Long-Term Functional Psychosis

Epidemiology in Two Different Counties in Sweden

BIRGITTA WIDERLOV
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Abstract

This thesis is based on two independent studies, the first in Stockholm County (index year 1984; n=302), and the second, a replication and validation study, in Uppsala County (index year 1991; n=455).

The general aim was to study all individuals with Long-term Functional Psychosis (LFP) within the two counties of Sweden from an epidemiological perspective and to perform specific studies on a subgroup of individuals with schizophrenia. In the Stockholm study, the total one-year LFP prevalence was 5.3/1 000; in the the rural, suburban and urban areas it was 3.4, 5.6 and 6.6/1 000, respectively. The total one-year prevalence of LFP in Uppsala was 7.3/1 000; in the rural, peripheral city and central city areas it was 6.0, 7.0, and 8.7/1 000, respectively.

Within the non-schizophrenic subpopulation, a pronounced difference was demonstrated between the two studies with substantially higher prevalence rates in the Uppsala study. The schizophrenic subgroup in Uppsala was re-diagnosed using parallel diagnostic systems (DSM-III, DSM-III-R, DSM-IV and ICD-10), and reasonably comparable prevalence estimates were obtained.

In both studies antipsychotic drugs were most frequently prescribed for the patients with schizophrenia, and the doses were considered as low to moderate. In the Uppsala study the doses of antipsychotic drugs decreased with a longer duration of illness, while the opposite was found in the Stockholm study.

The increased mortality rate among patients with schizophrenia was mainly due to unnatural causes of death and cardiovascular diseases, particularly among males.

The main methodological differences between the two studies were in the sampling procedures. In the Uppsala study, a larger number of care facilities were screened, and a broader set of diagnostic criteria were used for identifying cases from different registers.

Keywords: epidemiology, functional psychosis, schizophrenia, prevalence, rural-urban gradient, comparative study, antipsychotic drugs, diagnostic criteria, mortality

Birgitta Widerlöv, Department of Neuroscience, Psychiatry, University Hospital, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden

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It is impossible to be free from error. What is possible is to be constantly on the alert with a view to not erring; for we should be content if we avoid a few errors by never relaxing our attention to this objective.

Epictetus, Discourses 4.12.19

To those who suffer from long-term functional psychosis
LIST OF PAPERS


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<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
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<tr>
<td>CBT</td>
<td>Cognitive Behavior Therapy</td>
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<td>CPEQ</td>
<td>Chlorpromazine Equivalents</td>
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<td>DIS</td>
<td>Diagnostic Interview Schedule</td>
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<td>DSM-II</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 2nd Edition.</td>
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<td>DSM-III</td>
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<td>DSM-III-R</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed., Revised.</td>
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<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.</td>
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<td>ECA</td>
<td>Epidemiological Catchment Area studies</td>
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<td>ICD-10</td>
<td>The International Statistical Classification of Diseases and Related Health Problems, 10th revision</td>
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<td>LEAD</td>
<td>Longitudinal, Expert and All Data</td>
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<td>LFP</td>
<td>Long-term Functional Psychosis</td>
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<td>NAP</td>
<td>Non Affective Psychosis</td>
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<td>NCS</td>
<td>National Comorbidity Survey</td>
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<td>NIMH</td>
<td>National Institute of Mental Health</td>
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<td>SEK</td>
<td>Swedish crowns</td>
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<td>UBAC</td>
<td>Uppsala Data Center</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Introduction

Long-term mentally ill persons have always represented a particularly vulnerable group of individuals in all societies throughout the world. In a complex society like ours, this group may be even more exposed.

In order to define this most exposed group we have introduced the concept Long-term Functional Psychosis (LFP), which is described later in more detail. This approach has not previously been used in epidemiological studies. The LFP population is the most important target population within psychiatric and community care organizations, and the two organizations share total responsibility for these individuals.

This thesis is based on two independent studies, the first in Stockholm County and the second, a replication and validation study, in Uppsala County.

Historical background

Changes in the psychiatric care organizations

Psychiatric care for long-term functionally psychotic (LFP) patients has undergone dramatic structural changes during recent decades. These changes have primarily comprised deinstitutionalization and reorganization processes in geographically defined catchment areas (sectors), where the same psychiatric care organization is responsible for all psychiatric services in the area.

Along with these changes, community based care facilities have been developed to meet the needs of rehabilitation, social support and housing for this particular group of individuals (Freeman and Alpert 1986, Grove 1994, Warner 1994).

People with severe functional psychoses constitute the group of individuals for whom psychiatry still bears full responsibility, and they have also been the main target group for all ongoing mental health reforms in recent decades (Costa 1995, Costa 2006, Ågren et al 2005, Psykiatrisamordning 2006).
Both in Sweden and in the other Nordic countries, deinstitutionalization started rather late compared to many other European countries (e.g. Italy and Great Britain) and the United States (Grove 1994, Kringlen 1993, Kringlen et al 2001).

The “Nacka Project”, later named the Nacka Värmdö Psychiatric Sector, in Stockholm County (see Study I) was a pioneer in this area; in 1974 it became the first example of sectorized psychiatry in Sweden (Stefansson 1985). In Uppsala County, as was the case in many other parts of Sweden, these changes took place about 10 years later.

A parliamentary commission began an investigation in 1992 that resulted in a mental health reform in 1995 (Costa 1995, Socialstyrelsen 2003, Åberg 2005). Responsibility for the care of long-term mentally ill people was to be shared by psychiatric and community based care facilities, with the aim of providing adequate locally based care facilities and high quality treatment options for this particular group.

Evaluations carried out by local authorities, as well as by the Ministry of Health and Social Affairs (Socialdepartementet), have indicated that the reform process has gone slowly in Sweden, as has been the case in the rest of Europe (Kringlen 1993, Grove 1994, Socialstyrelsen 2003, Åberg 2005).

The deinstitutionalization and sectorization movements themselves, which emerged in response to many previous problems, lead to new complications (Widerløv 1990, Borgå 1993, Grove 1994). Societal responsibilities for LFP individuals have become less clearly defined following the involvement of many psychiatric and community care facilities (Socialstyrelsen 2003, Åberg 2005).

The lack of resources, particularly for the community-based care facilities, and problems in communication and cooperation between the two care organizations, have been reported as other important explanatory factors regarding the slow progress of the mental health reforms (Grove 1994, Costa 2006, Psykiatrisamordning 2006).

The reintegration of severely mentally ill people into the wider community has unfortunately been a more or less painful process. As shown in recent studies, it is obvious that this group, which was supposed to benefit the most from the closure of institutions, has in many cases paid a high price, often resulting in a lack of adequate care and a low quality of life (Grove 1994, Åberg 2005, Costa 2006, Götmork et al 2006).
Schizophrenia and other functional psychoses

Historically, patients in mental hospitals were individuals with severe long-term psychoses (Ingelby 1980). The predominant diagnostic group was schizophrenia, but patients with many other disorders such as paranoia and affective psychoses, which were equally care demanding, lived their lives inside the asylums (Bachrach 1983, Lamb 1981, 1984).

Schizophrenia is a psychotic disorder or a cluster of disorders characterized by fundamental disturbances in thinking, perception and emotions. For those affected, the disorder often causes many years of severe suffering and, for a smaller group, life-long disabilities with deterioration in functional capacity.

The two most common functional psychoses are schizophrenia and bipolar affective disorders. The distinction between the two diagnostic entities is often not easy to assess, and clinicians and researchers in different parts of the world have not always made the same distinction between the two diagnostic groups (Cloninger 1994, Warner 1994, Curtis et al 2000).

In 1886 the German psychiatrist Emil Kraepelin described (Kraepelin 1909, 1919) a group of patients with psychotic symptoms and differentiated them from patients with manic depression. He named this new group dementia praecox (dementia in early life). In defining dementia praecox, Kraepelin was particularly interested in showing how the illness differed from other forms of insanity, which in his opinion were more benign, thus giving the impression that dementia praecox was inevitably progressive and incurable. Kraepelin focused on the course of the illness and estimated that only 12 percent of the patients recovered more or less completely. He also differentiated three subtypes of the disorder; hebephrenia, catatonia and dementia paranoides. These conditions had earlier been considered as separate disorders.

In the early 20th century, the psychiatrist Eugen Bleuler, head of the renowned Burghölzli hospital in Switzerland, formulated a new unifying concept for the condition and also gave it a new name, schizophrenia. He believed that a specific psychological picture was fundamental in order to understand, classify and treat the disorder. From the fragmentation of thinking and feeling, Bleuler derived the term schizophrenia (split mind). He stressed from the beginning that he viewed schizophrenia as a group of disorders (Bleuler 1911). Bleuler demonstrated that the outcome of schizophrenia was often benign, with about 60 percent of his patients recovering sufficiently from their first episode to return to normal life.

In 1950 Kurt Schneider presented his concept of first rank symptoms of schizophrenia (Schneider 1959, Slater and Roth 1969, Socialstyrelsen 2000).
2003), later called positive symptoms. The primary symptoms were hallucinatory voices, hearing thoughts spoken aloud (echo de pensée), broadcasting of thoughts, bodily feelings of influence, thought withdrawal and delusional perception. Schneider was aware that these symptoms could also appear in conditions other than schizophrenia, such as in bipolar syndromes (see Paper IV). Schneider’s diagnostic criteria caused a broadening of the diagnostic classification, resulting in more individuals receiving the diagnosis of schizophrenia compared to the case with earlier diagnostic systems.

The Kraepelinian distinction between dementia praecox and manic-depressive illness has formed the basis of the classification of psychoses over the last 100 years. However, dissatisfaction with the Kraepelinian dichotomy (Murray 2005) has been growing, and recent studies suggest that the two psychotic groups have much more in common than previously thought, and that the Kraepelinian view of psychoses may need future modification (Taylor et al 1993, Curtis et al 2000, Ovsiew 2000, Walker et al 2002a, 2000b, Craddock and Owen 2005, Craddock et al 2005).

Discriminating between schizophrenia and other functional psychoses is still quite difficult and sometimes impossible (Socialstyrelsen 2003), since the pathogenesis in the development of a psychosis is far from fully understood. Many studies aim at investigating differences and similarities based on psychiatric genetics, neuropharmacological mechanisms, brain structures, neuropsychology and early environmental risk factors (Walker et al 2002a, 2000b). These approaches may open possibilities for a new and deeper understanding of the etiology and pathogenesis of functional psychoses. During the past decade, several investigators have even suggested that it is time to abandon schizophrenia as a nosological concept (Cloninger 1994, Warner 1994, Owen 2005; Craddock et al 2006).

The consensus view that has been increasingly adopted is that the causes of schizophrenia and other functional psychoses are multifactorial with strong genetic and biological influences. It has been suggested that multiple biological, social and psychological factors interact to produce increased vulnerability that can trigger psychotic episodes and shape the course of the illness (Häfner 1988, Cloninger 1994, Crow 1995, Hultman et al 1997, Mueser and McGurk 2004, Ågren et al 2005).

The emergence of a consensus about multifactorial causes of psychoses has resulted in increased availability of more diversified treatment strategies for these groups of patients. A combination of modern antipsychotic medication, cognitive behavior therapy (CBT) for
psychoses, psychosocial interventions and assertive community support usually lead to substantial improvement in quality of life and better integration within the community (Bebbington and Kuipers 1982, Perris and Skagerlind 1994, Beck and Rector 2000, Mueser and McGurk 2004). According to Butler and co-workers (2006), CBT has particular potential in the treatment of schizophrenia, where antipsychotic medications are not always sufficiently effective and non-compliance can be a problem.

Although schizophrenia is considered the most severe functional psychosis, other psychoses have also been proven to cause long-term functional disabilities (Widerlöv 1990, Borgå et al 1993). This may lead to a research agenda in psychiatric epidemiology best served by adopting broader inclusion criteria for functional psychoses (Craddock and Owen 2005).

Outcome studies

In contrast to the view of Kraepelin, several studies have supported the more favorable outcome in schizophrenic disorders suggested by Bleuler. A five-year outcome study in Sweden (Wieselgren and Lindström 1996) included 120 schizophrenic patients, diagnosed according to DSM-III-R criteria (APA 1987), and consecutively admitted to a special ward for young psychotic patients with a professionally trained staff. After five years of follow-up, they reported a good outcome for 30 percent, an intermediate outcome for 56 percent, and a poor outcome for 14 percent.

Long-term follow-up studies report even better results, with good global functioning in 40 to 60 percent of the patients (Harding et al 1987, Opjordsmoen 1991, Hegarty et al 1994).

An early study by M. Bleuler (1974), comprising 218 schizophrenic individuals and covering the course of illness over several decades, found a plateau in the progression of the illness after 5 - 7 years, with no further deterioration after that time. After that phase, antipsychotic treatment could often be reduced or completely withdrawn without any recurrence of schizophrenic symptoms.

Cost of psychiatric illness

Although schizophrenia is not a very frequent illness, it is among the most burdensome and costly disorders worldwide. The cost items included in different studies vary. Typical cost items are direct costs such as psychiatric in- and outpatient care and drugs, and indirect costs such as loss of production, reduced productivity and early retirement. Sometimes
lost production due to premature mortality is also included in the analysis. So far, no cost studies have been found that also include the increased somatic morbidity in this patient group.

The cost of illness studies are based on one-year prevalence figures (Wittchen and Jacobi 2005). Most cost estimates only represent expenditures for schizophrenic patients treated within a psychiatric health care system. The number of schizophrenic individuals who remain untreated is unknown. However, some studies estimate that only about 60-70 percent of persons with schizophrenia have received treatment (Socialstyrelsen 2003, Kohn et al. 2004, Rössler et al. 2005).

Andlín-Sobocki and collaborators (2005a, 2005b) reported that the annual cost per case of schizophrenia in 29 European countries ranged between 3 000 and 14 000 Euros, with a cost of 9 738 Euros in Sweden and the highest cost per case in Switzerland.

In Sweden, the National Board of Health and Welfare (Socialstyrelsen 2003) estimated that between 30 000 and 40 000 individuals with schizophrenic disorders needed treatment and support from different care facilities in society. The cost of illness in 1994 was 6.2 billion SEK (SBU 1997). The 1995 psychiatric reform resulted in a transfer of expenditures from psychiatric care facilities to other treatment facilities in the community. Recently (Jacobsson et al. 2002, Socialstyrelsen 2003), it was reported in a study of a representative sample of individuals with schizophrenia that the estimated annual cost per case, including different types of community care and the burden of relatives, was 454 000 SEK (~ 50 000 €). This implies a total annual cost of 13.6 to 18.2 billion SEK for an estimated 30 000 to 40 000 individuals with schizophrenia in Sweden.

Most studies investigate schizophrenia in the age group 18-65 years, but Cuffel and co-workers (1996) reported that the highest costs for schizophrenic individuals were for the youngest age group and for the oldest age group, 65 years and above.

Epidemiology

There are many crucial factors that could influence the results of psychiatric epidemiological studies. Differences between studies may depend on diagnostic systems, demographic, cultural and social factors, as well as differences in sampling techniques and the availability and reliability of data and record registers (Opit 1994).
Diagnostic criteria

Scandinavian psychiatry has for decades tended to use a rather narrow definition of schizophrenia, emphasizing the poor outcome according to Kraepelin (Wieselgren and Lindström 1996). In a large scale project, the World Health Organization (WHO 1973, 1979) investigated the diagnoses of schizophrenia around the world. Warner (1994) concluded that the diagnosis of psychosis in general, and schizophrenia in particular, was reasonably similar in the European and Third world countries.

Before 1980, the reported prevalence rates of schizophrenia differed greatly depending on the diagnostic criteria used (Hamilton 1985, Paper III). A high prevalence rate was reported from the previous Soviet Union that was caused by a broad diagnostic concept, which also included patients who could not be considered psychotic (Warner 1994, Smulevich 1989, Hamilton 1985, Brockington 1986).

Following the introduction of the DSM-III classification system (APA 1980), the American diagnostic criteria for schizophrenia were changed from some of the broadest in the world to some of the narrowest, thus markedly affecting reported prevalence rates (Brockington 1986, Warner 1994). Much greater attention was now directed to discriminating between manic depressive illness and schizophrenia. Introduction of the ICD-10 (WHO 1992, 1993) and the DSM-IV (APA 1994) diagnostic criteria opened up possibilities for more reliable comparisons of research results from studies where these diagnostic systems had been applied.

Screening and sampling techniques

The history of the psychiatric epidemiology of schizophrenia and other psychoses can be described in different phases, although the phases are overlapping.

Early studies (Ödegård 1952, Faris and Dunham 1967, Cooper and Morgan 1973, Strömgren 1968, 1987) during the 1940s and 1950s were mainly based on hospitalized populations, in accordance with Ödegård’s (1952) assumption that “most schizophrenics will sooner or later present themselves in hospitals,” which was a reality when mental hospitals were the only treatment facilities available.

The Midtown Manhattan studies (Srole et al 1963), which were unique at the time, were based on random samples of households, and initially used a concept of psychiatric impairment, and later a structured diagnostic instrument, the Schedule for Affective Disorders and Schizophrenia – Life-time Version (Endicott and Spitzer 1978).
During the 1970s, psychiatric epidemiology entered a new phase. A number of large national and cross-cultural studies were performed (Draguns and Tanaka-Matsumi 2003, Yeung and Greenwald 1992). The NIMH Epidemiologic Catchment Area Studies - ECA (Cooper and Helgason 1989, Kessler et al 1994) began in 1978, and included five catchment areas in the US with over 20 000 respondents. The studies examined the prevalence and incidence of “severe mental disorders” in the community, as well as in institutional settings, and thus both treated and untreated cases were included. The Diagnostic Interview Schedule (DIS) was used in the ECA studies, which were funded by the National Institute of Mental Health (NIMH). DIS is a diagnostic interview instrument used for research purposes that can be administered by trained interviewers who are not clinicians.

A decade later, the National Comorbidity Surveys – NCS (Kessler et al 2005a, 2005b) were designed to improve ECA efforts by incorporating DSM-III-R (APA 1987) diagnoses, and to determine the prevalence and comorbidity of psychiatric disorders. The NCS was the first survey administered to a national sample in a face to face household survey of adult individuals 18 years and above. These studies established the methods used in modern psychiatric epidemiology in the US as well as in the rest of the world (Kessler et al 1994; Kringlen et al 2001, Insel and Fenton 2005, Kessler et al 2005a, 2005b).

Important progress in the epidemiology of schizophrenia was made by the WHO, thus establishing a new phase of psychiatric epidemiology. A series of studies (WHO 1973, 1979, 2004, Sartorius et al 1986) investigated the occurrence of schizophrenia across nations. Jablensky and co-workers (1992) compared the true prevalence of schizophrenia within 16 different countries. All persons seeking their first contact with any care facility within the identified catchment area of a participating country were identified and screened for schizophrenia symptoms using the DSM-III-R (APA 1987).

The Nordic countries have a long tradition in epidemiological studies in psychiatry (Böök 1953, Larsson and Sjögren 1954, Essen-Möller et al 1956). Several population studies of all individuals in a defined geographical area have been presented, thus providing a good opportunity to map the total psychiatric morbidity in that area.

The first study based on a general population sample was the Lundby project, a longitudinal study of the mental health in a total population between 1947 and 1997 (Essen-Möller et al 1956, Hagnell and Öjesjö 1975, Nettelbladt et al 2005). All diagnoses were assessed in personal interviews by psychiatrists trained to reach high interrater reliability.
They used the same semi-structured interview, and diagnoses based on ICD-10 and DSM-IV criteria were added later (Nettelbladt et al 2005). Multiple sources of information were used such as case notes, registers and key informants. With the exception of early publications, no data on the prevalence of psychoses have yet been published.

Halldin (1984) carried out a similar study in Sweden that included an urban population in an area of Stockholm County (2,283 persons, aged 18–64 years). Direct interviews were performed by psychiatrists and diagnoses such as schizophrenic/paranoid conditions and other psychoses were included.

Large national registers have been used in several studies in order to investigate morbidity in random samples (Kastrup 1987, Munk-Jørøensen et al 1993). In a Norwegian study (Kringlen et al 2001) Oslo residents, aged 18–65 years, were drawn from the National Population Register. A total of 2,066 subjects were interviewed between 1994–1997 using the Composite International Diagnostic Interview in order to assess the prevalence of non-affective psychoses (NAP), including schizophrenia and paranoid conditions.

Lewis and co-workers (1992) investigated place of upbringing and the incidence of schizophrenia using data from a cohort of 49,000 male Swedish conscripts linked to the Swedish National Register of Psychiatric Care.

Using data from the Danish civil registration system and linking them to the Danish psychiatric care register, Pedersen and Mortensen (2001) investigated the relationship between urban city upbringing and the risk of schizophrenia among five million people born in Denmark between 1910 and 1986 (Pedersen 2006).

European studies conducted outside the Nordic countries have used different approaches to investigate the epidemiology of schizophrenia and other psychoses. For example, case register studies, investigating urban–rural differences and the occurrence of psychoses, have been carried out in northern Italy (Thomicroft et al 1993) and the Netherlands (Peen and Dekker 1997, Marcelis et al 1998).

In the Camden and Hampstead Schizophrenia Survey studies (Harvey 1996, Harvey et al 1996, Jeffreys et al 1997), schizophrenic individuals were identified using key informants. The surveys focused on the inner city of London regarding prevalence, incidence, migration and the relationship to sociodemographic factors.

Registers with data from all types of psychiatric and community services within a psychiatric sector or other geographically defined area have been important instruments in epidemiological research for defining
a truer prevalence of psychiatric morbidity. In our Stockholm County study (Paper I) we used the first psychiatric base data register established in Sweden (Stefansson 1985), and supplemented that with data from some community services. In the Uppsala County study (Paper II) all known psychiatric and community services were screened in order also to reach out to a population with no contact or intermittent contact with the psychiatric care organizations during the time of investigation (cf. Screening procedures).

An early follow-up study in Salford (Freeman and Alpert 1986, Bamrah et al 1991), which is comparable to our studies, was based on computerized case register data including all psychiatric contacts as well as community services in that area. These data were combined with a questionnaire answered by the general practitioners, and clinical information and case notes on each patient were added. A broad concept of schizophrenia was used including schizophrenia, schizoaffective psychosis, paranoid states, as well as the diagnostic category of psychosis not otherwise specified.

Prevalence, incidence and lifetime risk

The prevalence figure for a disorder is the consequence of three different factors: incidence, mortality and the rate of recovery (Warner 1994). The prevalence rate, i.e. the number of cases in a given time-period, varies more widely than the incidence rate, i.e. the appearance of the illness, which is usually collected from the first treatment contact when a person has been diagnosed as suffering from the disorder.

There are differences of a global nature in prevalence rates as well as regarding specific populations in various sociodemographic areas within different countries (Rössler et al 2005). It is clear that variations in the diagnostic criteria used can render comparisons of prevalence rates difficult to interpret.

In the NCS replication study (Kessler et al 2005a, 2005b), the 12-month prevalence of non-affective psychoses (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and psychoses not otherwise specified) was 3.0 per 1 000 inhabitants, and the lifetime prevalence was 5.0 per 1 000 inhabitants. However, the interview response rate of 70.3 percent was rather low (Kessler et al 2005a, 2005b). An early study of NAP reported a 12-month prevalence of 0.5 percent and a lifetime prevalence of 0.7 percent (Kessler et al 1994, Krönglen et al 2001).
The ECA studies have reported higher rates of “schizophrenic disorders” than in other investigations, with a one-year prevalence of 1 percent and a lifetime prevalence of 1.5 percent. Other earlier studies estimated the rate of “severe mental illness” at 2.8 percent (Warner 1985, 1994).

Kringlen and co-workers (2001) reported a low lifetime prevalence of 0.2 percent for NAP in a random sample of Oslo residents aged 18 - 65 years drawn from the Norwegian National Population Register.

Most studies in Sweden have primarily investigated schizophrenia. An earlier morbidity study by Halldin (1984) reported a 12-month prevalence rate for schizophrenia/paranoid condition and other psychoses of 0.6 percent, and for affective disorders it was 0.2 percent.

A number of studies have reported that the incidence of schizophrenia appears to be declining. In a review by Warner (1994) in which 15 studies were examined, three quarters of them indicated a decrease in the incidence of the illness since 1960, and one quarter of them revealed an unchanged or increased incidence.

In Denmark, Munk-Jørgensen and Mortensen (1992) reported a decrease of 50 percent for first ever admission rates between 1969 and 1988.

The WHO comparative studies demonstrated that the incidence of narrowly defined schizophrenia is quite similar in 10 widely differing countries (Jablensky et al 1992).

In a Finnish follow-up study (Lehtinen et al 1996), the annual incidence of functional psychotic disorders decreased from 2.9 to 1.9 per 1 000 inhabitants between 1970 and 1986.

The incidence of subjects with DSM-III schizophrenia (APA 1980) in London between 1986 and 1991 was 0.21 per 1 000 inhabitants (King et al. 1994, McNaught et al 1997). Members of all ethnic minority groups were more likely to develop a psychosis, but not necessarily schizophrenia. In contrast, Boydell and co-workers (2003) reported that the incidence of schizophrenia in the south-east part of London has doubled over the past three decades.

In a recent study by Mueser and McGurk (2004), the annual incidence of schizophrenia was estimated at 0.2 - 0.4 per 1 000 inhabitants.

For lifetime prevalence, i.e. the cumulative lifetime risk, similar figures of 0.7 to 1.0 percent are seen around the world (Häfner 1988, Keith et al 1991, Socialstyrelsen 2003, Mueser and McGurk 2004, Kessler et al 2005a, 2005b).
Cultural and demographic differences

Several authors have reported an increased prevalence of schizophrenia in the center of many modern industrialized cities, as well as in urban areas compared to rural areas (Freeman 1994, Faris and Dunham 1967, Lewis et al 1992, Edgerton and Cohen 1994, Torrey et al 1997, Allardyce et al 2001). When other psychoses are included, a similar but weaker trend has also been found (Lewis et al 1992). A Swedish study (Lewis et al 1992) investigated the association between area of upbringing and the incidence of schizophrenia. The incidence was 1.65 times higher among males brought up in cities than among those who had had a rural upbringing.

Pedersen and Mortensen (2001) reported in a Danish study that those who lived their first 50 years in the highest category of their 5-level urbanicity had a 2.75-fold increased risk of schizophrenia.

There seems to be a consensus among researchers that the prevalence and incidence of schizophrenia across a wide range of cultures and countries is similar both in developed and developing nations (Jablensky and Sartorius 1988, Draguns and Tanaka-Matsumi 2003, Mueser and McGurk 2004).

In a WHO study (Jablensky and Sartorius 1988) the incidence of schizophrenia was shown to be quite similar across 20 countries in different parts of the world. However, the course and prognosis of the illness is extremely variable, with a significantly better outcome in developing countries. Marsella (1988) reported that cultural variability increases as psychological disturbances become more severe. This has also been confirmed in a study of normal, borderline and schizophrenic individuals in Sweden and Nicaragua (Sundbom et al 1998).

Gender differences

Several studies have reported no significant differences between men and women in the one-year or the lifetime prevalence rates (Hambrecht et al 1992, Warner 1994, Mueser & McGurk 2004). However, the incidence of schizophrenia has been reported to be twice as high for men in the youngest age group (15 - 24 years). In the next life decade (25 - 34 years), the incidence of schizophrenia in women peaks (Cooper et al 1987, Gureje 1991, Warner 1994).

The most commonly reported gender difference in schizophrenia is a tendency for women to have a later age at onset than men, with a difference of about five years. This is followed by the well known fact that women have a more benign course of illness, including fewer hospital admissions and better social functioning (Widerlöv et al 1990,

Mortality

Excess mortality among individuals with schizophrenia has been well established in previous studies (Allebeck 1989, Harris and Barraclough 1998, Brown et al 2000, Ösby et al 2000a, 2000b, Hannerz et al 2001). A higher mortality among women than in men has also been reported (Babigian and Odoroff 1969, Allebeck and Wistedt 1986, Black and Winokur 1988). However, more recent studies show higher mortality among men with schizophrenia (Brown 1997, Harris and Barraclough 1998, Ösby et al 2000a) as compared with women. Rössler and co-workers (2005) reported that the relative mortality risk of male schizophrenic patients was 4.7-fold higher, and that of female patients was 2.3-fold higher compared with the age standardized general population.
AIMS OF THE THESIS

General aim:
To study all individuals with Long-term Functional Psychosis (LFP) in two different counties in Sweden from an epidemiological perspective, and to perform specific studies concerning the subgroup of patients with schizophrenia.

Specific aims:
1. To identify a total population of LFP individuals aged 18 years and over.
2. To estimate the one-year prevalence in relation to age, sex, diagnoses and demographic areas.
3. To examine to what extent differences in prevalence rates are dependent on the diagnostic criteria used.
4. To compare two similar epidemiological studies regarding methodology and results in two different counties in Sweden.
5. To study the prescription of antipsychotic drugs during a defined period in relation to sex, dosage, psychotic symptoms and duration of illness.
6. To study the pattern of care in a LFP population in Stockholm County.
7. To study the incidence of suicide and mortality in schizophrenic subjects.
SUBJECTS AND METHODS

The present thesis is based on two separate study populations collected during the index years 1984 (Stockholm County) and 1991 (Uppsala County).

Papers I and V comprise investigations of a study population of 302 individuals, aged 18 to 64 years and meeting the criteria of LFP, in three different demographic areas of Stockholm County. A supplementary LFP group of 39 subjects was later added (1989) and included in this thesis. Thus, the total study population comprises 341 individuals.

Papers II – IV and VI comprise investigations of 473 LFP individuals, aged 18 years and above, in three different demographic areas of Uppsala county.

Concept of Long-term Functional Psychosis (LFP)

In order to define a population of long-term mentally disabled individuals due to psychotic disorders, these studies have introduced and validated the concept of long-term functional psychosis (LFP). This approach may be useful in times of ongoing large reorganizations of psychiatric services, which have the main medical and treatment responsibilities for this group. Today, responsibility for support and housing is shared by different community services.

The concept of LFP corresponds closely to a general idea of “insanity”, which apparently exists in all cultures, and may therefore prove more valid than clinical diagnoses when communicating with caregivers outside of the psychiatric organization.

Besides schizophrenia, LFP covers paranoia under the diagnosis of paranoid disorders and, provided the illness is long-term, major affective disorders and psychotic disorders not elsewhere classified. The concept excludes organic and toxic disorders, where responsibility for treatment may at least in part be assigned to other specialties.
Definition of LFP

- Continuous signs of functional impairment for at least six months in areas such as work, social relationships and self-care abilities on some occasion during the person’s lifetime;
- Active psychotic symptoms for at least one week, or less if symptoms have been successfully treated;
- Prodromal/residual psychotic symptoms during the index year of the studies.

The psychotic phase may have been preceded by a prodromal phase with a clear deterioration in social functioning. A residual phase may have followed the active phase of the disturbance where some persistent symptoms could be noted, although without prominent psychotic symptoms.

In order to be eligible for inclusion in the study, the individuals must have had at least one episode of the psychotic symptoms, and must also have shown functional impairment during the index year. This definition of LFP corresponds closely to the DSM-III (APA 1980) and DSM-III-R (APA 1987) criteria for schizophrenia.

Diagnostic assessments

In the study of Stockholm County (Papers I and V) the diagnostic assessment was normally made based on medical records and case register information. All those with psychotic or affective disorders, and those diagnosed as borderline personality disorder, were rediagnosed according to the LFP concept and later according to the DSM-III criteria. If necessary, the psychiatrist or other psychiatric staff responsible for the patient, was interviewed. The LFP diagnosis was made on a 5-point probability scale answering the question whether the individual fulfilled the criteria during the index year (Widerlöv 1990). The answers “yes” and “probable” led to inclusion, while the other three options led to exclusion. Prior to this, the option “do not know” led to further collection of information to enable, if possible, a more securely anchored diagnosis (Widerlöv 1990, Borgå 1993).

In the study of Uppsala County (Paper II) the procedure was somewhat different than in the Stockholm study. Using information from all kinds of psychiatric registers, both manual and computerized, diagnoses were assigned according to ICD-9 (WHO 1978). The following ICD-9 diagnoses were included: Alcohol psychosis (291), Drug psychosis (292), Schizophrenia (295), Affective psychosis (296), Paranoia (297), Reactive
psychosis (298), Personality disorders (301A-D, H-J), and Hallucinations (780B).

The aim of this broad diagnostic perspective was to detect as many potential cases as possible during the screening phase, and then by using the DSM-III-R criteria to exclude the cases that did not fulfill the LFP definition.

In order to communicate with a number of different caregivers, a definition of long-term psychiatric illness was designed that included explanations of psychotic symptoms and the different phases of the illness according to prodromal and/or residual symptoms (Paper II).

The final diagnostic procedure took place in two steps. First, as much data as possible was obtained from the different caregivers. These data included interviews with key informants (e.g. psychiatrists, nurses, social workers, paramedicals), which led to the first preliminary judgment of tentative cases to be included in the final population. A standardized formula was used in this procedure.

In a second step a check-list was used that included items for diagnosing psychotic symptoms, duration of the illness and functional impairment. The check-list ended with a tentative diagnosis of LFP.

In 1994 the DSM-IV (APA 1994) was introduced, and the schizophrenic subpopulation was re-diagnosed. Paper III examines the extent to which differences in prevalence rates are dependent on the diagnostic criteria used. Assessments were made using four different diagnostic systems: DSM-III, DSM-III-R, DSM-IV and ICD-10.

In Paper VI, the original schizophrenic subpopulation from Papers II and III was diagnosed using DSM-III-R (APA 1987). The schizophrenic subjects finally presented in Paper VI have been re-diagnosed using DSM-IV criteria (APA 1994).

A summary of the diagnostic instruments used in the different papers is presented in Table 4.

Stockholm County study areas (Papers I and V)

Three different demographic areas in Stockholm County were chosen in order to compare them according to prevalence and conditions for LFP individuals. Stockholm is the capital of Sweden, with approximately 653,500 inhabitants at the time of the study (1984).

The areas had rather distinct characteristics and could be described as rural, suburban and urban. They bordered on one another, stretching from the outer archipelago to the southern part of the city center in Stockholm.
The total study area population in the index year (1984) was 89,414 inhabitants (Statistics Sweden, Demopak 1984), out of which 57,035 inhabitants were in the age group 18 – 64 years, and thus relevant for this study, Table 1.

Table 1. The general population of the Stockholm County study area. Number of persons aged 18-64 years according to gender and residence area.

<table>
<thead>
<tr>
<th></th>
<th>Rural</th>
<th>Suburban</th>
<th>Urban</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>6,193</td>
<td>18,421</td>
<td>3,949</td>
<td>28,563</td>
</tr>
<tr>
<td>Females</td>
<td>5,676</td>
<td>18,781</td>
<td>4,015</td>
<td>28,472</td>
</tr>
<tr>
<td>Total</td>
<td>11,869</td>
<td>37,202</td>
<td>7,964</td>
<td>57,035</td>
</tr>
</tbody>
</table>

**Rural study area.** The majority of persons in the rural municipality (a total of 18,719; 11,869 aged 18 -64) lived on a few large islands in the Stockholm archipelago, but the area also included smaller and more distant islands. The municipal center with half of the population is only half an hour bus drive from Stockholm, while it may take several hours to reach the more distant parts of the area. Many of the residents were employed in Stockholm, while others were employed in more local enterprises or self-employed as craftsmen, farmers or fishermen. The population was predominantly middle-aged, with a peak age between 35 – 44 years.

**Suburban study area.** The suburban municipality had a total population of 49,009 inhabitants (37,202 aged 18 – 64) at the end of the index year 1984. This area is to a greater extent connected to Stockholm, with a majority of employers working in the city region (Statistics Sweden, Demopak 1984).

The residential areas consisted of low status apartment buildings and areas dominated by detached houses. Some areas were characterized by old buildings, others by new developments.

The psychiatric services for the rural and suburban areas were covered by the same health care organizations, and were characterized by an emphasis on outpatient services and a low hospital bed/population ratio.

**Urban study area.** The urban parish had 11,686 inhabitants (7,964 aged 18 – 64 years) by the end of the index year. The population was fairly young, with a peak age between 25 – 34 years. The area is located in the southern central part of the city of Stockholm and was at that time a low-status, former working-class residential area, consisting of apartment
buildings. This area was undergoing a rebuilding process, but at the time of the study 43% of the apartments still had only one room and a kitchen.

The psychiatric services of this parish were more traditionally organized with a high hospital bed/population ratio. The inpatient wards were located both in a general hospital in the southern city center and in a more distant mental hospital.

Screening procedures (Papers I and V)

A psychiatric case register (Stefansson 1985), including 5,313 cases containing information on all adult patients visiting psychiatric inpatient and outpatient facilities in the rural and suburban areas, was the main source used in screening the study population in these areas. This register covered a period of ten years prior to the index year (1984). Each case register included a diagnostic assessment made by the clinician in charge (Figure 1).

No such case register had been established in the psychiatric sector covering the urban area. All inpatient and outpatient records, approximately 750 in all, in the urban parish had to be screened manually using existing inpatient and outpatient files.

In addition, for the three different areas (urban, suburban and rural), enquiries were directed to other caregivers serving Stockholm County Council: departments of forensic psychiatry, nursing homes, and patients’ “foster homes,” and an investigation of all inpatients in Stockholm County was carried out.

The first screening phase resulted in a total of 504 individuals, and these were further tested for inclusion in the study. In the next phase, 202 cases were excluded because they were not living or registered in any of the areas, or could not be defined as LFP. The remaining 302 subjects constituted the target LFP population, see Figure 1.

Later on, during the period 1989-1990, a complementary study was conducted (Borgå 1993). The methodology used was case finding through screening of psychiatric institutions and outpatient departments, general practitioners’ clinics and social welfare offices. The time-period covered by the screening was 10 years before, and five years after the index year (1984). Thirty-nine cases were found, of whom 27 had had no previous psychiatric contacts during the index year, in addition to 302 earlier identified subjects in the original study (Paper I). This was an increase of 13% compared with the original study.
Stockholm County
Index year: 1984

Case register population
Rural + suburban: N=5313
Urban: N=750
Manual screening

Study population
N = 473
M 233; F 240

Complementary population
N = 39
M 17; F 22

Final study population
N = 341
M 173; F 168

Uppsala County
Index year: 1991

Case register population
N = 2500 + all other caregivers in psychiatry and community

Study population
N = 473
M 233; F 240

Schizophrenia subgroup
Mortality study
N = 255
M 146; F 109

Schizophrenia subgroup rediagnosed
N = 273
M 157; F 116

Complementary population
N = 39
M 17; F 22

Final study population
N = 455
M 222; F 233

Inclusion criteria:
1. reg. in the area
2. LFP criteria

F = females; M = males; N = number of patients
Uppsala County study areas (Papers II – IV, VI)

The psychiatric catchment area of the northern part of Uppsala includes three areas with different demographic characteristics. These consist of two urban areas (central city and peripheral city) and one rural area.

At the end of 1991, the total population in the three areas was 84 730 inhabitants, of which 64 886 individuals were in the age groups covered by the study (18 years and older), Table 2. The two urban areas included belong to the city of Uppsala, a residential university town with approximately 180 000 inhabitants at that time.

Table 2. The general population of the Uppsala catchment area. Number of people aged 18 years and older according to gender and residence area.

<table>
<thead>
<tr>
<th></th>
<th>Rural</th>
<th>Peripheral city</th>
<th>Central city</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>11 590</td>
<td>8 582</td>
<td>11 293</td>
<td>31 465</td>
</tr>
<tr>
<td>Females</td>
<td>11 567</td>
<td>9 476</td>
<td>12 378</td>
<td>33 421</td>
</tr>
<tr>
<td>Total</td>
<td>23 157</td>
<td>18 058</td>
<td>23 671</td>
<td>64 886</td>
</tr>
</tbody>
</table>

Inpatient care was provided by a hospital department located in the central part of Uppsala, and the outpatient facilities were located within each of the three study areas.

Central city area. The total population in 1991 was 29 828, of whom 23 671 were aged 18 years or older. The age distribution was fairly equal between males and females with a peak for the age group between 18-34 years.

Some of the residential areas could be characterized as low-status areas with apartment buildings with small apartments. Nearly 75% of the population lives within the central city area. Further from the city center a more suburban-like area emerges with small villas and detached houses.

Peripheral city area. This area had 25 270 inhabitants in 1991, of whom 18 058 were 18 years or older. The age distribution is similar to that in the central city area, again with a peak for the 18-34 years age group. The suburban character of the peripheral parts of the area is more pronounced, with some more attractive residential areas.

Rural area. At the end of 1991 the rural area had a total population of 29 632, of whom 23 157 individuals were aged 18 years or older. As in the other areas, the age distribution showed a peak for the youngest age group (18-34 years), but in contrast to the other areas, it also showed a peak for the oldest age group (65 years and older). The area had a typical
rural character, with some parts sparsely populated. At the time of the study more than 65% of the population was living in the countryside and the rest were living in small communities, with around 5 000 inhabitants in the largest one.

Screening procedures (Papers II – IV and VI)

A number of different care organizations that were considered most likely to have information about long-term psychotic subjects within their catchment areas were screened. The aim of this broad perspective was to detect as many potential cases as possible during the screening phase.

The total screening procedure was carried out in six steps.

1. Different admission registers for the years 1981 – 1991, both manual and computerized (UDAC), were used in order to screen the psychiatric hospitals and child psychiatric clinics as well as the outpatient care facilities. Approximately 2 500 medical documents were used in this first screening phase. From this screening, the first broad definition of potential LFP individuals was assessed, and computerized lists of all subjects were established. This list of subjects was then distributed to all caregivers included in the following screening phase. The further investigations were aimed at estimating how many individuals from our list they could recognize, and how many individuals outside this list they could add from their care organization, and which individuals could be identified as presumably LFP subjects. The subjects who had no contacts or intermittent contacts during the index year could be identified as LFP through interviews with other caregivers and access to information in their files and records.

2. Inquiries were directed to the three psychiatric outpatient teams, three primary health care centers (mostly district nurses as key informants), the departments of forensic psychiatry, criminal offenders and psychogeriatrics, student psychiatric services, private practitioners in psychiatry, and a psychiatric center for refugees. Information and interviews obtained from psychiatrists, and occasionally other staff members, were the primary sources of information on which the decision to include subjects in the study population was based.
3. Interviews with key informants were conducted when screening cases in social welfare agencies, community home services, nursing homes, homes for the elderly, residential alcohol and drug treatment centers, care organizations for mentally retarded individuals, day care centers for mentally ill people, a shelter for homeless persons (Sagahemmet), and a rehabilitation team for long-term psychotic subjects (Bojan).

4. Computerized data from the social security department were screened in order to get information about all subjects receiving sickness pensions due to psychiatric illness.

5. A national registry of all criminal offenders (n=1 100) from the areas included in the study for the index year (1991) was matched with our list of presumably LFP subjects. Then, if necessary, inquiries were made based on further information about the individual in question and if they had knowledge about any additional subjects who could belong to the target population. An investigation in cooperation with staff from the national department of criminal offenders was carried out by using different computerized registers and interviews with staff from special wards within the prison system.

6. In the final assessment of the LFP diagnosis, the LEAD Standard was used (Spitzer 1983). LEAD involves three essential concepts: Longitudinal data, Expert evaluation and All Data. Longitudinal data, meaning symptoms during the entire episode of the illness, should be taken into account when assessing the diagnosis, which should be made by expert clinicians. All data provided by other professionals should also be used.

All these different steps were time-consuming procedures, but they were considered to be necessary for collecting information about subjects with no contact or only intermittent contact with other than psychiatric care organizations.

Reference populations (Papers I – VI)

In the Stockholm County study (Papers I and V) prevalence figures for the LFP population were compared with the general population of the catchment area. These figures are presented in Table 1.
In the Uppsala County study (Paper II-IV, VI) the prevalence figures were compared with a general population from that catchment area in the age group 18 years and older. See Table 2 for the distribution of males and females in the three areas studied.

Diagnostic criteria and the prevalence of schizophrenia (Paper III)

The aim of the study was to examine the extent to which differences in prevalence rates are dependent on the diagnostic criteria used. The LFP patients presented in Paper II were re-examined using four different sets of diagnostic criteria: DSM-III, DSM-III-R, DSM-IV and ICD-10. The main inclusion criteria for the LFP diagnostic groups in the different classification systems are summarized in Table 3. In the original Uppsala LFP study (Paper II), the patients were diagnosed according to DSM-III-R, and in the Stockholm LFP study according to DSM-III.
Table 3. Principal differences between diagnostic criteria for schizophrenia, schizoaffective disorder and delusional disorder in different classification systems.

<table>
<thead>
<tr>
<th></th>
<th>DSM-III</th>
<th>DSM-III-R</th>
<th>DSM-IV</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schizophrenia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criterion (A)</td>
<td>6 items</td>
<td>3 items</td>
<td>5 items</td>
<td>8 items</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>-</td>
<td>1 week</td>
<td>1 month</td>
<td>1 month</td>
</tr>
<tr>
<td>Age at onset</td>
<td>&lt; 45 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overall duration</td>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
<td>1 month</td>
</tr>
<tr>
<td>Incl. negative symptoms</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Symptomatology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>-</td>
<td>Psychotic &gt; 2 weeks</td>
<td>Psychotic &gt; 2 weeks</td>
<td>Both psychotic and affective symptoms</td>
</tr>
<tr>
<td>Delusional disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms included</td>
<td>Paranoid disorder.</td>
<td>Delusions of persecution or jealousy</td>
<td>Non-bizarre delusions</td>
<td>Non-bizarre delusions</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>Nonprominent hallucinations</td>
<td>Nonprominent auditory or visual halluc.</td>
<td>Tactile or olfactory halluc. related to delusional theme</td>
<td>Transitory auditory halluc. Depressive symptoms</td>
</tr>
<tr>
<td>Overall duration</td>
<td>1 week</td>
<td>1 month</td>
<td>1 month</td>
<td>3 months</td>
</tr>
</tbody>
</table>
chlorpromazine equivalents (CPEQ) according to Davis (1974). Clozapine, not listed in this schedule, was considered equivalent to chlorpromazine.

Pattern of care (Paper V)

The studied LFP population in this paper is defined above and in Paper I. The study comprised a total of 302 subjects (156 females; 146 males). When the LFP diagnoses had been made, the Axis I diagnoses of psychoses were assessed using DSM-III criteria. Seventy % had schizophrenic disorder, 15 % paranoid disorder, 12 % affective disorder, and 4 % psychotic disorder not otherwise classified. The sex distribution is presented in Table 1, Paper V.

Information about the care situation was recorded from psychiatric patient files, primary health care files, parish and official municipal records as well as computerized data on inpatient care from Stockholm County.

Social workers at all welfare offices were interviewed about their clients, when these had been included in the study, as to the extent and content of their contact. All primary health care departments were thoroughly screened in a similar way and outpatient visits by LFP individuals were recorded.

Types of neuropsychopharmacological drugs were recorded and dose levels of antipsychotic drugs were individually recalculated into CPEQ using a manual (Borgå 1993), constructed on the basis of Davis (1974) and Wyatt and Torgow (1976).

Mortality in the Uppsala County study (Paper VI)

All individuals with schizophrenia included in the total LFP population in Paper II were chosen in order to analyze the 10-year mortality rate from an epidemiological perspective. For each person with schizophrenia (n=255), age, sex, and residence area were matched with five persons from the general population (n=1 275) who were identified using national population registers. They were included in the study on the same index date as the schizophrenic subjects (January 1, 1991). The Swedish postal system was used to match individuals with schizophrenia and reference individuals from the general population by residence area.
The Swedish Cause of Death Register was used to analyze mortality. The register includes information about cause of death (ICD-10; WHO 1992) either from investigation by a clinician or from autopsy or forensic autopsy, as well as time and place of death. Information about emigration was obtained from Statistics Sweden. In the analyses of cause of death, tumors, circulatory diseases and unnatural deaths were studied.

A separate analysis was carried out on individuals with schizophrenia who died an unnatural death.

**Diagnostic instruments (Papers I - VI)**

A summary of the diagnostic classification systems used is presented in Table 4.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Diagnostic criteria</th>
<th>Statistical methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>DSM-III</td>
<td>Descriptive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paired t-test</td>
</tr>
<tr>
<td>II</td>
<td>ICD-9</td>
<td>Descriptive</td>
</tr>
<tr>
<td></td>
<td>DSM-III-R</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>III</td>
<td>ICD-9</td>
<td>Descriptive</td>
</tr>
<tr>
<td></td>
<td>ICD-10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DSM-III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DSM-III-R</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DSM-IV</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>DSM-III-R</td>
<td>Descriptive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Student’s t-test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linear correlation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mann-Whitney U-test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spearman rank correlation coefficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chi-square test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stepwise multiple regression</td>
</tr>
<tr>
<td>V</td>
<td>DSM-III</td>
<td>Descriptive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chi-square test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linear correlation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-parametric one-way analysis of variance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wilcoxon rank sum test</td>
</tr>
<tr>
<td>VI</td>
<td>DSM-III-R</td>
<td>Descriptive</td>
</tr>
<tr>
<td></td>
<td>DSM-IV</td>
<td>Kaplan-Meier method</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Log-rank test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cox regression analysis</td>
</tr>
</tbody>
</table>
Statistical methods (Papers I – VI)

A summary of the statistical methods is presented in Table 4.

Paper I: Wherever the data fulfilled statistical assumptions, pair-wise double-sided tests for proportional differences were carried out (using normal approximation).

Paper II: Differences in prevalence rates were tested by the Chi-square test.

Paper III: Only descriptive data. No statistical analyses were performed.

Paper IV: Differences between means were tested using Student’s $t$-test and correlations were sought using the linear correlation coefficient. However, as concerns the amount of drugs used, expressed in chlorpromazine equivalents, a skewed distribution was present and thus differences were tested by means of the non-parametric Mann-Whitney $U$-test, and correlations were sought by means of the Spearman rank correlation coefficient. Differences in frequency distributions were tested by means of the Chi-square test. The factors of importance for the dose levels in patients on antipsychotic drugs were tested by means of a stepwise multiple regression analysis, with the amount of antipsychotics expressed in mg chlorpromazine equivalents (CPEQ) as the dependent variable.

Paper V: Statistical analyses of the care variables were carried out using the Chi-square test, correlation analysis, non-parametric one-way analysis of variance, and the Wilcoxon rank sum test according to the SAS computer program (SAS/STAT 1987).

Paper VI: Statistical analyses were carried out using the SAS 8.02 system. In order to take into account loss to follow-up because of emigration, the Kaplan-Meier method, using the log-rank test for calculating statistical significance, was employed. In the analyses of cause of death, those who died by causes other than those under investigation were censored for the time of the event. The differences in mortality are presented as Risk Ratios (RRs), i.e. the ratio between the mortality among persons with schizophrenia and that among population referents matched for sex and age. Cox regression analysis was used for the multivariate approach. Hazard Ratios (HRs) were calculated from the parameter estimates of the regression analysis. HRs measure the contribution of a single characteristic (presence of schizophrenia, gender, age, etc.) to the mortality rate. Interaction effects between the variables were tested.
RESULTS

Total prevalence (Papers I-III and VI)

The total one-year prevalence of LFP in Stockholm County (Paper I; n=302) in those aged between 18-64 years was 5.3 per 1 000 inhabitants, see Table 5 and Figure 2. The prevalences in the rural, suburban and urban areas were 3.4, 5.6, and 6.6 per 1 000 inhabitants, respectively, thus producing a gradient from the rural to the urban areas. The differences between the rural – suburban areas and the rural – urban areas were statistically significant (p<0.01).

Table 5. One-year prevalence (per 1 000 inhabitants) of LFP in the Stockholm study. (Number of patients within brackets)

<table>
<thead>
<tr>
<th></th>
<th>Rural</th>
<th>Suburban</th>
<th>Urban</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total LFP</td>
<td>3.4 (41)</td>
<td>5.6 (208)</td>
<td>6.6 (53)</td>
<td>5.3 (302)</td>
<td>&lt; 0.01¹,²</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>4.5 (28)</td>
<td>5.6 (104)</td>
<td>6.1 (24)</td>
<td>5.5 (156)</td>
<td>NS</td>
</tr>
<tr>
<td>Females</td>
<td>2.3 (13)</td>
<td>5.5 (104)</td>
<td>7.2 (29)</td>
<td>5.1 (146)</td>
<td>&lt; 0.01¹ &lt; 0.001²</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>&lt; 0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 – 34</td>
<td>2.6 (11)</td>
<td>5.0 (67)</td>
<td>5.3 (21)</td>
<td>4.6 (99)</td>
<td>&lt; 0.05³</td>
</tr>
<tr>
<td>35 – 54</td>
<td>3.4 (20)</td>
<td>6.4 (115)</td>
<td>6.1 (18)</td>
<td>5.7 (153)</td>
<td>&lt; 0.01¹</td>
</tr>
<tr>
<td>55 – 64</td>
<td>5.7 (10)</td>
<td>4.5 (26)</td>
<td>12.9 (14)</td>
<td>5.8 (50)</td>
<td>&lt; 0.05² &lt; 0.001³</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.01⁴</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

¹rural-suburban; ²rural-urban; ³suburban-urban; ⁴18-34 vs 55-64; ⁵35-54 vs 55-64
Figure 2. Prevalence rates of LFP per 1 000 inhabitants

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Total Prevalence</th>
<th>M</th>
<th>F</th>
<th>N</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockholm study</td>
<td>1984</td>
<td>5.3</td>
<td>5.5</td>
<td>5.1</td>
<td>302</td>
<td>18 - 64 years</td>
</tr>
<tr>
<td>Uppsala study</td>
<td>1991</td>
<td>7.3</td>
<td>7.4</td>
<td>7.2</td>
<td>473</td>
<td>18 years</td>
</tr>
<tr>
<td>Paper II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia subpopulation</td>
<td></td>
<td>3.7</td>
<td>4.2</td>
<td>3.3</td>
<td>255</td>
<td>18 years</td>
</tr>
<tr>
<td>Thesis summary</td>
<td></td>
<td>Total prevalence</td>
<td>5.6</td>
<td>5.4</td>
<td>365</td>
<td>18 - 64 years</td>
</tr>
<tr>
<td>Non-schizophr. LFP</td>
<td></td>
<td>4.2</td>
<td>4.9</td>
<td>3.4</td>
<td>237</td>
<td>18 - 64 years</td>
</tr>
<tr>
<td>Schizophrenia LFP</td>
<td></td>
<td>4.0</td>
<td>4.7</td>
<td>3.3</td>
<td>208</td>
<td>18 - 64 years</td>
</tr>
<tr>
<td>Non-schizophr. LFP</td>
<td></td>
<td>3.1</td>
<td>2.5</td>
<td>3.6</td>
<td>158</td>
<td>18 - 64 years</td>
</tr>
</tbody>
</table>

F = females; M = males; N = number of patients
In the study population of Uppsala County (Paper II; n=473), the total one-year prevalence rate of LFP among inhabitants aged 18 years and over was 7.3 per 1 000 inhabitants, see Table 6 and Figure 2. The prevalence rates in the rural, peripheral, and central city areas were 6.0, 7.0 and 8.7 per 1 000 inhabitants, respectively, thus producing a gradient from the rural to the central city area. The differences between the peripheral city vs. central city area, and the rural vs. the central city area were statistically significant (p<0.05, and 0.001, respectively). Five patients (2%) were found outside the official health care system. These subjects with no contacts or intermittent contacts with the psychiatric health care system during the index year (1991) could be identified as LFP through other caregivers by means of interviews and files.

Table 6. One-year prevalence (per 1 000 inhabitants) of LFP in the Uppsala study. (Number of patients within brackets)

<table>
<thead>
<tr>
<th></th>
<th>Rural</th>
<th>Peripheral city</th>
<th>Central city</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total LFP</td>
<td>6.0 (139)</td>
<td>7.0 (127)</td>
<td>8.7 (207)</td>
<td>7.3 (473)</td>
<td>&lt; 0.01²</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>5.6 (65)</td>
<td>7.1 (61)</td>
<td>9.5 (107)</td>
<td>7.4 (233)</td>
<td>&lt; 0.001²</td>
</tr>
<tr>
<td>Females</td>
<td>6.5 (74)</td>
<td>7.0 (66)</td>
<td>8.1 (100)</td>
<td>7.2 (240)</td>
<td>NS</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Rural</th>
<th>Peripheral city</th>
<th>Central city</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 – 34</td>
<td>2.9 (18)</td>
<td>4.1 (25)</td>
<td>5.9 (51)</td>
<td>4.5 (94)</td>
<td>&lt; 0.01²</td>
</tr>
<tr>
<td>35 – 54</td>
<td>7.0 (52)</td>
<td>8.4 (64)</td>
<td>13.0 (108)</td>
<td>9.5 (224)</td>
<td>&lt; 0.001²</td>
</tr>
<tr>
<td>55 – 64</td>
<td>6.2 (19)</td>
<td>8.8 (16)</td>
<td>8.8 (20)</td>
<td>7.6 (55)</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 65</td>
<td>7.8 (50)</td>
<td>8.9 (22)</td>
<td>6.3 (28)</td>
<td>7.5 (100)</td>
<td>NS</td>
</tr>
</tbody>
</table>

\[ P < 0.01^4 \quad < 0.01^4 \quad < 0.001^4 \quad < 0.001^4 \\
< 0.05^5 \quad < 0.05^5 \quad < 0.001^7 \quad < 0.01^7 \]
\[ < 0.001^6 \quad < 0.01^6 \quad < 0.001^6 \]

1rural-suburban; 1rural-urban; 1suburban-urban
218-34 vs 35-54; 218-34 vs 55-64; 318-34 vs 65-; 418-34 vs 65-; 518-34 vs 65-

In Paper III, when the patients had been rediagnosed according to DSM-III-R, DSM-IV and ICD-10, it was found that the prevalences of schizophrenia, schizoaffective disorder and delusional disorder were somewhat lower according to the DSM-III criteria, while the same number of patients fulfilled the criteria according to DSM-IV. When the ICD-10 criteria were used, this resulted in a broader concept of
schizophrenia and a somewhat narrower concept of schizoaffective disorder. Thus, introduction of the new parallel diagnostic systems, ICD-10 and DSM-IV, will result in different but comparable prevalence estimates concerning schizophrenia, schizoaffective disorder, and delusional disorder.

In the mortality study (Paper VI) of persons with schizophrenia (n=273), 14 subjects were subsequently excluded from the follow-up because of double registration (5 patients) and administrative errors (9 patients). Four more patients were excluded because of confidentiality requirements for persons found outside the official health care system. The remaining 255 patients were included in the study population as of January 1, 1991.

In summary, the prevalence of the schizophrenic population turned out to be 3.7 per 1 000 inhabitants, with slightly lower figures in the mortality study (Paper VI) compared with the earlier study of LFP in the same cohort where the prevalence was 4.2 per 1 000 inhabitants (Paper II). This is the result of a correction in the number of included subjects (see above), and a change in the method of calculating the population of the area.

Prevalence of sex, age and diagnoses (Papers I and II)

Sex

In the study of Stockholm County (Paper I), the one-year prevalence according to sex was higher for males than for females in the rural area (p<0.05), see Table 5. There was a female gradient from urban to rural areas, with three times as many females in the urban area. Thus, the gradient between the areas was mainly due to the female subjects (p<0.01 rural-suburban; p<0.001 rural-urban).

When comparing the total figures for the sexes in the study of Uppsala County (Paper II) there were no statistical differences, see Table 6. When analyzed according to area, the prevalence was generally higher for males, except for the rural area. A gradient with a higher prevalence towards the city center was pronounced for both males and females, but was only statistically significant for the male subjects (central city vs. peripheral area p<0.05); central city vs. rural area p<0.001).
Age

In the Stockholm County study (Paper I) the lowest total LFP prevalence rate was found in the youngest age group (2.6/1 000) in the rural area, with increasing rates from the rural to the urban area (p<0.05). The most striking finding was the marked excess of LFP individuals in the oldest age group, 55 to 64 years, in the urban area (12.9/1 000), with statistically significant differences between the rural and urban areas (p<0.05) and between the suburban and urban areas (p<0.001), Table 5.

In the Uppsala County study (Paper II) the central city area showed a prevalence peak for the 35-54-year age group (13 per 1 000 inhabitants), while the rural area had the lowest rate for the youngest age group (2.9/1 000) and a peak for the age group 65 years or older (7.8/1 000), Table 6. In the peripheral city area the highest prevalence rate was also found in the age group 65 years or older (8.9/1 000), but with a consistent increase in the rates from the youngest age group to the oldest. The age differences between the areas were statistically significant (p<0.01), in the age group 18-34 years for the central city vs. the rural area (p<0.01), and in the age group 35-54 years for both the central city vs. the rural area (p<0.001) and the central city vs. the peripheral city area (p<0.01).

Diagnoses

In the Stockholm County study (Paper I) the prevalence of schizophrenia was higher among males than females (p<0.01). The prevalence figures were 4.4 and 3.0 per 1 000 inhabitants, respectively. The opposite trend was seen for paranoia (p<0.05) and for major affective disorder with psychotic features (not statistically significant). The figures for all the areas produce a one-year prevalence for paranoia of 0.5/1 000 inhabitants for males, and 1.1/1 000 for females. The corresponding figures for major affective disorder covered by LFP were 0.4 and 0.8/1 000 inhabitants, respectively. These differences were mainly due to the rural area. The overall one-year prevalence for schizophrenia varied from 2.6/1 000 for the rural area to 3.8 for the suburban area and 5.0/1 000 for the urban area.

The category Psychotic disorder not elsewhere classified, regarded as a residual category and seldom specified in epidemiological research, added 0.2 per 1 000 inhabitants in both the male and female populations.

In the Uppsala County study (Paper II) the highest prevalence rate occurred among the male schizophrenic subjects (5.0/1 000). The female subjects had higher prevalence rates for all of the other diagnostic subgroups, with the highest rate being that for affective psychosis.
The prevalence of LFP categorized according to diagnostic subgroups showed the highest rate for schizophrenia in the city center area (5.3/1,000), followed by the peripheral area (4.4/1,000) and finally the rural area (3.0/1,000), thus representing a gradient from the city center area to the rural area.

The gradient in prevalence rates from the city center area to the rural area was only observed with regard to schizophrenia, while schizoaffective, paranoia and unspecified psychosis were more evenly distributed between the areas (p<0.01).

Diagnostic criteria for schizophrenia (Paper III)

The prevalence of schizophrenia, schizoaffective disorders, and psychosis NOS according to the DSM-III, DSM-III-R, DSM-IV and ICD-10 are presented in Table 3 for males and females. According to DSM-III criteria, the prevalence was somewhat lower for both males and females, while DSM-IV criteria gave almost identical prevalence figures to those of the DSM-III-R. However, the ICD-10 was more inclusive resulting in a higher prevalence rate. The small number of patients with delusional disorder was unchanged according to the DSM-III-R, DSM-IV and ICD-10.

Antipsychotic drugs (Paper IV)

There were a total of 270 patients with schizophrenia (157 males, 113 females). Sufficient information concerning prescribed antipsychotic drugs was available for 264 individuals. Fifty-two patients (20%) were not prescribed any antipsychotic drugs during the defined period and 211 (80%) were prescribed antipsychotic medication during the index year 1991. Among the patients on antipsychotic drugs, 114 subjects (54%) had oral medication while 98 individuals (46%) had depot antipsychotic medication. Male patients were prescribed significantly higher mean daily doses (413 mg) of antipsychotic drugs, expressed as CPEQ (Davis 1974), than the female patients (307 mg; p<0.05). The doses of antipsychotic drugs decreased with a longer duration of illness. Almost 50 percent of the patients were treated with depot antipsychotic compounds. The dose levels of antipsychotic drugs were also significantly higher (p<0.01) if patients had been admitted to the hospital on an involuntary basis, were younger at first admission, and had spent
more days in the hospital during the index year. The mean number of
days spent in the hospital during 1991 was 33.5 (range 0 - 365) for male
patients and 19.4 (range 0 - 365) for female patients. Involuntary
treatment and the use of depot drugs were equally common in both sexes.

The age at onset of illness in this study was defined as the appearance
of the first psychotic symptoms. In line with other studies, males had an
earlier age at onset than females, 23.5 and 27.4 years, respectively
(p<0.01).

Care utilization (Paper V)
Psychiatric inpatient care
Nearly half (48%) of the LFP individuals in the Stockholm County study
were admitted to a psychiatric institution at least once during the index
year (1984), see Paper V, Table 2. Those admitted spent an average of
five months as inpatients. Approximately the same number of male (53%)
and female (47%) subjects were admitted. However, the males spent
twice as long time as inpatients than the females (p<0.001).

The frequency of admission was fairly independent of diagnosis.
However, the duration of inpatient care varied according to diagnosis.
Subjects with paranoid and affective disorders had shorter inpatient stays
of about three months, whereas the duration for admitted schizophrenic
patients and those with psychosis not elsewhere classified averaged about
six months (p<0.05).

The likelihood of hospital admission increased with proximity to the
city center. However, statistical significance is only reached when the
rural area is compared to the urban area (p<0.05).

Twenty-one percent of all LFP subjects were admitted on an
involuntary basis at least once during 1984, thus accounting for 43
percent of all LFP admissions. The rates were fairly equal for males
(22%) and females (20%). The suburban area had the highest rate of
involuntary admissions, 27 percent if calculated for all LFP subjects, and
55 percent of those admitted for inpatient care. The urban area had the
lowest rate of involuntary admissions (p<0.001).

Psychiatric outpatient care
Around two thirds of the LFP individuals had a psychiatric outpatient
contact during the index year (1984) with an average of ten outpatient
visits, see Paper V, Table 3. Twelve percent of the subjects utilized
neither inpatient nor outpatient care. Since the females were hospitalized less, they had more frequent psychiatric outpatient contacts (p<0.01). The psychiatric outpatient care organizations in the urban area had contact with a lower proportion of LFP individuals than those in the rural and suburban areas (p<0.001).

Primary health care
Approximately one third of the total LFP group had contact with primary health care services, but the mean number of contacts during the index year was 0.7, and only rarely for stated psychiatric reasons. The proportion of LFP patients with contacts (17%; p<0.01) as well as the mean number of contacts (0.4; p<0.05) were lowest in the urban group, see Paper V, Table 3. There were no differences in primary health care utilization with regard to sex and diagnoses.

Social welfare contacts
Thirty-one percent of the LFP subjects had contact with the social welfare office and the mean number of visits was 6.1 during the index year, see Paper V, Table 3. Fifty percent of these contacts solely concerned financial assistance. There were no statistically significant differences according to sex, diagnoses and areas. However, the paranoid subgroup had a substantially lower number of contacts during the index year (2.2; NS.) compared with the other diagnostic groups.

Antipsychotic medication
Seventy-five percent of the LFP subjects had antipsychotic medication at the end of the index year (1984), 22 percent in the form of depot antipsychotics, see Paper V, Table 4. The median dose for those medicated was 273 mg CPEQ daily (mean dose 328 mg daily), with higher doses for males than for females (p<0.01). Antipsychotic drugs were frequently used in all diagnostic groups including the affective group. The mean dose for those medicated was highest for schizophrenia and psychotic disorders not elsewhere classified (p<0.001).

The urban psychiatric organization prescribed depot antipsychotics much more frequently (p<0.001) than the other areas. Also, the median dose of antipsychotic drugs, calculated as CPEQ, was significantly higher (300 mg daily; p<0.05) in the urban area. There was also a difference between the rural and suburban areas with increasing dosages towards the city center (p<0.05).
Duration of illness and age at onset

Utilization of inpatient and outpatient care and support seems to be independent of duration of the illness. When the duration of illness was tested against the antipsychotic medication, however, the relationship was evident: the longer the duration, the greater the likelihood of antipsychotic medication ($r=0.18; p<0.01$). A positive correlation was also found between the duration of illness and the level of antipsychotic medication within the schizophrenic group ($r=0.18; p<0.01$).

When age at onset of the illness was tested against all care variables, it was shown that early age at onset increased the likelihood of inpatient care ($p<0.05$), the median length of hospital stay ($p<0.01$), and the dose of depot medication ($p<0.05$). Within the category of schizophrenia, which generally has an earlier age at onset than the other diagnostic groups, the same relationships were demonstrated for the likelihood of inpatient care and depot medication ($p<0.05$).

Mortality in schizophrenia (Paper VI)

The higher mortality rate among patients with schizophrenia in the LFP population was mainly the result of unnatural causes and cardiovascular diseases, especially among males vs females ($p<0.0001$). When migration was taken into account, the mortality rates among individuals with schizophrenia and population controls were 23.0 % and 11.2 %, respectively ($p<0.001$).

The highest mortality rate was found in the age group 45 – 64 years ($p<0.0001$), and the mortality rate was the highest among individuals living in the city area compared with those living in the less urbanized areas ($p<0.03$).

Among the patients with schizophrenia who died from unnatural causes, 8 individuals (5 males, 3 females) had committed suicide. Six of those suicides were performed in a violent way. Among the population controls, none of the four suicides found in this group was violent; they were all the result of intoxication.
DISCUSSION

Comparisons between the Stockholm County and Uppsala County studies

Methodological considerations

Over the years, methodological aspects have received increased attention in the area of psychiatric epidemiology (Eaton et al 1984, Warner 1994, Nettelbladh et al 2005). This thesis is based on two epidemiological studies, the first in Stockholm County, index year 1984, and the second in Uppsala County, index year 1991. Based on experiences from the Stockholm study, our ambition was to develop and improve the methods used in that study when repeating a similar study in Uppsala. The two studies have many of the same methodological aspects as in most other studies based on information from different registers.

The applicability of psychiatric patient registers in epidemiological research has certain limitations when studying morbidity, because the morbidity found in these registers might be considerably higher than that of populations applying for care (Stefansson 1985).

In order to define a total LFP population, many different sources of information had to be used, from manual and computerized registers to records and files from a variety of care facilities. A computerized database is always subject to limitations (Psykiatrisamordning 2006).

Some important factors had to be considered when choosing the methods used in the two studies.

First, the organizations in the three areas of Stockholm County differed from one another; the rural and suburban areas were part of a more “modern” psychiatric care organization (Nacka-Värmdö sector), while the urban area belonged to a more traditional organization. Second, there was a gap of several years between the two studies, which is important in times of rapid transition in the care of LFP patients. In the Stockholm County study we relied mainly on computerized psychiatric in- and outpatient case registers when collecting data. In the Uppsala
study, a greater number of psychiatric and community care facilities were involved, meaning that we could not rely mainly on computerized registers, but were more dependent on manually collected data. Third, differences were found in the study areas of the Stockholm and Uppsala counties regarding demographic characteristics and psychiatric care organizations. The psychiatric case register serving Uppsala County was not as developed and reliable as the one established earlier in the Nacka-Värmdö sector of Stockholm County.

The first psychiatric case register in Sweden was established in 1975 for research and evaluation purposes and was constructed in accordance with international models (Stefansson 1985). The register comprised all psychiatric in- and outpatient units in the defined catchment area and was the main source for screening the target population in these rural and suburban areas.

No systematic validity or reliability checks were conducted other than on a few occasions for some variables. According to diagnosis, a one-year follow-up was carried out of all outpatients during a two-year period (n=2,882), and changes tending toward a more severe diagnosis occurred in 4% of the cases. Accessibility of the psychiatric care organization to the total population was found to be good, and many cases of psychosis reached psychiatric care. In general, this case register was considered to be fairly reliable, and the required data that were reported were checked from time to time (Stefansson 1985).

The case-finding techniques in the urban area of Stockholm County were weaker because no such register was established. All medical records had to be screened manually in all the psychiatric care units within the sector.

The psychiatric in- and outpatient registers serving Uppsala County were found to be less reliable (UDAC 1981-1991), since in many cases required data were not reported to the register. In order to screen the LFP population, we also had to rely on manual registers and medical records.

Reporting of data from psychiatric outpatient facilities to the national patient register is still a problem in Sweden (Socialstyrelsen 2006), e.g. about 60% of the diagnoses are missing and as many as 30% of the outpatient care visits are not reported. However, official register data in Sweden are generally considered to have a high reliability when it comes to long-term treatment and diagnosis. Ekholm and co-workers (2005) found the Swedish Psychiatric Inpatient Register (SPIR) to be sufficient for assessment of a lifetime diagnosis of schizophrenic psychosis. For these patients, a research interview adds little new information.
Swedish diagnostic practice is generally considered to be good, and the Swedish concept of schizophrenia is narrow and reflects diagnostic caution rather than over-inclusiveness (Hultman et al 1999).

Large national registers like the ones used in the mortality study (Paper VI), the Swedish Cause of Death Register and Statistics Sweden, are considered to be highly reliable.

Screening procedures

The screening procedures in the two studies differed in many aspects, see Figure 1. In Stockholm County just a few caregivers outside of psychiatric services were screened.

The information from those caregivers was used merely as a supplement in order to define the LFP individuals already assessed from medical records and case register information within the psychiatric care organization. Thus, in contrast to the Uppsala study, other caregivers were not included in the identification of LFP individuals.

In the Stockholm County study, the complementary study performed in 1989 (Figure 2) added 39 LFP cases, of whom 27 had had no previous psychiatric contacts during the index year (1984), to the 302 subjects identified earlier in the original study (Paper I). Of these 39 additional subjects, 17 were identified by the social welfare services and the remaining 22 subjects by various medical services. The intention was to approach a truer prevalence of the LFP population by also screening some care facilities outside of the psychiatric care organizations. This gave us valuable information when designing the study in Uppsala, where we included all other known services in the catchment areas.

In the Uppsala County study (Paper II) a large number of caregivers were screened, meaning that all presumptive caregivers who could be involved in any contact with the LFP subject were thoroughly investigated. All data from the different caregivers became an important complement to information from the psychiatric registers in order to verify and establish a correct LFP diagnosis during the index year (1991). For many patients with previous rare or intermittent inpatient or outpatient contacts with the psychiatric health care system, sufficient data were often not obtained. Sometimes there was little information from the psychiatric health care sector, but by including information from other caregivers, presumptive LFP subjects could be included or excluded from the study. Without this important key information, a number of
individuals would have been excluded from the study, or individuals that should have been included could have been disregarded.

The combined information made it possible to determine whether or not the individual patient belonged to the LFP population. This type of data collecting closely followed the LEAD methodology described by Spitzer (1983).

In the Uppsala County study a broad diagnostic screening approach according to ICD-9 was used, while a narrower concept was used in the Stockholm study (DSM-III), which included fewer diagnostic categories (see Diagnostic assessments). This probably means that in the Uppsala County study we captured more presumably LFP individuals in the screening phase. Thus, by adding information from more caregivers we could finally identify the individuals belonging to the target LFP population.

### Diagnostic systems

Different diagnostic systems were used in the two studies because of changes in the DSM- and ICD-systems during the time period between the studies (index years 1984 and 1991), Table 4.

In the Stockholm County study (Paper I) the patients were diagnosed according to DSM-III (APA 1980), the most widely used diagnostic system in Sweden during the year investigated. This diagnostic system was used throughout the whole study including the complementary study in 1989-1990. An inter-rater reliability test on the material from the suburban and rural areas was assessed by Cohen’s kappa (κ), with κ = 0.93 for the LFP concept and κ = 0.73 for the diagnoses according to DSM-III in the target population (Öst 1979). The reliability test for the complementary study was performed in a similar way, with κ = 0.88 and κ = 0.66, respectively (Borgå 1993). No such test was performed in the Uppsala study.

In the Uppsala County study (Paper II) the primary diagnoses were made according to DSM-III-R (APA 1987) and ICD-9 (WHO 1978). Thus, the total number of subjects in this study comprises patients fulfilling the DSM-III-R criteria, where the diagnosis “schizoaffective disorder” has specific diagnostic criteria (Table 7). Later (Paper III), the patients with schizophrenia were re-examined using four different sets of diagnostic criteria: DSM-III, DSM-III-R, DSM-IV, and ICD-10. This resulted in the conclusion that introduction of these new parallel
diagnostic systems did not change the prevalence estimate in the total schizophrenic group, see Figure 2.

In all three different DSM manuals the overall duration of illness is defined as a minimum of six months, whereas the duration of the psychotic symptoms defined by Criterion A varies in the different manuals. The main differences between the classification systems are summarized in Table 3.

This difference could possibly have resulted in a more liberal inclusion of schizophrenic patients in the Stockholm County study than in the Uppsala County study. On the other hand, there was a diagnostic tradition in the Nordic countries that the loss of functional variables, i.e. occurrence of acute psychotic symptoms, should be longer than a week before a diagnosis could be assessed (Paper IV).

Within the DSM classification system the number of diagnostic categories has increased from 106 in DSM-I (APA 1952) to 292 in DSM-III (APA 1980); DSM-IV (APA 1994) comprises as many as 400 categories (Angst 1997). The term “nosologo-mania” was coined by van Praag (1995) for this development. Angst (1997) has advocated a more simplified view of psychiatric classification that is based on dimensional spectra of diagnostic subgroups rather than categorical diagnostic entities. When the pathogenetic causes of psychiatric disorders are better understood, etiological classification systems corresponding to real disorders may eventually emerge (Angst 1997).

Prevalence

The total prevalence rate of LFP was higher in the Uppsala County study, even following inclusion of the complementary study (n = 39) in Stockholm (Figure 2) and excluding some individuals (n = 18) from the schizophrenic subgroup in the Uppsala County study (Paper VI). In the age group 18 - 64 years, the prevalence rates were 7.1/1 000 inhabitants in Uppsala and 6.0/1 000 in Stockholm. In the schizophrenic subgroups the prevalence figures were 4.0 and 4.2 per 1 000 inhabitants in the Uppsala and Stockholm County studies, respectively.

In the non-schizophrenic subpopulation of LFP a pronounced difference was demonstrated between the two studies (Figure 2). The prevalence rates were 3.1/1 000 inhabitants in the Uppsala study and 1.8/1 000 in the Stockholm County study. Thus, the difference in the total LFP prevalence rate was entirely due to a broader inclusion of the non-schizophrenic individuals in the Uppsala study.
The higher prevalence rate of the total LFP population reported in the Uppsala County study might be explained by some important factors. First, differences in the sampling procedures; a larger number of care facilities were screened in the Uppsala County study. Second, a broader set of diagnostic criteria for identifying cases from different registers was used in the Uppsala County study.

Our findings are in line with several other studies. In a systematic review of the prevalence of schizophrenia, Saha and co-workers (2005) identified a total of 188 studies, out of 1,309 potential studies, from 46 countries that were published between 1965 and 2002. The prevalence rates were based on 132 “core prevalence studies” generating estimations based on the population residing within a defined catchment area. Seven papers from Sweden were included, three from this thesis (Papers I-III) together with an earlier study, cited previously, by Halldin (1984). Of the remaining three Swedish papers, two investigated a cohort of patients over 70 years (Nilsson 1983, Nilsson and Persson 1984), and one studied patients who were involuntarily admitted (Kjellin 1997).

The median point prevalence estimate was 4.6 per 1,000 inhabitants and the median lifetime prevalence was 4.0/1,000. The distribution of period prevalence was 3.3/1,000 and the 10 percent and 90 percent quantiles ranged from 1.3 to 8.2/1,000 (a 6.5-fold difference). In contrast to their expectation, Saha and co-workers (2005) found no statistically significant differences between the prevalence estimates for males and females, with a median rate of 3.75 and 3.55/1,000, respectively. The authors pointed out that methodological features might have influenced prevalence estimates. For example, studies that use comprehensive case ascertainment methods (e.g., “door-knock” surveys, inpatient and outpatient records, general practitioner surveys, and/or surveys based on other community sources) should identify more cases than those that rely on fewer recruitment sources (Saha et al 2005). This probably partly explains why the Uppsala County study reported higher prevalence rates of schizophrenia than the Stockholm County study.

Saha and co-workers (2005) pointed out that their review is in agreement with an earlier narrative review of 70 studies by Torrey (1987), who reported an overall prevalence estimate of 4.6 per 1,000.

Diagnosis and sex differences

The one-year prevalence rates for males and females in the different diagnostic subgroups are summarized in Table 7.
Common findings in the two studies were lower prevalence rates for females with schizophrenia and higher prevalence rates for females with affective disorders. For paranoia (Stockholm County study) and major affective disorder and psychosis NOS (Uppsala County study), the prevalence rates were substantially higher for the female patients. However, the non-schizophrenic diagnostic categories have different occurrences in the two studies, thus indicating a difference in the diagnostic assessment. This may be attributed in part to the use of the DSM-III manual in the Stockholm County study and DSM-III-R in the Uppsala County study, where the schizoaffective disorder had specific criteria. In DSM-III, schizophrenia has narrower criteria than in DSM-III-R (Kendler et al 1989). However, when the schizophrenic patients in the Uppsala County study were re-diagnosed (Paper III) according to DSM-III, DSM-III-R and DSM-IV, this resulted in the same prevalence rates for this diagnostic subgroup.

Our two studies have a common pattern, also reported from other studies, showing that males have a higher prevalence rate of schizophrenia, while females have higher prevalence rates of other functional psychoses (Kirkbride et al 2006). The sex difference in schizophrenia is significantly smaller in studies with sample years before 1980 than those with later sample years (Aleman et al 2003). It has been suggested (Sartorius et al 1986, Gureje 1991) that there is better diagnostic agreement about male psychiatric diagnoses than about female diagnoses, thus implying that women may have a different type of illness, and also that female sex is one of the best predictors of a remittent course.

Veen and collaborators (2004) reported in a follow-up study that diagnostic stability was high (91%) for schizophrenic disorders, but lower (30%) for other non-organic psychotic disorders. These findings emphasize the importance of including other functional psychoses in addition to schizophrenia in the LFP concept in order to get a wider and more complete gender perspective regarding this group of individuals.
Table 7. One-year prevalence (per 1 000 inhabitants) of DSM diagnoses in the LFP populations. Comparisons between the Stockholm and Uppsala studies. (Number of subjects within brackets)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Stockholm study DSM-III</th>
<th>Uppsala study DSM-III-R</th>
<th>(\chi^2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>4.38 (125)</td>
<td>4.99 (157)</td>
<td>1.13</td>
<td>n.s.</td>
</tr>
<tr>
<td>Females</td>
<td>3.02 (86)</td>
<td>3.47 (116)</td>
<td>1.01</td>
<td>n.s.</td>
</tr>
<tr>
<td>Paranoia (delusional disorder)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.49 (14)</td>
<td>0.16 (5)</td>
<td>5.23</td>
<td>(p&lt;0.05)</td>
</tr>
<tr>
<td>Females</td>
<td>1.09 (31)</td>
<td>0.33 (11)</td>
<td>12.99</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>- (0)</td>
<td>0.48 (15)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Females</td>
<td>- (0)</td>
<td>0.84 (28)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Major affective disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.42 (12)</td>
<td>1.18 (37)</td>
<td>10.40</td>
<td>(p&lt;0.01)</td>
</tr>
<tr>
<td>Females</td>
<td>0.81 (23)</td>
<td>1.53 (51)</td>
<td>6.73</td>
<td>(p&lt;0.05)</td>
</tr>
<tr>
<td>Psychotic disorder not elsewhere classified (psychosis NOS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.18 (5)</td>
<td>0.60 (19)</td>
<td>6.84</td>
<td>(p&lt;0.01)</td>
</tr>
<tr>
<td>Females</td>
<td>0.21 (6)</td>
<td>1.02 (34)</td>
<td>15.58</td>
<td>(p&lt;0.001)</td>
</tr>
</tbody>
</table>

Age groups

In the Stockholm County study (Paper I) the age group 18 to 64 years was studied (Table 5), whereas in the Uppsala County study (Paper II) the age groups comprised 18 years and above (Table 6).

The highest one-year prevalence rate in the original Stockholm County study was found in the oldest age group (55-64 years) in the urban area, Table 5. This was even more pronounced when adding the complementary group (n=39); the prevalence rate increased from 12.9 to 14.8 per 1 000 inhabitants in the urban area.

The high prevalence rate in the oldest age group in the urban area of Stockholm was the basis for the decision also to include the age group 65 years and above in the Uppsala study. This was considered important, especially following the time period of deinstitutionalization, in order to determine in what type of area an older residual population might be overlooked.
In the Uppsala County study the results showed a different pattern. The highest prevalence rate (13.0 per 1,000 inhabitants) was found in the age group 35 - 54 years in the urban area. In the oldest age group, 65 years and above, the highest prevalence rate (8.9/1,000) was found in the peripheral city area, corresponding more or less to the suburban area of Stockholm County.

The very high prevalence rate for the oldest age group in the urban area of Stockholm County might support both the social drift hypothesis and the breeder hypothesis (Freeman 1994, Warner 1994, Torrey et al 1997) in a deprived area of the inner city of Stockholm (see below, Demographic areas).

Demographic areas

In both the Stockholm and Uppsala studies there were gradients in the total prevalence figures from the rural to the urban areas (p<0.01). However, this gradient is statistically significant only for the female LFP subjects (p<0.01 rural-suburban; p<0.001 rural-urban) in the Stockholm County study (Table 5). The complementary study in Stockholm followed the same patterns as had been observed in the original study (Paper I). An even steeper gradient for the 1-year LFP prevalence as compared with the original results was recorded in the rural, suburban and urban areas: 4.0, 6.2 and 6.9 cases, respectively, per 1,000 inhabitants. Corresponding figures for schizophrenia were 3.0, 4.1 and 6.0, respectively.

In the Uppsala County study (Table 6) a statistically significant gradient was demonstrated only for the male LFP population (p<0.01 rural-urban; p<0.05 suburban-urban).

The link between urbanicity and the development of psychiatric disorders is well established in many studies. However, there are also inconsistencies in findings between countries as well as within countries. Factors such as migration, culture, infectious diseases, demographic rates and other social processes may affect geographical differences in the prevalence rates. The excess of severe mental illness in central city areas has been given two opposing explanations, “the breeder” hypothesis and the “social drift” hypothesis (Freeman 1994, Warner 1994).

Freeman (1994) labeled an explanation for the above as the “social residue” hypothesis, whereby psychiatrically healthier individuals selectively migrate from inner cities to suburbs, leaving behind the individuals who are likely to become severely mentally ill (Torrey et al 1997).
Recently, Peen and Dekker (2004) concluded from many studies that urban exposure during upbringing and later life was directly related to the risk of schizophrenia. Further, the risk of schizophrenia in people with a family history of the disorder is higher when they live in urban areas. They concluded that there seems to be a synergy between vulnerability and urbanicity.

Another important factor following deinstitutionalization was that different psychiatric care facilities were established in city center areas and later, in cooperation with community services, housing was provided for patients in those areas (Goldman et al 1983, Freeman 1994). This might be a part of the explanation for the higher prevalence rate in the Uppsala County study, where those facilities were first established in the city center.

In the Stockholm County study the rural - urban gradient was only significant for the female LFP patients. In Paper I we interpreted this result in terms of migration, either of the social drift or social selection type. Freeman (1994) suggested that a possible explanation for these differences was that affected individuals demonstrated more severe pathology in a more urban setting. This suggestion has in fact been supported by our studies from Stockholm County (Widerlöv 1990, Borgå et al 1992, Paper V). In addition, in the Uppsala County study higher mortality was reported among individuals with schizophrenia living in the central city than among those living in less urbanized areas (Paper VI).

To our knowledge, few studies support the significant gradient for females that was found in the Stockholm County study. A Swedish study (Sundquist et al 2004) found that with increasing levels of urbanization, the incidence rate of psychoses increased in both males and females. A follow-up study investigated the entire Swedish population, a total of 4.4 million males and females aged 25 to 64 years, during a two-year period until first hospital admission for treatment of psychosis. For males the risk was 68% higher in the most densely populated area of Sweden, and for females it was 77% higher.

Many studies have reported that higher prevalence rates of psychoses in urban settings are more pronounced in males than in females, corresponding to our findings in the Uppsala County study. In the Netherlands, Marcelis and co-workers (1998) reported an increased incidence rate of schizophrenia, affective psychosis and other psychoses associated with urban birth (birth cohort 1942 - 1978). Individuals born in the highest category of three-level urban exposure were around twice as likely to develop schizophrenia. The association was stronger for males.
and for individuals with early age at onset. The effect of urban birth was also stronger in the more recent birth cohorts.

In an earlier study from Sweden, Lewis and co-workers (1992) investigated the association between place of upbringing and the incidence of schizophrenia using data from a cohort of 49,191 male Swedish conscripts linked to the Swedish National Register of Psychiatric Care. The incidence of schizophrenia was 1.65 times higher among males brought up in cities than in those who had a rural upbringing. For the diagnostic category of “other psychoses” they reported a similar though weaker trend associated with place of upbringing.

Pedersen (2006) found no evidence of time trends in the urban-rural differences in schizophrenia risk among five million people born in Denmark from 1910 to 1986. At age 46, 1.84% of males and 1.05% of females born in the capital area had developed schizophrenia, while 0.81% of males and 0.56% of females born in the rural area had developed this disorder.

Contrary to their expectations, Saha and co-workers (2005) found in their review that the prevalence of schizophrenia did not differ according to urbanicity. They suggested that the inclusion of many sites from the developing world had confounded the expected urban-rural gradient.

Interestingly, Torrey and collaborators (1997) proposed an alternative way of looking at the urban-rural difference. The possibility must be considered that the predisposing factor for developing psychoses is in fact not an urban factor at all, but may rather be a rural protective factor.

### Antipsychotic drugs

In both studies (Papers I and II), antipsychotic drugs were most frequently prescribed for patients with schizophrenia. The figures were quite similar, 80.0 and 80.3%, respectively.

In the Stockholm County study the figures for the total LFP group showed that antipsychotic drugs were used at higher doses (31%) for medicated males (CPEQ = 210 mg/day) as compared with females (160 mg/day). The highest median CPEQ dose, 234 mg per day (p < 0.001), was found in the total schizophrenic group as compared with the other diagnoses (Paper V, Table 4).

The figures for the schizophrenic subgroup in the Uppsala County study showed a similar pattern according to sex. The male patients were prescribed significantly higher (35%) mean daily doses (413 mg CPEQ) of antipsychotic drugs than the females (307 mg; p < 0.05). Further, the
mean daily dose was substantially higher for the schizophrenic patients in the Uppsala County study. In both studies, however, the levels of antipsychotic drugs were considered as low to moderate in most patients with schizophrenia.

Among the patients on antipsychotic drugs, 54% had oral medication and 46% had depot formulations. In contrast, only 27% of the schizophrenic patients in the Stockholm study had depot medication. In the Stockholm study all other LFP diagnoses had a lower rate of depot medication than the schizophrenic group (p < 0.05).

New and better depot antipsychotic formulations were launched in between the two index years 1984 and 1991, which could at least in part explain the greater use of this treatment strategy in the Uppsala study.

In the Stockholm County study a positive correlation was found between the mean dose of antipsychotic drugs and duration of the illness (p < 0.01). The opposite was found in the Uppsala study, where the schizophrenic subgroup had a decreasing use of antipsychotic drugs with increased duration of illness (p < 0.05). This is more in line with psychopharmacological principles, in that elderly subjects have a reduced metabolism and elimination rate of drugs, and may be more sensitive to adverse drug reactions. Thus, a reduced dosage, or possibly discontinuation of their medication, is usually considered with increasing duration of the illness. For many years the consensus in Sweden has been to use the lowest effective dose in relation to age and diagnosis (Paper IV).

Care utilization

There were differences in the mean number of inpatient days in the two studies. In the Stockholm County study the total number for the schizophrenic subgroup was 89 days during the index year 1984. In the Uppsala County study the corresponding figures were 34 days for males and 19 days for females during the index year 1991. During the period 1984 to 1991, inpatient care declined substantially, which could explain the differences in results between the two studies (Socialstyrelsen 2003).

At some time during the entire course of their illness, many of the schizophrenic patients had been admitted to the hospital involuntarily. However, the figures for involuntary care also differed between the two studies. In the Stockholm study the total figure for the schizophrenic group was 42%, compared with 70% of the male and 65% of the female schizophrenic patients in the Uppsala study. The lower rate of involuntary
care in Stockholm may reflect the modern care policy in the Nacka-Värmdö catchment area, with more diversified care facilities in order to reduce the number of involuntary admissions (Stefansson 1985).

Age at onset

In the Stockholm County study, age at onset was defined as the time of the first diagnosis of a psychotic illness. In the Uppsala County study the time of the first appearance of psychiatric symptoms was defined as age at onset; however, this was the case only in the schizophrenic subgroup of the LFP population.

In Stockholm, age at onset in the final study population (n=341) was somewhat lower for schizophrenic and non-schizophrenic males, 27 and 31 years, respectively, compared with females where the ages were 28 and 35 years, respectively. In the Uppsala study, it was also the case that an earlier age at onset was observed for schizophrenic males than for females, 23.5 and 27.4 years, respectively. This is in line with other studies indicating that males in the Western world usually have about a five-year earlier age at onset (Loranger 1984, Gureje 1991, Hambrecht et al 1992, Häfner et al 1993). Later age at onset in women has been an important factor in explaining their better course and outcome of the illness (Gureje 1991, Kirkbride et al 2006). However, Wieselgren and Lindström (1996) found no sex difference in age at onset but a more favorable outcome for female patients with schizophrenia, both with respect to total outcome scores and single outcome measures. A previous study of the LFP cohort in Stockholm County (Widerlöv 1990; Borgå et al 1992) investigated social conditions and found that female LFP patients had significantly better outcomes than male patients.

Area characteristics

The catchment areas selected for the two studies (Papers I and II) had some important differences that have to be taken into account when comparing and evaluating the results.

The new psychiatric care organization established in the rural and suburban catchment areas of Nacka-Värmdö in Stockholm County (1974-1984) aimed at being accessible to the total general population, with long-term mentally ill persons as the major target group. The number of psychotic outpatients increased concomitantly with a decreasing number
of inpatients. Treatment in outpatient facilities was established but was not always found to be adequate. Community care facilities needed to be built up in order to support this particular patient group (Stefansson 1985).

The Nacka area was a typical suburban area closely associated with and dependent on the larger city of Stockholm. This area also included several low status sections with multiple social problems.

The urban area in the Stockholm study turned out to be an extremely low status area, and thus probably not representative for the total urban area of the city center of Stockholm. It is likely that the social character of this area, in a time of deinstitutionalization, caused an even more pronounced accumulation of LFP individuals.

At the time of the study, the urban area (Maria parish) was rapidly changing into a high status part of the central city area. Small apartments were restored into large luxury apartments. Many long-term mentally ill people could not afford to live there any longer, or they lost their homes because of less tolerance in the neighborhood. At that time, psychiatric care organizations and social services were not able to give these people sufficient care and support. Such changes were obvious, especially in 1989 when we investigated the complementary LFP group in this area.

In the sectorized care organization of Uppsala County, outpatient care facilities were still under establishment. Efforts were made to create a variety of outpatient treatments and support for long-term mentally ill individuals. A similar process was also carried out in order to establish community-based facilities. Unfortunately, there were obvious problems at that time involving communication and cooperation between these two care organizations, which caused major problems for all involved.

The catchment area of Uppsala County is probably representative of most mid-sized towns in Sweden and in other Western European countries.
REPRESENTATIVENESS AND GENERALIZABILITY

This thesis is based on two independent studies, the first in Stockholm County and the second, a replication and validation study, in Uppsala County. The experience and results from the Stockholm County study provided valuable information when designing the study in Uppsala. The Uppsala study confirmed many of the findings from the first study, but there turned out to be some interesting differences in addition to valuable new information.

No earlier studies had used the concept of Long-term Functional Psychosis (LFP) in order to define and investigate the main target group within psychiatric and community care. The methodological approach used in the Uppsala County study might have contributed to a closer true prevalence estimation of LFP individuals.

The total one-year LFP prevalence in the Uppsala study was estimated at 7.0/1 000 inhabitants, and for the schizophrenic subgroup it was 3.7/1 000. When extrapolating these prevalence figures to the total Swedish population, 18 years and older, for the index year 1991, the total number of LFP individuals was around 47 000, and the total number of schizophrenic individuals was around 25 000.

Limitations of the studies could be weaknesses in case registers and medical documents. Further, many informants were involved and we had to trust that the information they gave was reliable and valid. In the target population, some individuals were actively avoiding all contacts with care-givers by using many strategies such as changing their names and birth data, incorrect addresses, etc.

Multiple sources of information were found to be essential for accurate estimation of the prevalence of the LFP population. This is also confirmed in other studies (Saha et al 2005), and most recently by Perälä et al (2007).

The studies presented in this thesis are considered to be relevant and in line with other studies, and can hopefully contribute to future epidemiological research. Both genetic and environmental factors are deeply involved as risk factors for the development of different psychotic
disorders. Therefore, in accordance with McGrath’s (2007) opinion, it is important for psychiatric epidemiology to build stronger scientific links with social psychiatry, and with molecular and behavioral neuroscience. Hopefully, the studies can also be a valuable contribution in the ongoing dialogue between psychiatric care and community care concerning future health planning for the exposed and vulnerable LFP population.
CONCLUSIONS

The total one-year prevalence of LFP in Stockholm County was 5.3 per 1,000 inhabitants. The prevalences in the rural, suburban and urban areas were 3.4, 5.6, and 6.6 per 1,000 inhabitants, respectively, thus producing a gradient from the rural to the urban areas.

In Uppsala County the total one-year prevalence rate of LFP was 7.3 per 1,000 inhabitants. The prevalence rates in the rural, peripheral, and central city areas were 6.0, 7.0 and 8.7 per 1,000 inhabitants, respectively, thus producing a gradient from the rural to the central city area.

In the study of Stockholm County, the one-year prevalence according to sex was higher for males than for females in the rural area. There was a female gradient from urban to rural areas, with three times as many females in the urban area. Comparing the total figures for the sexes in the study of Uppsala, there were no statistical differences. When analyzed according to area, the prevalence was generally higher for males, except for in the rural area. In this study a statistically significant gradient was demonstrated only for the male subjects.

In the non-schizophrenic subpopulation of LFP, a pronounced difference was demonstrated between the two studies with a substantially higher prevalence rate in the Uppsala study.

When the schizophrenic patients in the Uppsala study had been rediagnosed according to DSM-III-R, DSM-IV and ICD-10, it was found that the prevalences of schizophrenia, schizoaffective disorder and delusional disorder were somewhat lower according to the DSM-III criteria, while the same number of patients fulfilled the criteria according to DSM-IV. When the ICD-10 criteria were used, this resulted in a broader concept of schizophrenia and a somewhat narrower concept of schizoaffective disorder. Thus, introduction of the new parallel diagnostic systems will result in different but comparable prevalence estimates.

Among the patients on antipsychotic drugs in the Uppsala County study, 54% had oral medication while 46% had depot antipsychotic medication. Male patients were prescribed significantly higher mean daily doses of antipsychotic drugs than female patients. The doses of
antipsychotic drugs decreased with a longer duration of illness. The dose levels of antipsychotic drugs were also significantly higher if patients had been involuntarily admitted to the hospital, were younger at the first admission, and had spent more days in the hospital during the index year.

In the Stockholm County study a positive correlation was found between the mean dose of antipsychotic drugs and duration of the illness. Nearly half (48%) of the LFP individuals in this study were admitted to a psychiatric institution at least once. Those admitted spent an average of five months as inpatients. Approximately the same number of male (53%) and female (47%) subjects were admitted. However, the males spent twice as long as inpatients compared to the females.

The frequency of admissions was fairly independent of diagnosis. However, the duration of inpatient care varied according to diagnosis. Subjects with paranoid and affective disorders had shorter inpatient stays of about three months, whereas the duration of care for admitted schizophrenic patients and those with psychosis not elsewhere classified averaged about six months.

Twenty-one of the total number of LFP subjects were involuntarily admitted at least once, thus accounting for 43% of all LFP admissions. The rates were fairly equal for males (22%) and females (20%).

Around two thirds of the LFP individuals had psychiatric outpatient contacts, with an average of 10 outpatient visits.

Approximately one third of the total LFP group had contact with primary health care services, but the mean number of contacts was 0.7, and only rarely for stated psychiatric reasons.

Thirty-one percent of the LFP subjects had contact with the social welfare office and the mean number of visits was 6.1 per year.

The higher mortality rate among patients with schizophrenia in the LFP population in Uppsala County was mainly the result of unnatural causes and cardiovascular diseases, especially among males.

The highest mortality rate was found in the age group 45 – 64 years, and the mortality rate was the highest among individuals living in the city area as compared with those living in the less urbanized areas.

Among the patients with schizophrenia who died from unnatural causes, eight had committed suicide. Six of those suicides were performed in a violent way.
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