-up period was one year and 10,861 subjects completed the second wave interview. A structured instrument, the Diagnostic Interview Schedule (DIS) was used by trained laymen. This diagnostic instrument consisted of pre-specified questions, directly connected to the Diagnostic and Statistical Manual of Mental disorders (APA, 1980). The final diagnosis was made by means of computer algorithms that simulate the application of DSM-III criteria. The annual incidence of DSM-III major depressive disorder per 1,000 person-years at risk was 11.0 for males and 19.8 for females (Eaton et al., 1989).

Also, a long-term prospective survey was conducted between 1981 and 1993 at the Baltimore site of the ECA study, which found 1-year overall incidence of 3.0 per 1,000 person-years at risk (Eaton et al., 1997). Another follow-up published in 2007 from the ECA study, comparing the two time periods 1981-1993 and 1993-2004 showed a decline of the incidence of depression in the latter period from 3.2 per 1,000 person years to 1.9 per 1,000 person years (Eaton et al., 2007).

A study that resembles the Lundby Study is the **Stirling County Study** in Canada (Leighton et al., 1963). Samples of the adult population (age 18-90+) were selected in 1952, 1970 and 1992. The 1952 sample consists of 1,003 subjects, the 1970 sample comprises 1,201 and the 1992 sample included 1,396 subjects from a geographically defined area in Canada. The interviews were carried out by trained laymen who used structured interviews. Additional information was provided from psychiatric records and death certificates for those who died. A computer program named the DPAX (DP stands for depression and AX for anxiety), which make use of a diagnostic algorithm was applied. The DPAX schedule contains questions about the essential features of depression. In the 1990s the DIS schedule was added (Murphy et al., 1990). The annual incidence rate for depression for males was 2.1 per 1,000 person years at risk and for females 2.5 (Murphy et al., 1988). The incidence rate remained stable over time in the Stirling County Study during the two time periods 1952-1970 and 1970-1992, (Murphy et al., 2000 a). The 40-year perspective overall annual incidence was 3.8 per 1,000 person-years.

Another well-known study is the Netherlands Mental Health Survey and Incidence Study (**NEMESIS),** which reported first incidence of DSM-III-R psychiatric disorders in a sample aged 18-64 of the general population (Bijl et al., 2002). This study had markedly higher incidence rates of major depression (17.2 per 1,000 person years at risk for males and 39.0 for females) than the Stirling County Study and the ECA study. The instrument to determine the diagnoses was the Composite International Diagnostic Interview (CIDI). The

CIDI is a structured interview designed for use by trained interviewers who are not clinicians (Smeets and Dingeman, 1983).

From Finland the **UKKI s**tudy (Lehtinen et al., 1996) using the ICD-8 classification has given estimates of depression. The original sample consisted of 1,000 persons aged 15-64 years. In the baseline survey the research methods consisted of personal interviews conducted by psychiatrists, questionnaires and psychological tests. Information was also gathered from records of health care. The first follow-up after 5 years applied a combination of a postal survey and a psychiatric interview. The second follow-up after 16 years included a semi-structured interview, questionnaires, psychological tests and registers. The UKKI study estimated the incidence of neurotic depression to 2.0 per 1,000 person-years in males and 2.7 for females.

More recently, the Finnish sub-sample (N=2,999) aged 18-64 of the European Outcomes of Depression International Outcome Study (**ODIN)**, showed much higher estimates of depressive disorders (Lehtinen et al., 2005). The methods in the ODIN survey was a combination of a postal survey of the whole sample and a diagnostic interview (SCAN-2) to all screen –positive individuals (WHO, 1994). The Scan-2 interview was used to assign caseness against ICD-10 criteria. The ODIN survey reported a total overall incidence of 20.5 per 1,000 person-years.

In Norway, **Sandanger** et al. performed a two– phase population study of 2,015 and 617 subjects. The authors reported an increasing incidence rate for depression from 1930-1991. They emphasized that the retrospective design of their study and recall bias raised questions about how certain the results were. The authors reported an incidence rate of depression according to ICD-10 of 4.4 for males and 30.4 per 1,000 person-years for females (Sandanger et al., 1999).

In the **Lundby Study** the investigators have been psychiatrists using semi-structured interviews. They also had access to other sources of information such as key-informants, registers and case-notes. In 1982, Hagnell et al. reported that incidence of first onset depression according to the Lundby system increased for both sexes (Hagnell et al., 1982). Also, Rorsman has presented estimate of first incidence depression from the Lundby Study (Rorsman et al., 1990).

Table 1. Incidence studies of depression.

Year	Study	Sample n	Follow-up	Annual incidence			
			Years	Males	Females	Total	Diagnostic criteria
1982	Lundby	2,550	25	3.7	7.7	5.5	Lundby diagnoses
1988	Stirling County	524	16	2.1	2.5	-	DPAX
1989	ECA study	10,861	1	11.0	19.8	15.9	DSM--III
1990	Lundby	2,612	15	4.3	7.6	5.9	Lundby diagnoses
1996	UKKI	747	16	2.0	2.7	-	ICD-8
1997	ECA study	1,920	15	2.0	3.6	3.0	DSM-III-R
1999	Sandanger	2,015	1*	4.4	30.4	18.1	ICD-10
2000	Stirling County	1,214	40	3.9	3.7	3.8	DPAX DIS
2002	NEMESIS	5,618	1	17.2	39.0	27.2	DSM-III R
2005	ODIN	1,939	1	-	-	20.5	ICD-10

Annual incidence refers to overall incidence per 1,000 years of risk.
*Follow up time was retrospectively recorded.

Estimates of incidence vary considerably between studies. Long term studies evidently results in much lower incidence than studies with shorter follow-up periods. Different explanations for this result have been proposed (Lehtinen et al., 2005). One reason could be that some episodes are not true first incidence episodes because respondents do not recall earlier episodes and another explanation could be that the new episodes are more effectively recognised in a short time follow-up period. Differences in case-finding methods could also be an explanation for the differences in the estimates. Murphy et al. (2000 b) have suggested that the difference in estimates according to the length of interval could be related to whether or not subjects are willing to be re-interviewed after a short interval. They also underlined that the refusal rate was higher in short interval studies compared to long-interval studies. Those that participated in the re-interview could be more "psychologically minded" and also more aware of the interest of the interviewer. The authors concluded that it will be important to develop better methods for distinguishing between the prodromal state and a diagnosable disorder. There is also a possibility that transient depressive states due to stress or negative life events are reported to a greater extent by lay-interviewers.

Gender differences

In a review on epidemiological research on women and depression, it was reported that depression was more common among females than males (Kessler, 2003). In most incidence studies there is a female preponderance with more females than males being affected by depressive disorders. An exception is the study of an Amish population, in which no difference of the incidence rate between the sexes was detected. The authors stated that the most obvious explanation of their finding was that alcoholism and sociopathy did not mask the expression of affective disorder in men (Egeland and Hostetter, 1983).

The reason for the increased risk for depressive disorders for females found in most other incidence studies remains unclear. Kessler (2003) suggested that the higher rates of depression for females depend on joint effects of biological vulnerabilities and environmental provoking experiences. In line with this hypothesis are findings that gender differences are less pronounced in societies where the traditional female role is valued similarly to that of males (Piccinelli and Wilkinson, 2000).

Another explanation that has been offered for the gender difference in incidence rates of depression includes a higher prevalence for anxiety disorders subsequently leading to depression, (Parker and Hadzi-Pavlovic, 2004). However, the hypothesis that the female preponderance in depression is secondary to a female preponderance in anxiety disorders could not be supported in their study (Parker and Hadzi-Pavlovic, 2004). Other reasons for the gender difference include higher degree of neuroticism (Goodwin and Gotlib, 2004) and sex-specific role stress (Lucht et al., 2003). Artifactual reasons have also been discussed as an explanation of the higher rates of depression for females. A reason could be a better female memory for remembering episodes and a female tendency to report more depressive symptoms resulting in higher chance to reach threshold for a diagnosis (Angst and Dobler-Mikola, 1984). Finally, in a review describing gender differences in unipolar depression, intrapsychic and psychosocial risk factors were pointed out as the most likely explanations of the higher depression risk in females (Kuehner, 2003).

Follow-up studies

Unipolar and bipolar depression

Emil Kraepelin considered mood disorders to be one group namely, manic-depressive insanity (Kraepelin, 1921). Karl Kleist coined the terms unipolar and bipolar in 1953, referring to unipolar mania and unipolar depression (Kleist, 1953). Karl Leonhard (1979) supported the theory that unipolar and bipolar diseases were separate entities. The dichotomy between unipolar and bipolar disorders was further established by the writings of Jules Angst, Carlo Perris and George Winokur (Angst and Marneros, 2001).

Methodological problems

Angst and Preisig (1995) describes some of the methodological problems inherent in studies of the course of affective disorders: selection of samples that are not representative, retrospective collection of data, change of the course by treatment and longitudinal changes of diagnoses.

Long term follow-up studies have been based on hospital samples, community samples and mixed samples. Hospital samples have several severe and recurrent cases risking poor long-term global outcome. Individuals in hospital samples probably have worse courses than subjects in community or out-patient samples. As previous recurrence is a major predictor of future recurrence, only the investigation of subjects with a first incidence episode of depression can give a true picture of what can be expected by a patient presenting with a depressive illness for the first time (Lee, 2003). Also, many individuals with depressive disorder in the community do not seek treatment (Hasin et al., 2005).

The definitions of terms are very important when studying the course of illnesses (Frank et al., 1991). The episode of the disease begins with the onset. Before the actual onset of an episode there could be a long process leading to the actual disorder. The time of the onset of an episode is often difficult to point out retrospectively and depends on thresholds for "caseness".

At onset the course begins with an episode and eventually the subject could reach a remission. A long-lasting full remission could proceed to a recovery which raises the possibility that the treatment can be discontinued. The subject could then again be at risk for a recurrence (Frank et al., 1991). Recurrence represents an entirely new episode. Relapse occurs if the subject has developed the criteria for the disorder under study before recovery. Outcome refers to the consequences of the psychopathology of the illness (Eaton, 2002).

Age of onset

Age of onset could be difficult to assess since often the first episode could be mild or untreated. Recall bias, selection of the sample, thresholds for caseness and different case-finding methods could influence the measured age of onset. Angst and Preisig (1995) reported the results of a 27 year prospective study of 186 unipolar depressives and 220 cases of bipolar disorders from a clinical cohort meeting DSM-III criteria for major depression and mania. Individuals with bipolar disorders had an earlier age of onset (33years) than patients with unipolar disorders (49 years). An outpatient study of first episode of major depressive disorder reported younger mean age at onset, 26.5 years for males and for females 24.3 years (Marcus et al., 2005). From the NEMESIS study the corresponding findings for age at onset for major depression were for males 32.0 years and 28.9 years for females (de Graaf et al., 2003).

Recurrence

Unipolar depressive disorders can be of mild impairment ranging to melancholy with severe disability and risk of suicide. As expected, the course

of depressive disorders is very varied depending on the selection of the sample.

Depressive disorders could be recurrent. Kraepelin (1921) stated that the prognosis for an individual attack of depressive illness is favourable, though he also stated that there is a risk that the disease would be repeated several times. Knowledge of the course and possible outcomes are crucial for decision-making about treatment for longer periods.

Angst and Preisig (1995) considered that the course is highly individual regarding number of recurrences and that the course of unipolar depressive disorders was benign. They concluded that 47% of unipolar depressives and 25% of schizodepressives experienced not more than three episodes during follow-up. They found that single episodes were rare if the follow-up period was long.

For 89 subjects who had been admitted with depressive illness and followed up for 18 years, poor long-term outcome was reported (Lee and Murray, 1988). The authors estimated that 95% of the survivors in the study had relapsed and mortality risk was doubled. From a study of a British cohort of mainly severe recurrent depressives followed 8-11 years, two-thirds suffered a recurrence (Kennedy et al., 2003). In this cohort 76% of the subjects were in-patients. Similar results were reported by Brodaty (2001) and co-workers, reporting 84% recurrence in an in-patient sample followed for 25 years. Also, Mueller et al. (1999) reported that a cumulative proportion of 85% (Kaplan-Meier estimate) of subjects with major depressive disorder experienced a recurrence within a 15-year-period.

A better outcome was reported by Kanai et al. (2003), who described a 57% cumulative probability of remaining well without subthreshold symptoms at two years. Their sample contained a substantial proportion of first incidence cases. Female gender and number of previous episodes of depression predicted recurrence. However, other studies have not detected a gender difference in recurrence or aspects of course (Rush et al., 1995; Simpson et al., 1997).

In a review of studies of long-term (at least 5 years) follow-up studies in community and primary care settings the reported rates of recurrence of depression were between 30-40% (van Weel-Baumgarten, 2000). Also, from a primary care setting it was reported that one third of a sample of patients with major depressive disorder had recurrent episodes (Vuoriletho et al., 2005). In a 13 year follow-up of subjects from a population-based cohort with first lifetime onset of major depressive disorder about 50% recovered and did not have any more episodes (Eaton et al., 2008).

Stability of diagnosis

Hagnell and Gräsbeck (1990 b) reported that depression contrary to anxiety syndromes maintains a diagnostic stability. Solomon reported from a 10-year prospective follow-up of unipolar major depressive disorder that 91% of the subjects maintained their diagnosis (Solomon et al., 1997). Angst and Preisig (1995) reported in their 27 year follow-up that a high proportion (23.9%) of initial unipolar patients later became bipolar. An 11-year prospective follow-up study reported that 3.9% unipolar patients developed bipolar 1 disorder later in the course (Akiskal et al., 1995).

Depression and suicide

A well-known and often quoted review article has shown that on the average 15% of subjects with depression die by suicide (Guze and Robins, 1970). However, a later meta-analysis study reported smaller figures for rates of suicide (Bostwick and Pankratz, 2000). The authors of this meta-analysis also concluded that there was a hierarchy of the suicide risk with the highest estimated risk for those ever hospitalized for suicidality. Hence, the prevalence of suicide varied from 8.6% for those ever hospitalized whereas it was 2.2% for mixed in-patient/out-patient populations. A study that recalculated the risk using contemporary data and modern computerized modelling technique estimated the life time risk for suicide at 6% (Inskip et al., 1998).

In a six to twelve year follow-up of 500 psychiatric outpatients, no suicide was reported among the subjects with primary affective disorders (N=158), (Martin el al., 1985). In a hospital sample the risk of readmission and suicide was related to severity of the diagnosis of depression (Kessing, 2004). In addition, males in the Lundby Study with a severe depression showed a high long-term risk for suicide, around 20% (Brådvik et al., 2008).

Risk factor or predictor studies

Follow-up studies can give information about risk factors for first-onset disorders. Risk factors could give clues to causation mechanisms if they are gathered before the outcome. If risk factors for mood disorders could be identified, prevention could be more specific and perhaps more effective. Risk factors could be of different kind: genetic, psychological and social. A broad range of possible risk factors for depressive disorders have been investigated.

Risk factors

Female gender was consistently reported as a risk factor for depressive disorders (Coryell et al., 1992). Family history of mood disorders had been reported as a risk factor (Angst et al., 2003). A twin study investigating genetic contribution to major depression found higher concordance rate of major depression among monozygotic twin-pairs (27%) than among dizygotic twin pairs (12%), (Torgersen, 1986). Recently, Holmans et al. (2007) identified three different chromosomal regions that probably contained genes that contributed to recurrent early-onset major depressive disorder.

Psychological risk factors including childhood adversities and negative life events have also been linked to major depression. Beck has proposed a developmental cognitive model of depression with early traumatic experiences and the formation of dysfunctional beliefs as predisposing events and congruent stressors in later life as precipitating factors (Beck, 2008). A prospective study found that childhood psychological health is an important independent distal factor for midlife affective disorder (Clark et al., 2007). Also, a cross-sectional study reported that childhood adversities were associated with depressiveness (Korkeila et al., 2005). Other studies have found that depressed patients experience more life events prior to onset than controls in general population samples (Paykel, 2003).

Social risk factors may be poor socioeconomic conditions. Participants from lower socioeconomic backgrounds had nearly a twofold increase in risk for major depression (Gilman et al., 2002). Alcohol disorders have also been proposed as an important risk factor for mood disorders. The majority of the respondents in the National Comorbidity Survey (NCS) study had a lifetime co-occurrence of alcohol disorders and other DSM-III-R disorders as anxiety and affective disorders (Kessler et al., 1997). According to a review made by Swendsen and Merikangas (2000), the association of alcoholism with depression is likely to be attributed to causal factors rather than a shared aetiology. They also concluded that alcoholism and depressive disorders are risk factors for each other.

Anxiety disorders were pointed out as putative risk factors for depressive disorders. Further, anxiety disorders and depressive disorders have been found to share similar genetic background (Kendler et al., 2007). In addition, Kendler et al. (2004) has proposed that an etiological model will require not only the additive effects of individual risk factors, but also multiplicative interactions between subsets of them.

The Sjöbring personality theory

Sjöbring has presented a theory of the main dimensions of the normal personality comprising four dimensions which are genetically determined and

are supposed to vary independently of each other (Sjöbring, 1973). He assumed that the personality dimensions showed a normal variation. These dimensions were Validity, Stability, Solidity and Capacity. He described Validity as the amount of energy a subject possesses. A supervalid individual is self-confident, full of energy and initiative, whereas a subvalid subject is fatigable, tense, cautious and lacking in self-confidence. Stability refers to the degree of capability of habituation of activities and subjective experiences. A substable subject is interested in people, active, concrete and warm but could be somewhat clumsy and heavy in his or her movements. The superstable subject is cool, abstract, clever and elegant in movements. The Solidity dimension describes the degree of firmness. A subsolid subject is quick, flexible and often easy becoming enthusiastic but is equally ready to give up and lacks endurance. On the other hand a supersolid subject is objective, slow, steady and comprehensive in judgement. Capacity is considered to be equal with intelligence.

A psychobiological model of temperament and character was developed by Cloninger who was inspired by the Sjöbring model (Cloninger, 1993). In this model four dimensions of temperament and three dimensions of character are measured. Harm Avoidance represents the tendency to be cautious, tense, apprehensive and easily fatigued and having a fearful disposition, whereas Reward Dependence is the tendency to be sociable, sensitive and dependent. The third temperament trait is Novelty Seeking which is the tendency to be sociable, excitable, impulsive and easily bored and the fourth temperament dimension is Persistence (i.e., overachieving versus underachieving). The character dimensions are called Self-directedness, Cooperativeness and Self-transcendence and correspond to different aspects of self-concept according to Cloninger. The temperament dimension High Harm Avoidance, and the character dimension, low Self-Directedness (executive functions, being responsible, purposeful and resourceful) and high Persistence (i.e., overachieving) have been linked to future onset of depressive disorder (Cloninger et al, 2006).

Personality traits as risk factors

The study of the personality and its interrelation with mental disorder has a long tradition in psychiatry. Nyström and Lindegård (1975a) found that psycho-asthenic traits (subvalidity according to Sjöbring) and symptoms such as anxiousness, fatigue, irritability, obsessive compulsive tendencies and a tendency to ruminate were overrepresented by patients in comparison to healthy subjects.

Decreased emotional strength and increased interpersonal dependency raised the risk for depression among high risk subjects (Hirschfeld et al., 1989). Previously, it was reported from the Lundby Study that asthenia, history of allergy and subjective complaints of mainly asthenic character (being anxious,

nervous, forgetful and having a tendency to show vegetative symptoms) increased the risk for future depression. A diagnosis of Psychopathy, however, protected men from developing depression (Rorsman et al., 1993). Similarly, males with elevated scores of symptoms labelled autonomic lability were more prone to develop unipolar depression (Clayton et al., 1994). Also neuroticism has been reported to be a significant risk factor for major depressive disorder (Kendler et al., 2004). Table 2 gives a survey of risk-factors for depressive disorders.

Table 2. Risk factor studies of depression.

Study	Type of population	Criteria of depression	Methods, personality scales	Risk factors found	Study design
Nyström and Lindegård, 1975 b	Male city inhabitants and car drivers N=3,019	Depression acc. to psychiatric in and out-patient registers	Marke-Nyman[1] temperament scale, scale[2] according to Lindegård	Asthenia, psychasthenic symptoms, ruminating, lack of endurance, sub-clinical depression	Prospective follow-up 6 years
Hirschfeld et al., 1989	First-degree relatives of out and inpatients N=399	Clinical interview using Research Diagnostic Criteria[1]	Self-report personality inventories[3]	Lower emotional strength, interpersonal dependency	Prospective follow-up 6 years
Rorsman et al., 1993	Population based sample N=2,003	Best-estimate consensus diagnoses, based on a semi-structured interview and registers	Clinical assessments by psychiatrists	Asthenia, allergy (asthenic subjective complaints)	Prospective follow-up 15 years
Clayton et al., 1994	Male military conscripts N=6,375	First incidence episode of depression acc. to Feighner criteria[2]	Freiburg personality inventory[4]	Autonomic lability including depressiveness	Prospective follow-up 17 years
Lindeman et al., 2000	Population based sample N=5,993	UM-CIDI short form[3]	Possible risk factors were selected based on review of the literature	Urban residency, smoking, alcohol intoxication, chronic medical condition	Cross-sectional
Gilman et al., 2002	NCPP[1] follow-up study N=1,132	DIS diagnostic interview schedule	Childhood socioeconomic status based on parental occupation	Low socioeconomic status in childhood	Prospective follow-up 18-39 years
Angst et al., 2003	Community sample N=4,547	Diagnostic interview DSM-III-R[4] DSM-IV[5]	SCL-90-R[5]	Frequent 'ups and downs' of mood, family history of depression/fatigue	Prospective follow-up 15 years
Kendler et al., 2004	Population based sample of twins N=7,517	Structured diagnostic interview	Eysenck Personality Questionnaire[6]	Neuroticism, female sex, life events	Combination of prospective and retrospective methods
Korkeila et al., 2005	Randomly sampled working age respondents N=21,101	Beck depression inventory (depressiveness)[6]	6-item scale of adversities checklist of recent life events, postal survey with self-reports	Childhood adversities were associated with depressiveness	Cross-sectional
Cloninger et al., 2006	Adults from a general population N=631	CES-D[7]	TCI[7]	High Harm Avoidance, Low Self-Directedness, High Persistence	Prospective follow-up 1 year
Clark et al., 2007	General population sample The 1958 British Birth Cohort N=9,297	Revised Clinical Interview schedule CIS-R[8], ICD-10[9]	Bristol Social Adjustment Guides[8] Rutter scales[9]	Internalizing and externalizing disorders in childhood and early adulthood	Prospective follow-up 45 years

(1) The Providence National Collaborative Perinatal Project

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Aims

1. To describe methodological problems in longitudinal research with reference to the Lundby Study (paper I).

2. To analyse incidence of depression, in the two time periods 1947-1972 and 1972-1997 (paper II).

3. To describe course of depression including age of onset, recurrence, stability of diagnosis and suicide rate (paper III).

4. To analyse putative risk factors for depression in the Lundby cohort (paper IV).

Material and methods

The Lundby Cohort

Professor Erik Essen-Möller started the study with his collaborators, three psychiatrists educated at the same clinic at the university hospital in Lund. The defined area consisted of two parishes in the south of Sweden. The aim of the Lundby Study in the beginning was to study the distribution of various personality traits, demographic characteristics, mental disorders and their interrelations in an unselected population. The investigators were thus equally interested in healthy subjects as well as in individuals with mental disorders. Accordingly, the fieldworkers made careful descriptions of all subjects. Essen-Möller and his co-workers were especially interested in the personality theory of Sjöbring and assessed the individuals in the population according to the Sjöbring variables. The research group performed the fieldwork in the summer of 1947 (Essen-Möller, 1956).

After the first follow-up in 1957 the Lundby Study became a longitudinal, prospective study of a total population (Hagnell, 1966). Hagnell and Öjesjö repeated the study in 1972 (Hagnell et al., 1990 a). The third follow-up took place in 1997 (Nettelbladt et al., 2005), fifty years after the first field-investigation.

The Lundby district

The Lundby district in 1947 comprised two adjoining parishes, Dalby and Bonderup, in southern Sweden at about 20-km distance from the old university town Lund. In the Lundby district a village with nearly one thousand inhabitants was situated. The area had one large industry and some smaller ones employing a few hundred subjects. In 1947 the district was mainly a rural, farming area that after 1947 gradually changed into a mainly suburban area where most people of working age commuted to neighbouring cities (Hagnell, 1966). This development has become even more pronounced in later decades. The population in the area has grown considerably and the former parishes are now a part of the municipality of Lund.

General characteristics of the Lundby population

The population at start comprised 2,550 individuals who were on the Lundby parish register on July 1, 1947, the 1947 cohort (Essen-Möller, 1956). In 1957 the population, irrespective of domicile, was re-investigated by one

psychiatrist (Hagnell, 1966). During the period 1947 to 1957, 253 died. In addition, 1,013 newcomers were added to the Lundby Study in 1957. Of these newcomers 228 were born into the area and the rest (N=785) had migrated into the area. This resulted in a new cohort, the 1957 cohort partly overlapping the original cohort and consisting of 3,310 persons, who were on the Lundby parish register on July 1, 1957. The subjects in 1957 had a median age of 34 (range 0-96 years). Information about deceased subjects since 1947 was collected. The total population in the Lundby Study consists of 3,563 subjects. After 1957, no new subjects were added to the study.

In 1972 a follow-up of the survivors (N=2,827), from the two partly overlapping cohorts was carried out by the two psychiatrists Hagnell and Öjesjö (Hagnell et al., 1990). Information about deceased subjects was also gathered and those that had moved away were traced and examined.

In 1997, fifty years after the first investigation, a follow-up was carried out. In 1997, 1797 subjects were alive (aged 40-96), and 1,030 subjects had died since 1972. Information about those who had died was gathered from different sources. The youngest participants in the 1997 field study were thus 40 years old. The migration had been substantial, and about 50% of the survivors from 1972 had moved out from the Lundby district. Fortunately, most of the migration was to neighbouring localities. In 1997, 601 subjects were living in the Lundby district and 1,196 lived elsewhere. The subjects that had moved were younger with a median age of 59 (range 40-90) for males and 58 for females (range 40-96). About 17% of the subjects living in “Lundby” had a diagnosis of mental disorder with at least medium degree of impairment and 13% of those that were living in other localities. The number of subjects in the different field-investigations and deceased individuals are presented in figure 1.

The field investigations in 1947, 1957 and 1972 had a low attrition around 1-2%, and the latest follow-up had an attrition rate for the interviews at about 13%. When all sources of information were taken together the longitudinal attrition, 1972-1997, was 6% (Nettelbladt et al., 2005).

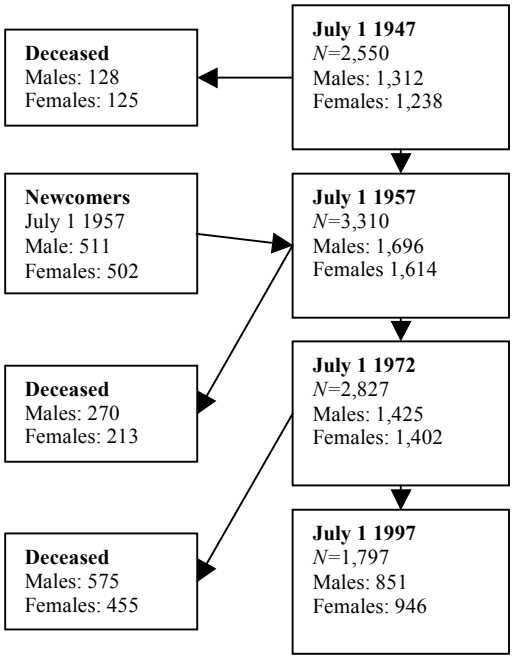

Figure 1. The Lundby cohort at the different cross-sectional days.

The collection of data

Psychiatrists educated at the same clinic carried out the fieldwork in all four field investigations. The interviews in 1947, 1957 and in 1972 were described elsewhere (Hagnell et al., 1990 a). The semi-structured interview in 1997 was modernised but kept its basic structure.

In the last field-investigation in 1997 an introductory letter was sent to the home addresses of the subjects. The background and the purpose of the Lundby Study were explained. After the introductory letter had been sent, individuals were contacted by telephone and an appointment was scheduled if the subject wanted to participate. Before the interview written information about confidentiality was given.

The 1997 investigation included the semi-structured interview and the field workers (psychiatrists) observations of the subject. The semi-structured interview comprised about 150 items which were to be answered and graded. The interview contained items about the subject's physical and mental health 1972-1997 and his or her contact with care. Suicide thoughts and attempts were asked for. Somatic illnesses and complaints, medication, smoking habits and appetite were discussed and recorded. Socio-demographic variables such

as age, gender, marital status, occupation and type of dwelling were recorded as in earlier field-investigations. The social situation including important relationships and eventual alcoholic problems and substance abuse were explored.

A clinical assessment of the subject according to the Sjöbring dimensions of personality was done as in all field-investigations (Sjöbring, 1973). Several structured questions aiming at exploring personality traits were asked. The interview also contained a free part when the individual often volunteered additional valuable information. If there was a clinical suspicion of cognitive impairment the Mini Mental Test was administered (Folstein et al., 1975).

The interview and information from other sources as registers, case registers, relatives and key-informants formed the basis for the final assessment. Most of the interviews took place in the homes or at work. Because of long distance and sometimes reluctance to be interviewed in ones home, 128 telephone interviews were done in the field–investigation in 1997. After the interview the subject was requested to sign a letter of consent which allowed the research team to collect hospital records.

Since 1957 a free description of the psychiatrist's impressions and diagnostic considerations after the interview has been done. Throughout the fieldwork in the last follow-up the fieldworkers discussed experiences from the interviewing and were supervised and supported by the experienced fieldworkers Olle Hagnell and Leif Öjesjö.

Assessment

A set of various case-finding methods and definitions inspired by Leighton (1963) were used in the field investigations from 1957. For caseness three broad categories were applied:

a) the subject had been admitted to a psychiatric hospital
b) the subject had consulted a psychiatrist
c) the psychiatrist diagnosis of mental disorder based on information from all available sources

Of these different definitions the last one was the most used. The Patient Register (2004) containing information about all in-patient care and the out-patient register (The Dalby-Tierp register, 2004) were important sources for "case ascertainment". All hits in registers were followed up with collections of available records.

The diagnostic process started with the two main categories Diagnosis 1 (Mental illness) and Diagnosis II (Habitual states).

Diagnosis I comprises "a comparatively clear-cut illness which has a perceptible onset and is mostly transient. It implies a deviation from the person's usual way of functioning which is so obvious that it is possible for a layman to recognise. It should show itself as a real suffering for the individual or as an interference with the work capacity or both" (Hagnell, 1990 a).

Diagnosis II includes more permanent conditions such as mental retardation and personality disorders (Psychopathy, Character neurosis). It also includes alcohol and substance abuse. Diagnosis II also comprises psychosomatic complaints. Of special importance for knowledge about subjects with abuse or dependence of alcohol was the local County Temperance Board which existed up to the mid-1970s (Hagnell et al., 1986).

All types of mental disorders were analysed by

1. Symptom pattern
2. Degree of impairment
3. Frequency of episodes
4. Duration of episodes

Symptom patterns

Previously, in the Lundby Study the symptoms were grouped according to the likeness yielding 18 diagnostic categories (Hagnell et al., 1990 a). Before the 1997-investigation started some of the 18 previously used categories were condensed yielding 11 diagnoses in order to enable a better fit with DSM-IV and ICD-10. The excluded diagnoses were: nervous fatigue present with psychosomatic symptoms in the shape of epigastric pain, mixed neurotic symptoms that involve the personality to a deeper degree, neurotic symptoms and somatic illness, epilepsy and psychiatric syndrome, pathological ageing, senile psychoses and senile dementia.

The fieldworkers in 1997 evaluated the diagnoses according to this simplified Lundby diagnostic system and according to DSM-IV and ICD-10. A Lundby diagnosis can correspond to several diagnostic categories in DSM-IV and ICD-10.

The remaining diagnostic categories in the Lundby Study were:

Anxiety proper
Anxiety + other psychiatric symptoms
Tiredness proper
Tiredness + other psychiatric symptoms
Depression proper
Depression + other psychiatric symptoms

Mixed neurosis
Schizophrenia
Other psychoses
Organic syndrome
Dementia (Vascular/Multi-infarct Dementia and other type of dementia)

Degree of impairment

In the Lundby Study an impairment rating according to Leighton (1963) has been given for every episode of a mental disorder between 1947 and 1997. In 1972-1997, the six degrees of impairment can roughly be approximated to GAF-scores (APA, 1994).

Table 3. Impairment degrees and GAF scores.

Degree of Impairment	GAF
Excellent function	81-100
Minimal degree	71-80
Mild	61-70
Medium	51-60
Severe	31-50
Very severe	1-30

In several reports from the Lundby Study three degrees of impairment; mild, medium and severe were applied: “Severe impairment practically involves a total inability to work, or at least a marked reduction in functional capacity. If judged to be permanent, the dysfunction would entitle the subject to an invalid pension (at least 50% reduction of the ability to work). Individuals in this group either depend on daily help or are completely taken charge of. Severe impairment may involve depressions with retardation or delusions or schizophrenia. Medium impairment is not as pronounced as in severe impairment. The subjects have usually suffered more from their symptoms than in mild impairment. Naturally, there are no sharp limits to severe and mild impairment. Mild impairment means that daily work is usually possible, although with a lower achievement. The mental symptoms make a psychiatrist think that something should be done therapeutically” (Hagnell, 1966).

Duration of episodes

The onset and termination dates of all episodes of mental disorders were recorded. As it is often difficult to decide when a disorder 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, the subject was considered as not healthy and

hence not at risk for recurrence. Other sources as case-notes were also used in order to get as accurate information as possible (Mattisson et al., 2007).

Diagnostic procedure

The method in the Lundby Study regarding assessment of diagnoses has a clinical approach and relies on several sources. The investigators had access to other sources of information: data from registers, key-informants, case notes from hospitals and out-patient clinics. A hit in a register was always followed up with a request of information. Of special importance was the in-patient register covering information about all in-patient care in Sweden 1972-1997 (Patient-register, 2004). The diagnostic assessment was carried out by the research team after gathering of all available information. After discussion in the research team a best estimate consensus diagnosis was agreed upon.

Only one diagnosis per episode of disorder was recorded. The Lundby diagnostic system is hierarchical, with organic brain disorders taking precedence over psychotic disorders, which in turn overrides neurotic disorders such as depressive disorders and anxiety disorders.

Diagnostic agreement over time

When average prevalence before and after 1972 were compared it appeared that certain diagnostic categories (tiredness/tiredness+, mixed neurosis, other psychoses and organic syndrome) were unevenly distributed indicating a problem of diagnostic reliability over time. These diagnostic categories were re-evaluated. Furthermore, all subjects with two or more episodes before 1972 were also re-evaluated in order to calibrate the episode length 1947-1972 with the ones of 1972-1997. Finally, all individuals who had got a diagnosis on the cut off date 1 July 1972 were re-evaluated. Those diagnoses between 1947 - 1997 found to be inconsistent by the standards of the somewhat changed classification system in 1997 (Nettelbladt et al., 2005) were re-evaluated by the main field investigators (M.B. and C.M.). This procedure probably improved the interrater-reliability over time.

Deceased individuals

A schedule was applied, where information from registers, case notes and key-informants (mostly relatives and care-givers) was recorded. Official death certificates and autopsy reports were available. Contacts with medical care including psychiatric care were registered. Somatic and mental disorders were noted before evaluation was carried out.

Socio-economic level

In 1997 all subjects of working age at all investigations were classified according to the principles laid down in Swedish socio-economic classification (Swedish socioeconomic classification, 1982).

i) Blue-collar workers: unskilled and semiskilled workers, and skilled workers.
ii) White-collar workers: assistant non-manual employees, intermediate non-manual employees, and employed and self-employed professionals, higher civil servants and executives.
iii) Self-employed (other than professionals).

Table 4. Socioeconomic level of the living subjects in 1997 (N=1797).

	Males	Females	Total
Self-employed	115	82	197
White-collar	274	344	618
Blue-collar	462	520	982

Field-working experiences: personal comments

As a field-worker I carried out 673 interviews during 1997-2000. This task was very enriching with many interesting encounters with the subjects behind the figures. I learned a lot from the participants in the Lundby Study and often enjoyed listening to their personal life-histories.

When doing interviews it is a different situation from the one in daily clinical work for the examiner-doctor. The usual patient doctor relation is not at hand. Before entering the home of the subject the field worker showed his or her identification card and gave the subject written information about the project. The examiner-doctor is an intruder and work alone and must trust on his/her capabilities to carry out the fieldwork. Complications and difficulties may occur, and it is up to the fieldworker to deal with unforeseen problems. It is truly demanding, but interesting to do fieldwork. The majority of the subjects in this study collaborated very well and was very generous with their time and helpful towards the fieldworkers. Many subjects offered a coffee break and commented on research in positive terms. Very few individuals expressed negative remarks during the interview. Most of the interviews took place in the home milieu and this was probably beneficial since subjects tend to be more relaxed in their own setting. Also, quite often the subject demanded help from

other family members concerning dating episodes of disorder and other important questions.

It is, of course, crucial that the quality of the fieldwork is high, since the collected data is the foundation for the diagnostic procedure as well as for the statistical analyses. It is also important to respect the integrity of the subject, and not to persuade individuals to answer all questions if he or she does not approve.

The papers, methods

Paper I The paper describes the Lundby Study during fifty years and some of its methodological difficulties as changing diagnostic systems, changing way of naming symptoms, inter-rater reliability between different teams of field workers and representativeness.

All subjects even those that had moved away were traced and examined. A semi-structured interview had been used in all investigations. The Lundby diagnostic system, The DSM-IV and ICD-10 were applied in the field investigation 1997. Experienced psychiatrists had according to the clinical tradition in the Lundby Study performed the field-work. Multiple sources of information (Patient Register, 2004 and Dalby-Tierp Register, 2004) supplied the data from the interviews. Best-estimate consensus diagnoses had been used after gathering of all available information from different sources as registers and hospital records.

Information on the 1030 deceased subjects since 1972 was collected from multiple sources such as relatives, other key-informants (care-givers), the Cause of Death Register (Cause of Death Register, 2004), the Patient Register (Patient Register, 2004) consisting of information about all in-patient care 1972-1997 and a local out-patient care register covering the Lundby district (Dalby-Tierp Register, 2004). Attrition according to gender, age, socio-economic classification and migration was analysed.

Paper II This study includes the whole Lundby cohort of 3563 individuals and compares incidence figures for depressive disorders for the two time periods 1947-1972 and 1972-1997. The symptom pattern of depression according to the Lundby criteria is described as follows: “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). Subjects with a clear depressive disorder with a lowered mood and other symptoms such as anxiety or obsessive symptoms were also included. The DSM-IV and ICD-10 were applied in the field investigation 1997. The episode of depression was also scored according to degree of impairment. In this study three degrees of impairment; mild, medium and severe were applied.

The diagnostic procedure depends on information from the interview and additional sources. Subjects with only mild depressions were not counted as cases and consequently the threshold for “caseness” was depressive episodes

with at least medium degree of impairment. Cases with depression having had a previous episode of Tiredness with depressive symptoms or Anxiety with depressive symptoms were excluded in order to ensure that the cases with depression were true first incidence cases.

The first incidence rates for the two time periods 1947-1972 and 1972-1997 were compared. Cumulative probabilities were calculated.

Paper III In this study 344 subjects, 116 males and 228 females with first incidence depression during the study period were followed from the day of recovery from the first depression. Subjects with other types of mental disorders with at least medium degree of impairment before onset of depression were excluded (N=65). Also, subjects who had been suffering from depression before entering the cohort were excluded (N=43). Subjects with prior alcohol problems were also excluded from the study (N=27).

Threshold for "caseness" were episodes of depression with at least medium degree of impairment. The duration of an episode was recorded.

The Lundby diagnostic system was used in the same way as in paper I. DSM-IV and ICD-10 diagnoses were also applied in the last field-investigation. For those subjects who had their first episode of depression before 1972, DSM-IV diagnoses were added in retrospect. The subjects were categorized by gender and number of years of follow-up. The course was studied with regard to age of onset, recurrence of depression related to duration of follow-up, transition of diagnoses and suicide rate. Risk factors of suicide were also analysed.

Paper IV The aim of this study was to identify risk factors for depressive disorders in the Lundby Study. The study comprises all subjects including the original 1947 cohort containing 2,550 subjects and the cohort created 1957 with 3,310 subjects (the cohorts are partly overlapping). Subjects with previous episodes of depression before entering the cohorts were excluded. Also, subjects that had suffered from disorders (schizophrenia and dementia) that exclude the diagnosis of depression after onset in the Lundby hierarchical diagnostic system were excluded. As threshold for caseness for depression again, medium degree of impairment was chosen. After exclusion of subjects that had suffered from depression or other specified disorders, the 1947 cohort contained 2,470 subjects and the 1957 cohort contained 3,123 subjects. 418 subjects, 261 females and 157 males from the partly overlapping cohorts experienced their first depressive disorder during follow-up.

The items in the Lundby Study can broadly be divided into normal personality traits scored according to the Sjöbring personality theory, other personality traits, subjective complaints, sociodemographic variables as age, marital status, socioeconomic status and previous episodes of mental disorders. Some of these items were assumed to be putative risk factors.

Exploratory factor analyses of personality traits and subjective mental complaints were carried out in order to reduce the number of possible risk factors (Table 4). A final solution was chosen after consensus in the research group. Possible risk factors for all and for the sexes separately with time to depression as outcome were analysed by means of Cox regression analyses in univariate and in multivariate models. Age was included in all models.

Table 5. The content of constructed risk factors.

Year of assessment	Risk factors	Original items scored by interviewer or self-reported*
1947, 1957, 1972	Down/semi-depressed	Heavy, gloomy, semi-depressed, down*
	Nervous/tense	Tense, restless, insecure, strained, vegetative, lachrymose worried*, nervous*, susceptible to adversity*, cries easily*, difficulty to collect ones thoughts*
	Abnormal/antisocial	Indolent, hyperthymic, fanatic, suspicious, explosive, aggressive, emotionally labile
	Blunt/deteriorated	Torpid, blunt, empty, intellectually deteriorated, disturbed memory
	Paranoid/schizotypal	Unresponsive, reserved, paranoid, bizarre, schizoid
1947-1997	Anxiety disorders*	Generalized anxiety disorder, panic disorder
	Tiredness*	No obvious relation to somatic diseases, nervous fatigue, low threshold for fatigue*
	Alcohol disorders*	Alcohol abuse/dependence according to DSM–criteria
	Child neurosis	Nervous symptoms before 15 years
	Separation	Becoming single due to a divorce or death of a spouse
1957, 1972	Affective lability	Affective lability
	Tired/distracted	Tired, poorly concentrated
		Tires easily*
	Sensitive/frail	Sensitive, brittle, frail
	Easily hurt	Difficulty forgetting being wronged*, feels unjustly treated*
	Rigid/dry personality	Inflexible, difficulties in adjusting

* Anxiety disorders, Alcohol disorders and Tiredness disorder were assessed as continual variables 1947-1997

Statistical methods in the papers I-IV

All statistical analyses were performed in SPSS (Statistical Package for the Social Sciences), version 11.1.1.

Paper I contains information about attrition, describe concordance between diagnoses from different field investigations and calculate age-standardized incidence rates for first incidence neurotic disorders over time in the Lundby Study. Calculations of incidence rates of neurosis were based upon individuals who at the start of follow-up were free from the outcome under study. For the sexes separate crude incidence rates were calculated for the time period 1947-1997, which was divided in 5-year intervals. The concordance between diagnoses in the 1997 investigation and the three previous investigations

(1947, 1957, 1972) was calculated. Kappa coefficients were calculated for different diagnostic entities.

In **paper II** the aim was to compare the first incidence rate of depression in the two time periods 1947-1972 and 1972-1997. Incidence rates were calculated for each gender separately, and were computed for the three age intervals 15-39, 40-69, 70-99 during the two time periods. For the comparison of average annual incidence over time standardisation was done. Age- and sex-specific probabilities of contracting depression were calculated as well as cumulative probabilities.

The aim in **paper III** was to describe the long-term course and outcome of first incidence depression for each sex. The subjects were categorized by gender and number of years of follow-up after their first onset of depression. Calculations of 95% confidence intervals for median time to recurrence of depression were carried out. The probability of remaining free of recurrence was illustrated by means of a Kaplan-Meier curve. Risk factors for suicide were determined by means of Cox regression analyses.

In **paper IV** personality traits and subjective mental complaints were analysed by means of exploratory factor analyses (principal component with oblique rotation) to identify variables that measured similar items in order to reduce the number of possible risk factors. A final solution was chosen after consensus in the research group. The item had to load more than 0.5 in order to get included in the constructed risk factor.

Sex prediction interaction terms were included for the different cohorts in order to analyse eventual differences regarding the influence of risk factors on the sexes. The relation between the first incidence Lundby diagnosis of depression and putative risk factors was evaluated. Cox regression analyses with time dependent risk factors for first incidence depression as outcome were carried out for the whole sample and for the sexes separately. Age was included in both the univariate and the multivariate models.

Ethical approval

The Lundby Study has received approval by the Research Ethics Committee of the Medical Faculty at the University of Lund.

Results and comments papers I-IV

I This paper describes the Lundby Study during fifty years and discusses if it makes sense to do repeated surveys. It presents result from the last field-

investigation 1997-2001 and discusses methodological difficulties in doing longitudinal studies.

The Lundby population was investigated 1947, 1957, 1972 and in 1997. The population in 1947 consisted of 2,550 individuals. In 1957, 1,013 newcomers to the area were included resulting in 3,310 subjects that were followed up. In 1972, there were 2,827 survivors that were followed up and in 1997, 1797 subjects. About 50% of the population had moved out from the Lundby district, and 36% of the subjects (1,030/2,827) had died 1972-1997.
In the field-investigation 1997-2001 sufficient information was available for 94% (2,659/2,827) of the subjects.

Observation years

Subjects in the study population as in the Lundby Study are under "risk" until refusal to participate, onset of the disorder, death or end of study period. The number of observation years under risk to be contracted by any psychiatric disorder for the first time with a degree of impairment of three or more was 97,873.

Diagnostic agreement over time

For the broad categories Mental disorder and Neurosis the kappa values were substantial (kappa=0.6) and for Organic brain syndrome moderate (kappa=0.5). The findings of the kappa values suggest that a high degree of reliability is difficult to achieve over long periods and between different teams of field-workers. A re-evaluation was carried out, and probably this procedure improved the inter-rater reliability over time.

In the Lundby Study different generations of fieldworkers have succeeded each other but all have been recruited from the same psychiatric clinic. Psychiatrists are influenced of contemporary diagnostic procedure and cultural context. The Lundby Study had during the study period a high-grade of continuity, since former field-workers supervised new collaborators, probably enhancing diagnostic agreement over time. The clinical approach with the use of different sources was probably beneficial for the diagnostic accuracy. On the other hand, the long time-span of the Lundby Study could also had given difficulties in assessing mental disorders due to changes in the way subjects conceptualize, express and name symptoms (Jorm et al., 2006).

Incidence of neuroses

First incidence of neuroses was assessed from 1947 to 1997. In both sexes first incidence of neurosis with at least medium degree of impairment vacillates

over time. A sharp decline was detected for the time period 1972-1977. However, it was levelled out for females, but did not disappear for males, when the degree of impairment was increased to very severe and severe. Part of the decrease of incidence may be due to recall bias and fewer sources of additional information after 1972. Different diagnostic procedure between the teams could also be an explanation, and it could also reflect a true decrease.

Diagnostic systems

The Lundby Study started before the first edition of DSM was published in 1952 (Committee on Nomenclature and Statistics, American Psychiatric Association, 1952). Since then, the DSM system has developed and now DSM-IV is widely used in research and in clinical practise. The DSM system has a descriptive approach and the diagnoses are based on criteria. The ICD and the DSM systems have developed their classification system parallel and their systems are alike but differences exist. The Lundby Study has used its own simplified diagnostic system, adapted to fieldwork.

An assessment of the degree of impairment could be helpful regarding the question if a case is of clinical significance. Clinical descriptions of the subjects' personality and symptoms have been written throughout the study period, giving opportunities for comparisons over time.

Diagnostic schedules

Since the beginning of the Lundby study psychiatrists did the fieldwork and used a semi-structured interview with a clinical approach. Information was gathered from multiple sources, which probably strengthened the quality of data. The diagnostic schedule based on criteria must of course keep up with linguistic usage and scientific development (Murphy et al., 2000). Highly structured interviews give acceptable reliability and validity but it is maybe not realistic to expect that they will match trained clinicians diagnostic skills (Kessler et al., 1997).

Bias

Recall bias can be counterbalanced to a certain extent by using multiple sources of information like case records and information from relatives, registers and key-informants. Recall bias was a greater problem in the 1997-investigation since 25 years had passed since the investigation in 1972. Because of recall bias the estimates of different disorders in the Lundby Study must be considered as minimal estimations. It is also likely that those with severe cases of disorder are less likely to forget their episodes of mental disorder, while milder episodes are more easily forgotten (Eaton, 2002).

Attrition

Attrition or non-response is another methodological problem that is difficult to tackle. It is crucial that participants do not drop out, because it can jeopardize the validity of the results. Non-response in longitudinal studies could be caused by sample mortality and sample loss (Badawi et al., 1999). About 36% of the subjects (1,030/2,827) in the Lundby Study had died between 1972 and 1997. Sample loss could be attributed to difficulties in tracing individuals. Fortunately, this is a minor problem in Sweden because of the personal identification numbers.

The attrition due to refusal to participate in the Lundby Study has been very low, but was higher in the latest field investigation. The higher attrition rate could be due to differences in methods. Before 1997, no fixed appointment was scheduled for the interview. A request to participate in a study by telephone is probably easier to refuse than to say no to a field-worker standing on the doorstep. Also, younger individuals had occasionally problems to find a suitable time for an interview and some older subjects found the investigation weary. A less authoritarian society may have contributed to the higher attrition rate in 1997.

The attrition rate by age in both genders was highest in the younger age interval varying between 6-8% for males and 7-13% for females. The attrition rate was also higher for those who had moved out from the Lundby district compared to those that had stayed. In respect of different socio-economic strata, the attrition rate was evenly distributed and varied between 4 and 7%. Attrition rate for the interviews was 13%. In the 1997 field-investigation the longitudinal attrition rate for the period 1972-1997 was 6%.

Representativeness

The population in the Lundby Study was from the beginning in 1947 members of a rural society probably representative of a Swedish unselected population. It is somewhat difficult to say today what the Lundby cohort represents. Maybe one can say that the subjects represent a historical, Swedish ageing cohort. The subjects in the cohort had been exposed to the rapid changes in the society that has taken place in Sweden as in many other countries in the western society. For instance, the migration of the subjects (50%) in the Lundby cohort mirrors the change in the society towards urbanisation.

II This paper reports the incidence of depression in the Lundby Study comparing two different time periods. The incidence of depressive disorder decreased in the Lundby Study, when the periods 1947-1972 to 1972-1997 were compared (Table 6 and 7). Females had higher incidence rates in all age groups compared to males in both time periods. The average annual incidence

was lower for women and tended to be lower for men 1972-1997 as compared with 1947-1972. The cumulative probability for developing a depression was 22.5% for males 30.7% for females 1972-1997. In 1947-1972 the corresponding figures were 22.8% for males and 35.7% for females.

In 1978, Klerman et al. stated that in contrast to the age of anxiety that followed World War II, an age of melancholy may be developing. Hagnell (1982) also presented findings according to this suggestion. Also, Sandanger reported an increase in incidence rates, but retrospective methods were applied. The authors also discussed the apprehension that modern society has more mental-illness provoking factors and less support for the individual (Sandanger et al., 1999).

On the other hand, the Stirling County Study reported stable incidence rates of depression over a study period of 40 years. The researchers followed two cohorts consisting of subjects at risk for first depression. One cohort was followed from 1952-1970 and the other cohort from 1970-1992. They discussed that improved living conditions, improved health care and increased educational opportunities has been historical trends in North America and may be regarded as health promoting factors (Murphy et al., 2000a). According to the Stirling County Study another socio-historical trend has been that more women had entered the labour force in Atlantic Canada during the study period.

In line with the findings of Murphy et al. (2000a) a new follow up from ECA showed a declining trend for depressive disorder in Baltimore, USA (Eaton et al., 2007). The authors reported that prevalence increased among middle-aged women, but suggested that incidence of depressive disorder either is stable or declining. The authors underlined important limitations in the study as attrition and that only one community was included in the study.

Roughly, the same changes in the society including better opportunities for females have taken place in Western Europe as in North America. In the present study the trend of increasing rates of depressive disorder in the Lundby Study has terminated and even a decrease for women was detected. However, the NEMESIS study, using CIDI has given much higher incidence rates for depressive disorders, maybe suggesting differences in methodology between studies.

One explanation could be that the DSM criteria for major depressive disorder had become too broad, incorporating normal psychological responses to grief, negative life events and losses in the concept of major depressive disorder (Wakefield et al., 2007). Another explanation of the divergent results of incidence rates could be differences in case-finding methods. Psychiatrists trained in the clinic could be more prone to critically analyse symptoms than trained lay-interviewers (Gräsbeck, 1996). A potential weakness could also be that structured schedules like the Diagnostic Interview Schedule (DIS) rely on

the judgments and insights of the respondent (Eaton et al., 2000). In their study comparing the DIS and Schedules for Clinical assessments in Neuropsychiatry (SCAN) only fair agreement of diagnosis of major depressive disorder (k=0.20) was obtained. In a similar study comparing the DPAX and DIS diagnosis of current and lifetime depression, moderate level of agreement (kappa=0.40 and kappa=0.33) was reported (Murphy et al., 2000c).

Females have higher rates of incidence of depression in the Lundby Study as well as in the ECA and NEMESIS study. In both cohorts of the Stirling County Study (cohort 1, 1952-1970, cohort 2, 1970-1992) the incidence of depression was higher among women than men in, but these differences were not statistically significant. Advancing understanding of female depression will require future epidemiologic research to focus on first onsets and to follow incident cohorts of young people with different measures (Kessler, 2003).

Table 6. The incidence of first time depression in the Lundby Study for males 1947-1972 and 1972-1997 per 1,000 person-years. Cum prob refers to cumulative probabilities

Age interval	First incidence cases	Observation years	Incidence rate	CI (95%)	Cum prob (%)
1947-1972					
15-39	39	13,660.9	2.9	2.0-3.8	6.9
40-69	53	13,511.3	3.9	2.9-5.0	17.2
70-99	6	2,583.1	2.3	0.5-4.2	22.8
total	98	29,755.3	3.3∗	2.6-4.0	
1972-1997					
15-39	15	5,317.8	2.8	1.4-4.2	6.8
40-69	35	14,070.9	2.5	1.7-3.3	13.5
70-99	14	3,839.8	3.6	1.7-5.6	22.5
total	64	23,228.5	2.8∗	2.1-3.5	

∗ Age-standardised

Table 7. The incidence of first time depression in the Lundby Study for females 1947-1972 and 1972-1997 per 1,000 person-years. Cum prob refers to cumulative

Age interval	First incidence cases	Observation years	Incidence rate	CI (95%)	Cum prob (%)
1947-1972					
15-39	60	12 543.9	4.8	3.6-6.0	11.3
40-69	75	11 896.9	6.3	4.9-7.7	26.6
70-99	12	2712.2	4.4	1.9-6.9	35.7
total	147	27 153.0	5.5∗	4.6-6.4	
1972-1997					
15-39	25	5169.9	4.1	2.3-5.8	9.7
40-69	49	12 436.5	3.9	2.8-5.0	19.7
70-99	22	4476.3	4.9	2.9-7.0	30.7
total	92	22 082.7	4.1∗	3.7-5.0	

∗ Age standardised

III This paper describes the course of depressive disorders for subjects who had experienced their first episode in the Lundby cohort during follow-up. In the Lundby population of 3,563 subjects, 436 individuals with depression according to the Lundby system had their first episode of depression. From these 436 individuals, 92 subjects who had suffered from other types of mental disorders, including alcohol problems were excluded. Hence, 344 subjects' course and outcome after their first incidence depression were followed prospectively.

The median age at onset was around 35 years for individuals followed up for 30-49 years. The recurrence rate in the Lundby Study was about 40% but varied from 17 – 76% depending on length of follow-up. For those followed up for 30-39 years after onset of first depression, having a median age at onset, the proportion who had a recurrence was 46% for females and 42% for males. The recurrence rate increased to around 75% for those with 40-49 years of follow-up. Few subjects were followed over 40 years in this study. The median time to recurrence was 4.6 years (CI 1.9-8.3). A change to other diagnoses than depression was registered in 21% of the total sample, alcohol disorders in 7% and bipolar disorders in 2%. The suicide rate was 5%. The risk factors for suicide were male gender and severe degree of impairment, whereas age and alcohol disorder did not turn out as risk factors.

Age at onset

Other follow-up studies report a wide range of age at onset for unipolar depressive disorders, from 24 years to 49 (Marcus et al., 2005., Kennedy et al., 2003; Angst and Preisig, 1995). A two peak distribution of age of onset with peaks in twenties and forties has also been suggested (Angst and Preisig). In this study the overall median age at onset was 44.5 (range 18-83) for men and 47.0 (range 15-89) for women which is rather high compared to the Marcus study, which reported 26.5 years for males and 24.3 for females. Subjects with suicidal risk were excluded in the Marcus study, but comorbidities were allowed. In our study subjects with earlier psychopathology were excluded. Maybe differences in selection of the study sample could explain the divergent results. Late onsets in depressive disorders do also occur. To sum up, differences in age of onset could be due to several factors as increasing awareness of the diagnosis depression more recently, selection of the study sample, recall bias and different thresholds for caseness.

Recurrence rate

The recurrence rate of depressive disorders depends on length of follow-up which the result in our study illustrates. Also, recurrences can occur even after long intervals of health (Mueller at al., 1999). The characteristics of the sample followed are of importance when interpreting results. The rather low overall recurrence rate in our study could be due to the sample being community-based and that first incidence cases are studied. A similar recurrence rate between 30% and 40% has been reported in a review article describing the course of depressive disorders in the community and primary care (vanWeel-Baumgarten et al., 2000).

A study of severely depressed in-patients reported that around two-thirds of the individuals who were followed up suffered a recurrence (Kennedy et al., 2003). Further, an even higher recurrence rate (84%) was reported from an in-patient sample also with severely depressed subjects from Australia (Brodaty et al., 2001). In-patient samples seem to have higher recurrence rates compared to community-based samples.

Kennedy and his co-authors concluded that the long-term outcome does not appear to have changed the last 20 years. Accordingly, Brodaty suggested that severe depressive disorders have poor long-term outcome but added that patients with chronic outcomes can improve when followed over long periods. The introductions of new pharmacological treatments do not seem to have reduced the recurrence rate for unipolar and bipolar inpatients during the period 1994-1999 (Kessing et al., 2004). One of the weaknesses in our study is that we lack detailed information about anti-depressive treatment for some of the subjects with depressive disorder in the Lundby Study.

Transition to other diagnoses than depressive disorder

The diagnosis of depression was rather stable over time. In the study 14% of the males and 4% of the females developed alcohol disorders, and 6% of the males and 12% females were later diagnosed with a neurotic disorder. Six percent of the males got dementia or organic disorder, whereas the corresponding figure for females was 10%. Transition to bipolar disorders took place in 2%, which is markedly lower than that reported by Angst and Preisig (1995). They reported that 24% later became bipolar. Also, 19% of patients hospitalized for unipolar depression later developed bipolar 1 disorder in a 15 - year prospective follow-up (Goldberg et al., 2001). An explanation could be that their samples were based on hospitalized patients that were followed up. However, only 3% changed their diagnoses to bipolar disorder in a Cambridge cohort with mainly severe depressive subjects followed 8-11 years (Kennedy et al., 2003). None of the subjects developed bipolar affective disorder in a group of 49 subjects with severe depressive disorders followed for 25 years (Brodaty et al., 2001). Hence, the rate of unipolar to bipolar conversion has been shown to vary considerably across samples with depressive subjects. Differences in diagnostic procedure and time of follow-up may be an explanation for divergent results.

Suicide rate

An early often quoted review article by Guze including several follow-up studies of subjects with primary affective disorder reported that on average the suicide rate was 15% (Guze and Robins, 1970). However, by using a computerized modelling technique in a later review based on earlier studies the mortality in suicide in affective disorders was estimated to 6% (Inskip et al., 1998). The suicide rate in the follow-up in the Lundby Study was 5%, which is close to that estimate. Martin and collaborators (1985) reported that excess mortality was not observed among out-patients (N=253) with primary affective disorder in a follow-up period of seven years 253. The difference in suicide rate may be explained by differences in samples. Hospital samples with more severely affected patients, probably contains more patients with greater suicidality. Also, gender is important since males show a higher long-term risk for suicide than females (Brådvik et al., 2008). Male gender and severe degree of impairment were found to be significant risk factors in our study.

IV This paper describes risk factors for depressive disorders in the Lundby Study. The Lundby diagnosis of depression represents the DSM-IV diagnostic categories; major depressive disorder, depression NOS and adjustment disorder with depressed mood. Before the calculations were performed 18 subjects were excluded because of substance induced mood disorders, alcohol induced mood disorders, mood disorder due to a medical condition and a few cases with dysthymia. Altogether 418 subjects, 261 females and 157 males

were identified with the Lundby diagnosis of depression. Of the 418 subjects 253 (60.5%) had major depressive disorder, 112 (26.8%) had depression NOS and 53 (12.7%) had adjustment disorder with depressed mood. A broad range of risk factors including the Sjöbring variables was investigated in the 1947 cohort and in the 1957 cohort.

As in several other studies more females were struck by an episode of depression (Marcus et al., 2003), (Culbertson, 1997). In a review article on gender differences in unipolar depression Kuehner (2003) suggested that intrapsychic and psychosocial gender role related risk factors may contribute to the higher risk in females.

The risk factors that appeared in the univariate analyses of the 1947 cohort were for the whole sample the personality traits nervous/tense and subvalidity. Superstability was a protective factor. Anxiety disorders and alcohol disorders were also significant risk factors for the whole sample. For males the significant risk factors were nervous/tense, anxiety disorders and subvalidity whereas superstability was a protective factor. For females the personality factors nervous/tense and abnormal/antisocial were significant risk factors.

In the multivariate models for the whole sample nervous/tense and subvalidity were risk factors and superstability a protective factor. For males in the separate multivariate analysis, nervous/tense, subvalidity and child neurosis were significant risk factors. For females as in the univariate analyses the personality factors nervous/tense and abnormal/antisocial were significant risk factors.

The risk factors that were significant for the whole sample in the 1957 cohort in the univariate analyses were nervous/tense, anxiety disorders, alcohol disorders and the personality traits tired/distracted and easily hurt. For males anxiety disorders, alcohol disorders and child neurosis were significant, whereas females had the risk factors nervous/tense, abnormal/antisocial, anxiety disorders, tired/distracted and easily hurt. In the multivariate models anxiety and alcohol disorders and the personality trait easily hurt were statistically significant risk factors for the whole sample. For males, anxiety disorders, alcohol disorders and child neurosis were significant risk factors and females had the personality traits nervous/tense and abnormal/antisocial as risk factors.

In this study we did not find that separation enhanced the risk for subsequent depressive disorders. However, this was not the case in a study in a non-clinical sample that found that marital disruption increased the risk for depression among female subjects (Coryell et al., 1992). An explanation could be, that as threshold for caseness was medium degree of impairment and the association with stressful life events is reported to be stronger with milder forms of depression (Chen et al., 2000). Divorces could be a solution leading to psychological relief and lesser problems. However, a negative result should

not be interpreted as evidence, since a small sample size could contribute to negative findings (Patten et al., 2003).

The relationship of personality to depressive disorders has attracted much interest in psychiatric history. The term temperament is best reserved for genetically determined tendencies, whereas character generally refers to learnt attributes originating in developmental experiences within the family structure. Personality has the broadest meaning incorporating both temperament and character (Akiskal et al., 1983). The findings of predepressive personality traits as nervous/tense and subvalidity were roughly consistent with earlier findings that neuroticism is associated with depressive disorders (Nowakowska and Strong, 2005). The personality trait of neuroticism has also been shown to be a strong risk factor for both major depressive disorder (Hirschfeld et al., 1989) and generalized anxiety disorder (Hettema et al., 2004).

Major depressive disorders and generalized anxiety disorder appear to have strongly correlated genetic risk factors, but other factors than the personality trait of neuroticism contributed to the risk for both disorders (Kendler et al., 2007). Not surprisingly anxiety disorders were a risk factor for depressive disorders in several analyses.

A difference between the sexes was that childneurosis only was a risk factor for males. This finding must also be interpreted with caution since the Lundby Study was not designated to identify psychiatric problems in childhood and adolescence and there is certainly a lack of information. However, the finding may fit with the conclusion of Clark that men may be more susceptible than women to the effects of psychological ill health in early adulthood on affective and anxiety disorders (Clark et al., 2007).

Alcohol disorders represented a risk factor for males in the regression analyses of the 1957 file. The number of individuals observed with the risk factor alcohol disorder had a substantial male predominance (19.9% versus 1.5%). In a Finnish study problems with alcohol were connected with depressive symptoms (Salokangas and Poutanen, 1998).

The influence of some risk factors differed significantly between the sexes. The interaction analyses were statistically significant for the risk factors abnormal/antisocial personality trait and childneurosis. Since not all risk factors showed significant differences in the interaction analyses, the interpretation of the separate analyses for males and females must be interpreted with caution.

Individual risk factors may also affect subjects differently depending on their actual circumstances. For instance, subjects in lower socio-economic groups may be more vulnerable for negative stressful life events (Susser et al., 2006).

It is a challenge to develop risk factor studies further in the psychiatric field in order to detect causal mechanism, which may be very complex.

General discussion

From what has been said, the Lundby Study with its long period of follow-up and repeated field-investigations entail many methodological problems, but also a possibility to prospectively study depressive disorders in a population-based cohort study. The following discussion will focus on some of the major issues: case definition, attrition rate, incidence, course and risk-factors.

What is a case?

A challenge and a remaining difficulty in epidemiologic research in the psychiatric field is case definition (Eaton et al., 2007). In order to be able to compare incidence and prevalence in different populations and over time, we need valid and reliable diagnoses. Both the ICD and DSM systems have developed criteria and provide descriptions of syndromes in order to achieve reliable diagnoses. The diagnostic systems have also developed elaborated manuals with detailed descriptions of diagnostic categories and separate diagnoses. If a subject fulfils the criteria for a disorder according to these diagnostic systems he/she either has the diagnosis or not. An individual can also get several diagnoses. The categorical approach opposes the dimensional approach or continuous approach that assumes that all subjects have symptoms, but when a certain level is reached he/she becomes a case. A broadening of diagnostic criteria could result in higher prevalence's and a narrowing of criteria the reverse. Studies of long-term courses may be used to validate diagnoses, if assessments yield evidence for stable symptom constellations over time (Angst and Preisig, 1995).

Structured schedules have been developed in order to tackle the "case" problem. Some of the schedules could be administered by lay-interviewers (Murphy, 2002). The schedules differ in terms whether they focus on the clinical status at the time of the interview or on the subjects' history of psychiatric disorders. A schedule follows a diagnostic algorithm that requires the presence of essential symptoms and also usually specifies duration in time.

In later epidemiological studies a further development to highly structured interview instruments has emerged (Eaton et al., 1997). Several structured instruments as PSE, DIS, CIDI and SCAN exist (Wing et al, 1990). The value of reliable and standardised instruments for case identification in population studies is indisputable. However, studies of prevalence and incidence had shown discrepancies in rates even with standardised instruments (Regier et al, 1998). Further, the high estimates that had been reported from the mental disorders estimated in the ECA and the National Comorbidity Survey (NCS)

(Kessler et al., 1997) have raised questions about the clinical significance of these disorders in the population.

In addition, for accurate estimation of prevalence of rare disorders like psychotic disorders, multiple sources of information are essential (Perälä et al., 2007). Also, subjects suffering from severe mental disorders as schizophrenia may be institutionalized and hard to find if registers not are available (Bijl et al., 1998). The Lundby Study had in all field-investigations included subjects in long-term care or living in sheltered housings.

The Lundby diagnostic system is a simplified diagnostic system adapted to fieldwork. Consequently, the Lundby diagnostic system includes few and more broadly defined disorders. The Lundby Study has also from its start relied on the clinical approach with psychiatrists as field-workers and also used multiple sources for information and assessment of "caseness". The impairment ratings have also been useful for establishing thresholds for caseness.

In the 1997 field investigation the Lundby diagnostic system was used and the DSM and ICD systems were simultaneously applied. The Lundby diagnosis of depression corresponds to several DSM-IV diagnoses. There was a sufficient diagnostic agreement between the DSM-IV diagnosis of major depression and the Lundby diagnosis of depression. The disadvantages with the clinical approach in the Lundby Study as in other cohort studies are the high costs and also that these methods are time-consuming and demanding for the research-group. It is believed that experienced psychiatrists are better qualified in analyzing symptoms of mental disorders than lay-interviewers (Kessler et al., 1997).

Attrition

A challenge for epidemiologic population research is to get subjects to participate in psychiatric studies, which gather delicate personal information. Mental disorders could result in deprived living-conditions that make individuals hard to find for follow-ups. Because of this different proportions of cases and non-cases could be lost to follow-up and result in unequal attrition. Follow-up studies demand also efforts in order to get subjects to remain in the study. The prospect of some reward for participation could also influence the response rate. A continuous personal relationship between researcher and study participants and distribution of newsletters may effectively limit attrition in longitudinal investigations (Susser, 2006). In this sense the limited number of investigators from the same psychiatric clinic may have been an advantage in the Lundby Study. In Sweden the occurrence of personal identification numbers facilitate tracing of individuals. Changing of names could be an obstacle against finding subjects for follow-ups if identification numbers not are available.

In the Dutch NEMESIS study at the one year follow-up the attrition was substantially, around 20%. Gender was not related to attrition, but non-respondents were more often younger, poorly educated, urban and not cohabiting, not in paid employment and not ethnic Dutch compared to respondents (de Graaf et al., 2000). In the Baltimore ECA follow-up the attrition was mostly due to death or change in residence. Subjects at both ends of the range were also more likely to be lost to follow-up (i.e., those 18-65, as well as those over 65). The total cumulated attrition was 53% (Eaton et al., 2007).

In the Lundby field-investigation 1997, the attrition rate was higher than in previous investigations, and the younger and middle aged subjects had the highest attrition rates. The reasons for this may be several, as difficulties finding time for an appointment, negative attitudes towards research and a less authoritarian society.

A crucial attrition factor in the Lundby study with its long time span has been the mortality. Other sources of information have been useful, but still there is less information about some subjects that had died during the study period. On the whole the attrition rate was rather low (1-6%) despite the long period of follow-up.

Incidence of neurotic disorders

The incidence of neurotic disorders is dependent on many factors. In the Lundby Study first incidence of neurosis vacillated over time, but a sharp decline was observed for the time period 1972-1977 (Nettelbladt et al., 2005). The decline levelled out for the women when the degree of impairment was raised. More serious disorders are easier to remember and could be detected in registers. Nevertheless, the decline in incidence could thus be due to methodological reasons as recall bias, selective attrition and fewer sources of additional information after 1972. Part of the decline in incidence could also of course reflect a true decreased morbidity in the population.

Incidence of depressive disorders

It has been suggested that the incidence of depressive disorders in cohorts born after World War II is increasing. However, temporal findings could be due to possible artefacts as selective migration, changing diagnostic criteria, differential mortality and changes in the cultural meaning of depression (Klerman and Weissman, 1989). Because we traced and examined subjects that had moved away and kept the Lundby diagnostic system, these possible artefacts may have been less pronounced in the Lundby Study. On the other, migrated subjects had a higher attrition rate compared to subjects that had stayed in the area in the Lundby Study (Nettelbladt et al., 2005).

Factors that could increase the rate of incidence could be a more generalized willingness to report symptoms and to participate in studies. Limitations of recall and memory could decrease incidence rates (Klerman and Weissman, 1989). A possibility that transient depressive states due to stress and bereavement-related sadness are over-reported by lay-interviewers and diagnosed as major depressions has been suggested (Wakefield et al., 2007). Due to recall failure it may be difficult to know retrospectively if an episode was "a true first incidence episode". If recurrent episodes are rated as first incidence episodes it could lead to biased estimates of incidence particularly in studies with short time of follow-up.

Hence, it is complicated to calculate and measure incidence rates without bias. Also, many factors may influence reports on the incidence rate of depressive disorders. Due to all these factors it is difficult to assess secular trends in incidence rates. Few studies are enabled to analyze these trends (Eaton et al., 2007). The Stirling County Study (Murphy et al., 2000), the ECA study (Murphy et al., 2000), and the Lundby Study did not find an increase in the incidence rates of depressive disorders over time as earlier suggested by Klerman and Weissman (1989).

Course studies

In order to study the course of a psychopathology you need at least two waves of observations. Careful definitions of terms are also essential when studying course of disorders. A recurrence represents an entirely new episode and can occur only during recovery, whereas a relapse is a return of symptoms satisfying the full syndrome criteria for an episode during the period of remission (Frank et al., 1991, Öjesjö et al., 2000).

The natural history of depressive disorders is best studied by a prospective follow-up of subjects with first life-time onset in a population-based sample. This procedure diminishes the selection bias of studies with retrospective design. Still several methodological problems exist in follow-up studies. For example, sources of error may be attrition, censoring and recall bias.

Attrition could be due to death of participants in the study, migration to other areas and refusals for different reasons. Since the Lundby cohort is ageing many subjects had died during follow-up. Information was often provided from relatives, key-informants and case-notes but occasionally data was lacking. Subjects in the Lundby Study that had migrated to other places could most of the times be traced due to personal identification numbers. If the subject was incapacitated by illness a proxy interview was usually carried out.

Censoring refers to the fact that the period of observation is limited in time. If the period of observation is too short, few recurrences could be expected. Also,

a proportion of the sample which is in an episode, when the follow-up ends, can make it impossible to estimate the average duration of an episode. Even if the study is prospective, retrospective information are often asked for giving problems with establishing onsets, termination and duration of episodes.

Few field investigations over a long time period could enhance problems with recall bias. For example, if the first episode is untreated and undetected by relatives it probably increases the risk of not being identified. Multiple sources of information decrease these methodological problems.

Difficulties in recalling the first episode of disorder could also influence information about the age of onset. In our study we had a high overall median age at onset (44.5 for men and 47.0 for women), but those subjects that were followed over 30 years after their first onset of depression had a lower age at onset around 35 years. In addition, subjects with any kind of disorder below the age of 15 were all diagnosed as childneurosis. Also, in the Lundby Study even subjects in all old ages were investigated even if they were institutionalized.

In paper III it was reported, as in other studies, that longer follow-up periods resulted in more recurrences. As previous recurrence is a predictor for future recurrence the investigation of first incidence cases can give a better picture of what can be expected after a first episode (Lee, 2003). In our study we had an overall recurrence rate about 40%, but for those few that were followed for over 40 years, 75% percent of the males and 76.5% of the females had a recurrence.

Coryell et al. (1995) stated that there is a rather wide range in the change from unipolar to bipolar reported in the literature from 0%-37.5%. In our study few switched to bipolar diagnoses (2%). Reasons for this finding may be the accuracy of the diagnostic classification, but also the relatively small number of participants.

The suicide rate is a useful measure of the seriousness of a depressive disorder. The lifetime risk of suicide is generally quoted as 15% for affective disorder. However, in a study using data from twenty-seven mortality studies the life-time risk of suicide for affective disorder was estimated at 6% (Inskip et al., 1998), thus considerably lower than the earlier estimate but more close to the finding in our study (5%). The suicide rate also varies with the type of sample studied, out-patients studies reports fewer suicides than hospital samples. Also, severity and gender are linked to the suicide rate (Brådvik et al., 2008).

Risk factors for depressive disorders

Genetic, environmental and social risk factors influence the general risk of developing a depression (Kendler et al., 2004).

The Lundby Study is consistent with other studies of risk factors reporting dominance of females diagnosed with depression. The findings that some personality traits as nervous/tense and subvalidity (according to the Sjöbring personality theory) increase the risk for future depression are in line with previous research. Also, an earlier study has linked the validity dimension to subsequent mental illness (Nyström and Lindegård, 1975a). The Sjöbring dimension superstability came out as a protective factor against depressive disorder in the study. Superstable subjects are described as "cold", "elegant" and showing emotional distance to other people. They are highly integrated and appear to be steady in mood. Maybe this kind of personality is less prone to develop depressive disorders.

Anxiety disorders may precede or co-exist with depressive disorders. Akiskal (1990) proposed that secondary depression may be exhaustion that develops in response to chronic anxiety. In this view anxiety may be conceptualized as a stressor or risk factor that promotes future depression. Further, Wittchen and Friis (2001) reported that pure generalized anxiety disorder constituted a risk factor for secondary depression. These disorders are closely related genetically and major depression and generalized anxiety disorder could be regarded as genetically same disorders (Kendler et al., 2007). Several of the analyses in our study showed that anxiety disorders could be a risk factor for the Lundby diagnosis of depression.

The co-occurrence of alcoholism and psychiatric disorders is common (Kessler et al., 1997). Consistent with previous research, alcohol disorders appeared as a risk factor in our study. Separation did not increase the risk for subsequent depressive disorders in our study. Early parental loss, recent life events, and marital status were not associated with incident depressive disorder in a study from Canada, but the authors concluded that the statistical procedures may have been vulnerable to a too low sample size (Patten et al., 2003). Negative results like separation not being associated with depression in our study must therefore be interpreted with caution.

Even though the Lundby Study was not designed to study mental problems in children and therefore lack detailed information, child neurosis turned out as a risk factor for depressive disorders only in males. This is roughly consistent with the work of Clark et al. (2007).

A limitation is that no established personality inventory for assessing personality traits was applied. However, the semi-structured interview performed by psychiatrists contained several structured questions exploring personal disposition. The strengths in this study are that possible risk factors were gathered before outcome and that the first incidence episode of depression was used in a community–based sample.

Populations, sexes and subjects can be differently influenced by risk factors. Risk factors for depressive disorders can be considered from many domains of life and maybe be different throughout the life span. For example for aged subjects various medical conditions probably are more important than childhood circumstances (Krishnan, 2002). The risk factors for depression found in this study represent factors as certain personality traits, alcohol disorders, anxiety disorders and child neurotic symptoms. This may support the notion that depressive disorders are multifactorial diseases Murphy et al. (2000).

Conclusions

■ Methodological skills are demanded when doing longitudinal studies. Low attrition rates over 50 years and reasonable diagnostic uniformity make comparisons over time justifiable in the Lundby Study.

■ Methodological problems in longitudinal studies like the Lundby study are recall bias, changing diagnostic systems, tracing of persons, mortality, attrition, interrater-reliability over time, ageing of the participants and changing representativeness.

■ When the two time periods 1947-1972 and 1972-1997 were compared, there was a statistically significant decrease for females in average annual incidence of depression from 5.5 per 1,000 person-years to 4.1 in the latter period. For males there was a decrease from 3.3 per 1,000 person-years to 2.8 in the latter period.

■ The calculated recurrence rate is about 40% from a sample with first incidence depressive disorders in the Lundby study. The calculated risk of recurrence depends on the length of follow-up.

■ The risk of suicide is around 5% for first incidence depressive disorders in the Lundby study. General risk factors for suicide were severity of depression and male gender.

■ A broad range of risk factors for depressive disorders was identified in the Lundby study. Some of the risk factors influenced the genders differently. The personality trait nervous/tense and anxiety disorders were risk factors for both genders. For males tiredness disorder, alcohol disorders and the personality trait subvalidity were risk factors for developing a depression. “Superstability” was a statistically significant protective factor for males. For females personality traits such as being easily hurt, abnormal/antisocial and tired/distracted were associated with depressive disorders.

General summary in Swedish

Lundbystudien är en prospektiv undersökning av den psykiska hälsan i en normal population. Den startades 1947 av professor Erik Essen-Möller och pågår fortfarande. Undersökningen kom att omfatta befolkningen i två socknar, Dalby och Bonderup. Totalt ingick 2550 personer i alla åldrar i 1947-undersökningen och majoriteten av befolkningen samtyckte till att medverka i studien. Lundbystudien innehåller ett litet utsnitt av nutidshistoria, psykiatrihistoria och beskrivningar av många fängslande levnadsöden.

Det ursprungliga syftet med Lundbystudien var att undersöka om Henrik Sjöbrings personlighetsteori kunde tillämpas i en normalbefolkning. Forskargruppen ville undersöka om Sjöbrings personlighetsdimensioner var normalfördelade i befolkningen. Sjöbring, som var professor på psykiatriska kliniken i Lund beskrev ett system med fyra personlighetsdimensioner: validitet (mängden psykisk energi), soliditet (grad av rörlighet eller impulsivitet), stabilitet (balans i stämningsläge) och kapacitet (intelligensen). Personer som har låg grad av energi och lätt uttröttbara skulle vara subvalida, medan de supervalida är uthålliga, energirika och företagsamma. De subsolida är impulsiva, ombytliga och rörliga, medan de supersolida är objektiva, eftertänksamma och tenderar att bli orubbliga. Subsolida personer är lättare influerade av känslomässiga stämningar, och ändrar lätt uppfattning och kan ha dålig uthållighet. De substabila personerna är känslomässigt varma, intresserade av relationer och ofta jordnära, medan de superstabila är kyliga, sakliga, idébetonade och ofta intresserade av abstrakta idéer. De superstabila skall ha mera elegans i sitt rörelsemönster jämfört med de substabila som kan vara lite klumpiga. Erik Essen-Möller var starkt influerad av Henrik Sjöbrings personlighetsteori. Han och hans medarbetare var från början lika intresserade av de friska individerna som de med psykiska störningar. Psykiatrerna fick från början ett mycket gott gensvar av den utvalda populationen.

1957 gjordes en uppföljning av undersökningen av O. Hagnell, som lade till ytterligare 1013 personer som antingen flyttat eller fötts in i området. Efter 1957 har inga nya personer lagts till utan de som tidigare ingått i studien har följts upp. 1972 utfördes en andra uppföljning av O. Hagnell och L. Öjesjö. Den senaste fältundersökningen utfördes 1997-2001 med P. Nettelbladt som projektledare.

Populationen i Lundbyområdet var på fyrtio- och femtiotalet en landsbygdsbefolkning som successivt urbaniserats i takt med den övriga samhällsutvecklingen. Under uppföljningstiden har den allmänna levnadsstandarden höjts, lantbruket har alltmer mekaniserats och tjänste- och informationssamhället har vuxit fram. Hälsovården och sjukvården har utvecklats och blivit mera tillgänglig. Möjligheterna att utbilda sig har ökat och utbildningsväsendet har utvecklats och diversifierats. Stora sociala

förändringar har skett, familjerna har blivit mindre, könsrollerna har förändrats och samhället har ökat sin komplexitet.

Den långa uppföljningstiden på 50 år är unik, men har medfört många metodproblem som deltagares svårigheter att komma ihåg episoder av sjukdom på grund av glömska, bortfall på grund av vägran att delta, överensstämmelse i diagnostiska bedömningar och förändring av diagnostiska system. Ändringar i hur personer både benämner och upplever symptom kan också spela roll vid diagnostik och påverka resultaten.

Forskarna som 1947 lämnade sina skrivbord var pionjärer som gav sig ut på fältarbete. I princip har fältarbetet varit likartat vid de olika undersökningarna, men datoriseringen har förenklat bearbetningen av all information som samlats in. Ett stort problem har varit diagnosernas tillförlitlighet och överensstämmelsen mellan de olika forskarteamens diagnostik. Dessa problem tacklades med en omvärdering av flera diagnoser, vilket kunde göras på grund av psykiatrernas beskrivningar av personernas symptom.

Populationen kan inte sägas vara helt representativ för en nutida svensk befolkning, eftersom det finns mycket få utomnordiska invandrare. Personerna som ingår i studien har dock varit exponerade för den dynamiska samhällsutveckling som ägt rum i Sverige de senaste 50 åren. En fördel med Lundbystudiens är den unikt långa uppföljningstiden som möjliggör att man kan studera långvariga sjukdomsförlopp. En annan styrka är det låga bortfallet samt användandet av olika informationskällor som register och journaler som ökar tillförlitligheten i diagnostiken.

Depression räknas som en av folksjukdomarna på grund av sin stora förekomst i befolkningen. Lundbystudien har ofta citerats när det gäller frekvensen av depressioner i befolkningen. Studien har tidigare rapporterat om ökande frekvens av depressioner. Fortsatt ökning av depressiva tillstånd kunde inte bekräftas i den senaste uppföljningen. Liksom tidigare fann vi att det är vanligare med depression hos kvinnor än hos män. Vi mätte förekomsten av depression i två 25 årsperioder; 1947-1972 och 1972-1997. Vi fann att den genomsnittliga incidensen (förstagångsinsjuknandet) av depression var lägre i den senare perioden. Den kumulativa (ansamlade) risken att insjukna i depression 1947-1972 var 22.8% för män respektive 35.7% för kvinnor. I den senare perioden 1972-1997 var risken 22.5% respektive 30.7%.

Depression kan vara en återkommande psykisk sjukdom som kan leda till långvarig funktionsnedsättning. Vi studerade sjukdomsförloppet efter förstagångsinsjuknande i depression hos 344 personer. Vi fann en återfallsfrekvens omkring 40%, men återfallsfrekvensen varierade mellan 17% - 76% beroende på hur lång uppföljningstiden var. Män och kvinnor hade likartade sjukdomsförlopp efter debuten av en depression.

Den mest fruktade komplikationen till depression är suicid. Vi fann en suicidfrekvens på 5%, vilket är mindre jämfört med andra studier, där man rapporterat en suicidfrekvens på 15%. Dessa studier har mestadels beskrivit personer som varit inlagda på sjukhus, vilka sannolikt har en allvarligare prognos än de som enbart behandlats i öppen vård. Vi undersökte vilka riskfaktorer som predicerade suicid och fann att manligt kön och svårare depressioner ökade risken för självmord.

Riskfaktorer som är insamlade innan insjuknandet kan ge ledtrådar om kausalitet. En fördel med Lundbystudien är att den är prospektiv, det vill säga framåtblickande och att personerna är undersökta, oftast innan sjukdomsepisoden. Riskfaktorstudien påvisade ett flertal olika faktorer som ökade risken för att insjukna i depression. Det vi hittills sett är att vissa personlighetsdrag som nervositet och subvaliditet (låg grad av energi) liksom tidigare ångeststörning ökade risken för insjuknande i depression, medan personlighetsdimensionen superstabilitet skyddade. Nervösa symptom i barndom och ungdom ökade risken för depression hos män, medan kvinnorna hade vissa personlighetsdrag som lättkränkthet, uttröttbarhet, antisociala drag som ökade risken för insjuknande. Alkoholmissbruk eller alkoholberoende var en viktig riskfaktor för insjuknande i depression för män i denna undersökning.

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