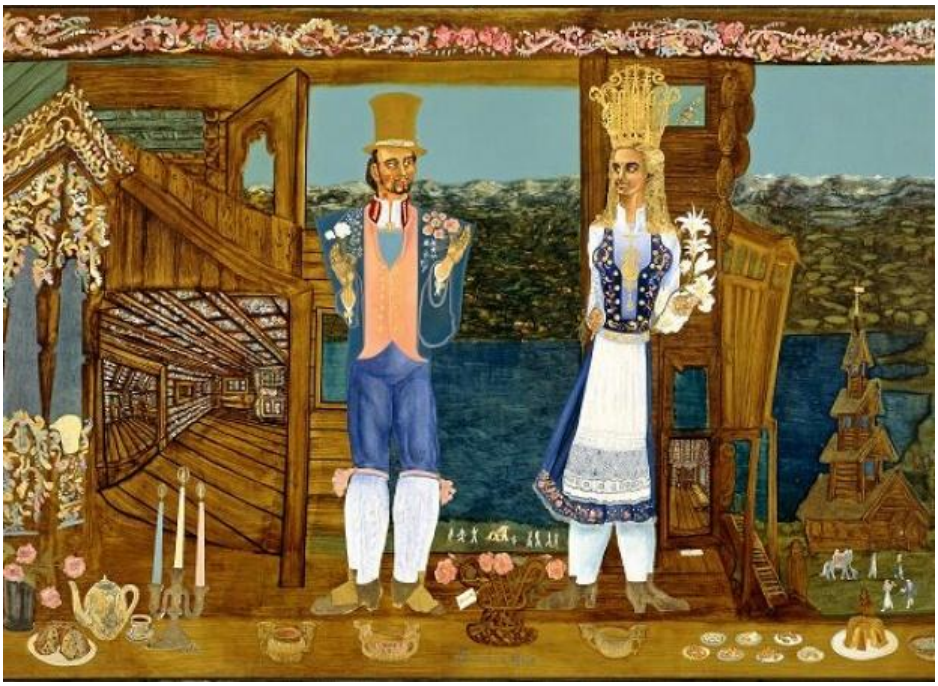
UNIVERSITY OF TROMSØ UIT

FROM THE FACULTY OF MEDICINE,
INSTITUTE OF CLINICAL MEDICINE

Schizophrenia: Gender differences in diagnosis and mortality in admitted patients



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A dissertation for the degree of
Philosophiae Doctor

June 2012

06.12.2011 09:22:00

Schizophrenia: Gender differences in diagnosis and mortality in admitted patients

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Thoughts and emotions are the two functions of the brain that define us as a species and define us as individuals. Schizophrenia affects both, and is therefore the most human of all diseases.

Kari Stefansson, founder of deCODE Genetics

Contents

1. Background

Within the framework of the "Finnmark and Troms Psychosis Project" during the mid-nineties a group of clinicians worked together to coordinate their clinical work and to exchange experiences in the field of early psychosis (1). We also tried to conduct a study of incidence of schizophrenia in the two counties Finnmark and Troms, using the Structured Clinical Interview for DSM Disorders, SCID (2). This turned out to be more difficult than expected – some of it due to the huge geographical area of 26 000 km^2 to be investigated, and some of it due to extensive discussions on the use of structured diagnostic tools in such an early phase of psychosis. During these years there was considerable ideological discussion on the topic of diagnoses and stigma among psychiatrists in Tromsø, probably more so than in the rest of Norway.

The incidence study was never completed, but preliminary results showed a much higher incidence in males than in females. At this time there was a growing assumption in the literature (3-5) that the incidence of schizophrenia in men was higher than in women, after a long period of assumed similar incidence rates (6-8). There was also a growing understanding of possible gender differences in symptomatology, illness course and outcome. As basic knowledge on how a diagnosis is used is an important prerequisite for interpreting epidemiological findings, we wanted to describe more closely the diagnostic process, with possible gender differences, before conductance of further epidemiological studies. Our hypothesis was that there was more clinical uncertainty involved in assigning the schizophrenia diagnosis to women than to men, and we wanted to use the case register for admissions to the two psychiatric departments at The University Hospital of North Norway to conduct the analyses.

The results from the first study (Paper I) inspired us to conduct an experimental study to determine whether patient gender *as such* affected diagnostic practice (Paper II). Two studies on mortality had also been performed, using regular reports on mortality of patients with mental illness in Norway (9-12) since 1916, and the same case register at the University Hospital with follow-up 1980-1992 (13-14). These studies documented an increase in standardized mortality ratios (SMRs) compared to earlier periods, especially high for men. With the studies on gender differences in diagnostic practice as baseline knowledge, we decided to conduct a 27-years follow-up study by investigating the difference in age-adjusted mortality rates between men and women with schizophrenia, and SMRs compared to the general population (paper III).

2. List of papers

1. Høye A, Hansen V, Olstad R (2000) First-admission schizophrenic patients in northern Norway, 1980-95: Sex differences in diagnostic practice. Nord J Psychiatry 54: 319-325

2. Høye A, Rezvy G, Hansen V, Olstad R (2006) The effect of gender in diagnosing early schizophrenia. An experimental case simulation study. Soc Psychiatry Psychiatr Epidemiol 41: 549-555

3. Høye A, Jacobsen BK, Hansen V (2011) Increasing mortality in schizophrenia: Are women at particular risk? A follow-up of 1111 patients admitted during 1980-2006 in Northern Norway. Schizophr Res 132: 228-232

3. Introduction

Schizophrenia is a syndrome characterized by a complex symptomatology, affecting most aspects of cognition, emotion and behaviour. After more than 100 years of research and inquiry there is still a lack of an integrative explanation for the diversity of signs, symptoms,

course and treatment of schizophrenia, even though the attempts have been many within different theoretical frameworks. The classification of schizophrenia highlights an important conflict of modern psychiatry – namely; how to link the clinical relevance of a concept to its validity and reliability. The development and background of the diagnosis and concept of schizophrenia is therefore of relevance to all research within the area, and it is therefore essential to present some of the general history and theoretical background in this chapter.

3.1 Schizophrenia - the diagnosis

Before the nineteenth century references to insanity mostly occurred in "all-or-none" terms; with description of pure signs, leaving little room for subjective experience (symptoms). This has been described in the book "The History of Mental Symptoms" by GE Berrios (15). Throughout the nineteenth century, however, there were several attempts made to classify the historical, nonspecific concept of madness or insanity, influenced also by the discussion of the relation between thought and language. Early descriptions of "thought disorders" rely on the assumption that language and thought are not the same thing, exemplified by the French physician Jean-Etienne Dominique Esquirol (1772-1840) who already in 1838 distinguished between nonsense talk secondary to abnormal sensations (hallucinations) and primary pathology of the "*faculty that is in charge of coordinating ideas*". As outlined by Berrios, the development of descriptive pathology within the area of psychiatry can be looked at on the basis of six historical factors: 1) the descriptive needs of the new asylum officers, and the new patient cohorts, 2) the availability of psychological theories that might support stable descriptions, 3) the changing notions of signs and symptoms in medicine in general, 4) the introduction of subjective symptomatology, 5) the use of time as a contextual dimension and 6) the development of quantification. The creation of descriptive psychopathology started around the second decade of the nineteenth century, it represented a major shift in the perception of insanity

and it took about 100 years to complete. The changes since then have been quite small, revisions and refining of the categories taken into consideration.

The term *psychosis* was introduced by the physician Karl Friedrich Canstatt (1807 -1850) in 1841, and used from the second half of the century in the German-speaking countries (16). The term was understood as a cerebral pathology expressed by psychic symptomatology, with a differentiation of the categories of *endogenous* and *exogenous psychoses* made by the neurologist Paul Julius Möbius (1853-1907). Emil Kraepelin (1856-1926), professor of psychiatry in Heidelberg and Munich, introduced a differentiation of Möbius' terms by introducing a new conceptual framework making a distinction between *dementia praecox* and *manic depressive insanity (*17, 18*)*. Kraepelin described dementia praecox as a brain disease characterized by a downward course to a state of chronic impairment, featuring neurological abnormalities, physical anomalies and deterioration of the intellect. Many of Kraepelins "psychic symptoms" were considered by him as manifestations of thought disorders (17, 19). His ideas were supported and introduced in France, where his categorization had encountered much opposition, by the French psychiatrists Paul Sérieux (1864-1947). The term *schizophrenia* (from Greek: *schizen* - "to split" and *phren* – originally "diaphragm" but later changing, by metonomy, to "soul, spirit, mind") was first used by the Swiss psychiatrist Eugene Bleuler (1857 – 1939) at a meeting of the German Psychiatric Association in Berlin on April 24, 1908 (20):

"*For the sake of further discussion I wish to emphasize that in Kraepelin's dementia praecox it is neither a question of an essential dementia nor of a necessary precociousness. For this reason, and because from the expression dementia praecox one cannot form further adjectives nor substantives, I am taking the liberty of employing the word schizophrenia for revising the Kraepelinian concept. In my opinion the breaking up or splitting of psychic functioning is an excellent symptom of the whole group*".

Bleuler collected material directly from his clinical work, and his theory of "schizophrenia" linked Kraepelin's neuropathological description to Freud's psychoanalytic concepts and terms, with the help of psychologist Gustav Jung (1875-1961). Bleuler realized that schizophrenia was not a single disease (Bleuler E. 1911: *Dementia praecox or the group of schizophrenias*. Translated by Zinkin J. New York, International University Press 1950), and he considered the splitting of different psychological functions, resulting in a loss of unity of the personality, to be the most important sign of the disease. He described the pathognomonic symptoms to be thought disorder, affective disturbance, autism and ambivalence, but considered hallucinations and delusions to be symptoms of lesser importance. Neither Kraepelin nor Bleuler used the terms "positive" or "negative" symptoms, this was a distinction first mentioned by John Hughlings Jackson (1835 -1911) to try to explain the mechanisms underlying psychotic symptoms. Jackson's attempt to make distinctions between different sets of symptoms was influenced by Darwinian evolutionary theories of the brain being organized in different hierarchical evolutionary layers.

Albeit a somewhat different view on symptomatology and importance of different symptoms to describe the syndrome, both Kraepelin, Bleuler, Jackson and others during the same period tried to understand symptoms in terms of underlying neurological mechanisms specific of the syndrome, and to understand the interplay between neurological and psychological mechanisms. Their findings encouraged the need to formulate operational rules for defining schizophrenia, to specify whether or not a patient will be placed within a particular definition of schizophrenia according to the presence or absence of a given set of features.

Throughout most of the twentieth century Bleuler's perspective with "the four A's" (Associations, Affect, Ambivalence and Autism) dominated the nosology of schizophrenia (20). This emphasis did, however, change during the 1960's and 1970's. Influenced by the

work of the phenomenologist Karl Jaspers (1883-1969), the German psychiatrist Kurt Schneider (1887-1967) discussed the importance of form rather than the content of a sign or a symptom, and his description of so-called first-rank symptoms had a strong influence on the concept of schizophrenia (17). The Schneiderian first-rank symptoms were based on easy-to-recognize psychotic symptoms such as hallucinations and delusions, and, as described by Nancy C. Andreasen, "*satisfied the fundamental need to find an anchor in the perplexing flux of the phenomenology of schizophrenia*" (17). Schneiderian symptoms were included into the first major structured interview Present State Examination (21), and thereafter in structured interviews and diagnostic criteria as seen in the Diagnostic and Statistical Manual (DSM-III) from 1980.

3.2 Diagnostic reliability, validity and utility

The history of mental symptoms can be explored through four complementary perspectives (15): Descriptive psychopathology, etiological theory, pathogenesis and taxonomy. The concept of schizophrenia must be viewed in light of all these dimensions, and throughout the last decades there has been an increasing tendency towards reifying taxonomy to comprise all four of them. In extension, the development of diagnostic criteria in psychiatry has profoundly affected several aspects of clinical practice in both positive and negative terms. The standard frame of reference has certainly enabled diagnostic agreement and facilitated clinical communication. Research on morbidity, health services, treatment and outcomes has been facilitated and refined by the greatly improved diagnostic *reliability*. Diagnostic reliability in this setting means that a diagnosis must be inherently repeatable – that is; under the same conditions different clinicians or researchers must be able to generate the same diagnostic conclusions.

The literature on general *validity* within research is abundant, and a thorough discussion of the subject is not within the aims of this thesis. However, it has been increasingly recognized

that the fundamental issue of validity of psychiatric diagnoses cannot be solved by explicit decision rules and description of diagnostic entities, and some important issues must be kept in mind when discussing diagnostic practice in psychiatry.

The word "valid" is derived from the Latin *validus* ("strong"), and it is defined as "*well founded and applicable; sound and to the point; against which no objection can fairly be brought*" (22). In research, the general use of the word addresses the nature of reality – whether or not a concept describes what is "real". In 1970, Robins and Guze (23) published one of the most influential articles in the development of psychiatric classification. They stressed the importance of diagnosis and classification, and suggested an approach for validation. The five criteria they proposed have since then been the standard criteria for establishing so-called diagnostic validity: clinical description, laboratory studies, specification of exclusion criteria, follow-up studies to determine outcome and studies of familial aggregation. Since then Andreasen (24, 25) has refined these validation criteria by including more recent knowledge within areas potentially capable of linking symptoms and diagnoses to etiology; such as neurochemistry, molecular genetics and cognitive neuroscience.

The validation of psychiatric diagnoses is meant to establish them as "real entities" (23), but to acquire diagnostic validity as described above it is in fact necessary to accept the implicit assumption that the given disease entity "schizophrenia" is "real" - with a higher or lower degree of validity. As research on genetic and neurodevelopmental etiology progresses it may very well be that the "real" entity is to be found somewhere else than in a given diagnostic description.

The DSM-system was in many ways developed as a result of the work of Robin and Guze. Nevertheless, the originally developed "provisional consensus agreement" of the DSM-system was based on clinical evaluation by a small group of psychiatrists, and was probably

never intended to be used as a full description of mental disorders. The unquestionable need for defined disease entities has, unfortunately, hampered an open discussion on the shortcomings of the systems both in research and clinical practice – once a disease entity is listed and defined in a precise, complex way as in the DSM- and ICD-systems, it tends to be reified.

Even if most contemporary psychiatric disorders (even schizophrenia) cannot yet be describes as valid disease categories, they may still be valuable concepts, as stated by Kendell and Jablensky (26). They underline, however, the importance of not underestimating the distinction between validity and *utility*. Kendell and Jablensky propose that a diagnostic rubric may be said to possess utility "*if it provides nontrivial information about prognosis and likely treatment outcomes, and/or testable propositions about biological and social correlates*". In other words, the utility indicates whether the diagnosis is of clinical importance when it comes to outcome prediction or choice of treatment. Utility may therefore be a graded characteristic, while validity cannot. There may be uncertainty about the validity of a syndrome or diagnosis because crucial empirical knowledge is lacking, but a diagnosis cannot be "partly valid". Diagnostic categories defined by their syndromes should, according to Kendell and Jablensky, only be considered valid if they have shown to be discrete entities with clear boundaries or qualitative differences that separate them from other syndromes at the level of the defining characteristic. They argue against defining validity such that no syndrome of unknown etiology could be accepted as a valid category - because understanding of etiology is not an all-or-none issue, and because clear boundaries may be apparent long before the underlying etiology is known. Schizophrenia, as most other psychiatric disorders *and* many somatic disorders, is a clinical syndrome (or several syndromes) with largely unknown etiology, and the issues of reliability, validity and utility must therefore be kept in mind. Even so, it is important that a lack of validity (in the strict

sense) does not hold us from open-mindedness towards investigating on the basis of the existing concepts. It is important to remember that it is research on the basis of the current schizophrenia concept that has brought on the new, basic questions on e.g. etiology, and that investigating the boundaries of the current syndrome is crucial to obtain new knowledge.

3.3 Schizophrenia diagnosis today

Schneider's first-rank-symptoms and the attempt to identify symptoms fundamental for the "core" of schizophrenia set the terms for the classification process from the 1960's (27). Schneiderian symptoms were included in the International Pilot Study on Schizophrenia (28), the Present State Examination (21), and from then on refined and processed in different versions of structured interviews. From the beginning of the seventies two different sets of systems evolved – one in USA, and one of more European origin. Newer versions of these two different sets of diagnostic criteria are still used throughout the world – the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, DSM IV (29) and the World Health Organization's International Classification of Diseases, Tenth Revision, ICD-10 (30). The DSM-system is used in almost all studies conducted in the US and also in many studies that comprise use of biological markers, while the ICD-system is the system clinically used in Europe and in many international epidemiological studies.

Even though there have been continuous efforts by the work groups of the two systems during the last decades to achieve as much concordance as possible, there are still important differences between the systems that complicate international research. In most respects, the DSM has a narrower conceptualization of schizophrenia than the ICD, as a consequence of an explicit effort to narrow the concept as it had been used in the US until the IPSS-study was conducted. Both DSM and ICD require one month of active symptoms and the presence of psychotic symptoms such as delusions and hallucinations, but while

DSM requires 6 months of overall duration of symptoms, only one month is required in ICD. There are also some differences in subgrouping, e.g., in the DSM schizotypal disorder is placed among the personality disorders, while in ICD it is placed under the general heading of schizophrenia.

In Norway, ICD-8 was used up to 1987, when there was a change to ICD-9. According to Scandinavian tradition, clinicians had up to then tended to postpone the diagnosis of schizophrenia, taking into consideration Langfeldt's chronicity criteria (31, 32). Even if the criteria did not change, an explanatory appendix was included in the ICD-9 version, probably to influence Norwegian clinicians to consider giving the schizophrenia diagnosis at an earlier point in the disease course to adjust Norwegian practice to international standards. ICD-10 for mental disorders has been used in Norway from 1997.

During the last years, there has been an extensive discussion in international research literature on the concept of schizophrenia. In some ways, the present meets the past – the focus on purely descriptive symptoms is being heavily criticized, and the attempts of Kraepelin, Bleuler and others to understand symptoms in terms of their underlying neural mechanisms have to some extent had a new renaissance (33). The issues of validity, reliability and utility mentioned above have also been of importance when it comes to the discussion of the schizophrenia diagnosis. Many researchers argue that the schizophrenia concept must be fundamentally changed, and that defining complex psychiatric disorders on externally observable phenotypes (such as behaviours) is not at all optimal for getting closer to knowledge on etiology, treatment and outcomes (34, 35).

It is underlined that the current world of schizophrenia most likely include multiple, phenotypically overlapping syndromes, and also that it will be essential to think in dimensions instead of categories.

Before classification can be meaningful, there must be a conceptualisation of syndromes, as outlined by Keshavan MS et al in the article with the descriptive title "*Schizophrenia. "Just the facts" 6. Moving ahead with the schizophrenia concept: From the elephant to the mouse* (36):

"*If we are to make real progress in unravelling the nature of the many disorders that are all currently called schizophrenia, the field must boldly step outside the schizophrenia box".*

In some of the current literature there is also a strong link to the attempt of Kraepelin, Bleuler and others to describe the clinically distinctive and typical elements of schizophrenia – the "something" experienced by clinicians, the fundamental discussion of what schizophrenia really "*is*". Parnas (27) and others claims that the "core" of schizophrenia is inevitably linked to all domains of consciousness and experience of "self", and that the overall change in patients with schizophrenia stretches far through the single symptoms and signs. Parnas argues that the existing operational definitions only capture a fragment of this clinical core – "*The clinical core manifests itself, and is graspable, as a larger whole, a Gestalt emerging across a manifold of symptoms and signs*" (27). A phenomenological description of these fundamental features of schizophrenia is therefore claimed to be crucial, to understand both the etiology and the clinical manifestations of the syndrome.

Due to the uncertainty of diagnosis in an early phase of psychosis, it has also been argued that there are only three primary categories with that should be considered, on the basis of treatment consequences – psychosis as defined within the group of schizophrenia diagnoses, bipolar disorder and depressive disorder with psychotic features (37, 38).

A revision of DSM IV is planned in 2012, and it remains to see to what degree the international debate on the schizophrenia concept will be reflected in the revision.

3.4 Incidence and mortality

The incidence of a disease is the rate at which new cases occur in a population during a specified period. In the simple situation that the population is relatively constant, incidence is measured as the number of new cases/population at risk × time during which the persons became ill. For example: the number of new cases of schizophrenia in Norway in 2011/ 5 million Norwegians. In the more complicated situation when the follow-up differ for different subjects and may also be many years, we calculate person-years and estimate the incidence rate as the number of new cases during follow-up/total number of person-years of follow-up. The word "mortality" is derived from "mortal", which come from the Latin "mors" (death). Mortality is the incidence of death. We may calculate e.g., the total (all-cause) mortality, sex-specific mortality (mortality in men and women separately), age-specific mortality (e.g., mortality in subjects aged 50-59) or cause-specific mortality (e.g., mortality of suicides).

The s*tandardized mortality ratio (SMR*) is a measure of mortality in a study population, relative to mortality in a reference population. The SMR answers the following question: "How does the number of observed deaths compare with the expected number of deaths, if our study group had the age-specific mortality rates of the reference population during these study years?"(39). In our study, this means that the SMRs compare the observed number of deaths in the group of patients with schizophrenia with the expected number of deaths in the same group, as predicted by age- and sex-specific mortality rates in the Norwegian population. This was done by calculating the number of deaths to be expected among the patients if the mortality rates of the general population in Norway according to age (5-year groups) and calendar year (5-year groups) during follow-up had prevailed.

SMRs from different countries are difficult to compare, due to large differences in mortality in general populations. Several studies do, however, show a significantly higher risk of

premature death in persons with schizophrenia than in the general population (40, 41, 42 - 44). Ösby et al (45) showed a marked increase in all-cause SMR for both men and women over a period of 23 years, a trend that was also seen in a meta-analysis by Saha et al (46) based on standardized mortality ratios from 25 countries. A meta-analysis by Brown et al, on the other hand, showed no increase in all-cause SMR between the 1970s and the 1990s (47). Findings on gender differences have also been somewhat equivocal - Brown et al (43) found slightly higher all-cause SMR in men, but the difference was not statistically significant, while Mortensen and Juel (48) found age-specific SMRs to be higher for women than for men.

3.5 The use of case registers

The first psychiatric case register in the world was created in Norway by psychiatrist Ørnulf Ødegård (1901-1983); the Norwegian Case Register of Serious Mental Disorders (9-12). He regularly documented morbidity and mortality in hospitalized psychiatric patients from 1916. The register was used in several Norwegian studies, e.g., in linkage with twin registers (49 - 51). The quality of the register did, however, gradually decline from the late sixties. The use of psychiatric case registers had grown also in several other European countries during the sixties and seventies (52), but due to lack of funding, political reasons and excessive concerns on privacy issues several of them were closed down in the eighties, including the Norwegian register mentioned (closed in 1988). During the last three decades, however, the use of psychiatric registers in research has grown, especially in the Scandinavian countries. Use of electronic patient records has expanded, and general technological development has been extensive. The ability to follow patient populations longitudinally throughout a long time span and the possibility to link with other data sources opened new options in psychiatric epidemiological research, as well as in health management. Improved confidentiality is also important.

Psychiatric case registers can be institution-based or population-based. As Tansella states (52), *institution-based* means a systematic collection of data on individuals treated at a specific hospital or psychiatric service, while *population-based* means patient- centred longitudinal records of contacts with a defined set of psychiatric services, originated from a defined population. In both cases, information is stored in a cumulative file so that each patient can be followed over time. Both types of registers can be used for research and management purposes, as well as for clinical quality assurance and improvement. Nevertheless, as use of psychiatric case registers has grown, the distinction between administrative health care registers and case registers for research purposes has faded away. Most registers can be used for both administrative purposes as well as for quality improvement and research, if one keeps in mind the different legislative regulations linked to the actual purpose of data usage and strict rules of confidentiality.

As the population registers in the Nordic countries were centralized and computerized, the personal identification number has been used in all national statistic systems. This person number is unique and independent, because it is the sole identifier for one particular individual and for that person alone. It is also permanent. Thus, the person number provides a personal identifier that enables handling for comparing, sorting and record linkages (53).

The largest psychiatric case register used for both research and health care management can be found in Denmark (The Danish psychiatric case register). Denmark has had a person-identifiable patient register with national coverage from 1977, as have Finland and Sweden - from 1969 and 1987, respectively (54). Until 2008, there was no nationwide registration in Norway of admission to hospitals that included the personal identification number. The Norwegian Patient Registry has first and foremost had health administrative purposes, including activity based financing. The data have not yet been of satisfactory quality for psychiatric research. There are a few Norwegian population-based epidemiological studies

containing some measurements on mental health and/or psychiatry (The Tromsø Study, the Nord-Trøndelag Health Study (HUNT)) that may be used for linkage with regional case registers or research registers. In Denmark, Finland and Sweden the person-identifiable case registers have provided data for e.g. a recent study on general life expectancy of patients with mental disorders, including comparison between the countries (55). Due to the lack of such a register in Norway until 2008 there has been no possibility to follow similar national cohorts, but hopefully this will be possible within some years.

Better register-based research has certainly given an indispensable contribution to psychiatric epidemiology and knowledge. Register-based studies are cost-effective in terms of collecting data on large samples (54-58) over long time periods, and they make it possible to obtain sufficient statistical power in analyses of low-prevalence syndromes such as schizophrenia. They also provide gentle research methods, because no actual burden is placed on the patient involved – strict privacy issues of course taken into account. According to an overview by Mortensen (59) register-based studies can be used in studies of 1) prevalence and incidence, 2) treatment course or episodes of care, 3) studies of defined patient groups selected from the register and followed separately in other clinical, randomized or epidemiological studies, 4) studies of risk factors of mental illness where both exposure and outcome data come from the same register and 5) record linkage studies combining data from the register with other sources. Much of the knowledge we have about the schizophrenia syndrome today is based on register studies – e.g. incidence rates, the high mortality compared to the general population and the role of urbanity, migration status and obstetric complications as risk factors (60). In the present thesis, a case register has also been used to obtain more knowledge on clinicians' practice and the concept of a diagnosis. In addition, the challenge of treatment and outcome measurement in psychiatry often makes it difficult to conduct randomized controlled trials within other areas than

medication treatment. In a world where randomized controlled trials are considered the "gold standard" of evidence-based medicine, this may in fact lead to a kind of "evidence-based bias". In any case, analyses from register-based studies are an important means to generate hypotheses that can be further explored in randomized controlled trials and clinical studies. Well-conducted register studies may therefore give considerable additional value to the general area of psychiatric research. They also give us data about the true case mix of the patient population as well as the normal treatment of them. This is contrast to the often substantially selected group of patients that are included in most randomized clinical trials and the more careful treatment and follow-up usually offered them.

3.6 Sex and gender differences in schizophrenia

The words *sex* and *gender* are commonly used interchangeably, even if their linguistic definitions are quite distinct - *sex* refers by definition to the biological and physiological characteristics, while *gender* refers to behaviours, roles, expectations, and activities in society. The reason why the terms are confusing and used interchangeably in the area of psychopathology is probably the lack of clear knowledge on presumed etiology, which is also the case for differences between men and women. Deaux (61) underlines that a simple distinction between "sex" and "gender" without any assumptions about etiology may be a more useful approach, and he suggests "sex" for comparisons "..*in which people are selected on the basis of the demographic categories of male and female*" and "gender" for comparisons involving "...*the nature of femaleness and maleness, of masculinity and femininity*". This view was supported by Lewine (62). Still, the correct or at least consistent use of the terms is not easy, as can also be seen in this thesis where biological and/or cultural differences between men and women (or males and females) are not always easy to separate!

Recently, there have been several attempts to distil schizophrenia science into a set of facts (35, 36), and to distinguish between basic facts, etiological facts, pharmacological and treatment facts, pathological facts and behavioural facts. Differences between men and women with schizophrenia will inevitably arise from this interplay of sex hormones, neurodevelopmental and psychosocial sex and gender differences, and even if there are significant differences between men and women in several aspects, the degree of overlap seems to be substantial. The findings with regard to differences in men and women with the disease are also equivocal when it comes to sex differences in family history, obstetrical complications, minor physical anomalies and physical soft signs; it is therefore reason to believe that the neurodevelopmental model of schizophrenia accounts for the majority of schizophrenia in both sexes. When it comes to etiological facts, there is a complex interplay of genes and environmental factors that contributes in development of the schizophrenia syndrome, which genetically seems to be a catch-all term for several sub-syndromes. According to an update by Center for Human Genome Variation at Duke University (63), there may be anywhere between 100 and 10 000 genes with mind-damaging mutations, but how they function depends on a person's other genes and a multiplicity of factors in their environment.

An important theory with considerable support is the hypothesis that estrogen provides relative protection to premenopausal women (3, 64 - 66). The effects may be structural or functional. Structural effects are due to developmental change before brain maturation, extending from the prenatal period to puberty. The female brain shows earlier establishment of neuronal connections, lateralization of brain functions and axonal myelination (67) compared to the male brain. This relative immaturity of the early male brain and slower rate of development may make it more vulnerable to early brain insults, resulting in structural brain abnormalities associated with early onset and more negative

symptoms. The hypothesis of estrogen having a functional antipsychotic effect by modifying neurotransmitter functioning and thereby being a protective agent raising the threshold for psychotic symptoms may explain much of the gender differences in disease course (60, 61, 63).

3.6.1 Incidence and prevalence

Kraepelin stated already in 1893 that men were three times more likely than women to show the described features of dementia praecox. Despite Kraepelin's observations there was little research focusing on sex differences until the late 1980's. The annual incidence of schizophrenia was reported to be from 5.0 to 20.0 per 100 000 (3) and it was generally accepted not to vary according to sex (6, 68).

During the last decades, the earlier assumptions that schizophrenia is equally distributed in different cultures and between males and females have been questioned (4, 67, 69 -71). A meta-analysis based on all publications on incidence of schizophrenia from 1980 -2001 by Aleman et al (72) provided evidence for a sex difference in the risk of developing schizophrenia, as did the systematic review of 158 studies by McGrath et al (40). In the review by McGrath et al the median annual incidence of schizophrenia was found to be 15.2 per 100 000. The central 80 % of estimates varied over a fivefold range (7.7 – 43.0 per 100 000), and there was prominent variation between sites. The incidence rates also differed significantly between men and women; the median (10, 90 percent percentiles) rate ratio for male: female estimates was 1.4 (0.9, 2.4).

The sex differences in incidence are, however, not reflected in prevalence - the review of 188 prevalence studies by McGrath et al showed a median lifetime prevalence of 7.2 per 1000 inhabitants (3.1, 27.1), with no significant difference between males and females.

Neither Saha et al (73), nor a Finnish study from 2007 (74), showed any difference in prevalence between men and women.

The discussion of incidence and prevalence rates in psychiatry invariably comprises the application of diagnostic criteria (41), and the estimation of incidence and prevalence has to a great extent depended on the diagnostic inclusion criteria used. Lewine (62) demonstrated that the stricter the diagnostic criteria, the higher the proportion of men compared to women with schizophrenia. This is also stated by Leung and Chue - the broader the inclusion criteria, the smaller the difference in incidence between men and women (67). The described use of meta-analyses and reviews of different studies may therefore provide the most comprehensive knowledge on the incidence and prevalence of schizophrenia.

3.6.2 Age of onset

It is a quite robust finding across many studies that men have a 3-5 years earlier age of onset of schizophrenia than women. According to the review article by Leung and Chue (67) sex difference in age of onset has been shown to exist irrespective of culture, definition of onset (first sign of a mental disorder, first psychotic symptom, age of diagnosis, first treatment, first hospital admission) or definition of illness (various diagnostic systems including different versions of DSM and ICD). Leung and Chue point to the fact that earlier age of onset in men does not seem to appear due to differences in health-seeking behaviour of the patient or the family, and Faraone et al found sex difference in age of onset to persist after correction for sex differences in the age distribution of the population (75).

The distribution curves for age at onset do not only show a shift towards older age for women. Men show a modal incidence in their late teens and early twenties (ages 15-25) and perhaps a second, small peak around middle age (65, 67, 76). Women also show modal onset in their early ages, but the peak is lower and broader (ages 15 -30) followed by a

second, more pronounced peak than men at ages 45-49, and a third peak over the age of 65. Thus; there seem to be a switch from male predominance in incidence during the early twenties to female predominance in incidence in older ages. These distributions seem to be in accordance with the estrogen theory mentioned above. According to Leung and Chue (67) the age of onset sex difference is more evident in sporadic schizophrenia than in schizophrenia with high degree of family loading, as also found by Suvisaari et al (77).

3.6.3 Symptom presentation and course of illness

It is by no means evident in what way gender predicts symptomatology and course of illness (1,41,54). Häfner (65) argues that there are no gender differences in symptomatology, and without consideration of age there are no gender differences in symptom-related course of illness. However; Häfner claims that the effect of oestrogen on the level of gene expression and transmitter functioning results in higher age of onset and a reduced severity of illness until menopause. In an Australian study from 2008, Morgan et al (78) looked at gender differences and psychosis across different diagnostic groups, and found that women in all diagnostic groups reported better premorbid functioning, a more benign course of illness, lower level of disability and better social integration than men. The differences between men and women across the diagnostic groups were more obvious than within each group, even if women with schizophrenia were more severely disabled than women in the other diagnostic groups.

Even though there is considerable overlap in symptomatology between the sexes, it still seems to be substantial evidence that men with schizophrenia display more negative symptoms, while women have a higher frequency of affective symptoms. This may be partly explained, as stated by Flor-Henry (79), by women being more likely to express affective symptoms than men overall, and that the difference is related to general gender differences when it comes to affective expressivity.

Abel et al (76) and Leung and Chue (67) hold forward that older age of onset and a higher degree of affective symptoms generally predict better outcome and are associated with female sex in the majority of studies. Early age of onset and negative and disorganized symptoms are associated with worse short and medium outcomes, and are also associated with male sex. Females therefore seem to have better short-term and middle-term outcomes than men, but the differences attenuate in the long term. There is no strong evidence that age of onset or sex predict course and outcome independently of symptom profile at presentation.

Overall, findings seem to suggest that the complex picture of hormonal and neurodevelopmental sex-specific brain abnormalities in schizophrenia may be largely associated with the sex-specific factors contributing to normal brain development. Nevertheless, as described by Häfner, the scarcity of knowledge of differences in the development, morphology and functioning of the female and male brain do not allow any definite conclusions. Sex and gender differences in schizophrenia also reflect sex differences in the healthy brain, general cultural gender differences and general social effects when it comes to symptomatology and disease course. As Flor-Henry said already in 1983 (79): "*Sex differences in symptom expression in schizophrenia may be related to gender differences (in illness expression) rather than schizophrenia per se."*

4. Aims of thesis

The aims of this thesis were:

1. To describe the diagnostic process in a cohort of first-admitted patients with schizophrenia, with emphasis on gender differences.

2. To determine whether gender *as such* had any influence on diagnostic practice among psychiatrists in Norway and in the Arkhangel region in Russia, based on a case simulation.

3. To investigate whether there are difference in age-adjusted mortality or standardized mortality ratios (SMR) between men and women with schizophrenia in the counties of Troms and Finnmark.

5. Material and methods

5.1 Material

5.1.1 The case register of Psychiatric Division at the University Hospital of North Norway (Papers I and III)

The creation of a case register for all admissions to the Psychiatric Divisions of the hospital was initiated by Vidje Hansen in the mid-eighties, as an institution-based, administrative register. The original purpose was to use this computerized register to overview patient flow, but throughout the last two decades it has been increasingly used for research purposes. The register starts with new admissions from 01.01.1980, covering all admissions to the two divisions, and includes patients already being in-patients at start. The updating for the period 1993 to 1995 was done by the author, and from then on, the updating and quality control has been done by Vidje Hansen and Anne Høye in collaboration. At present, the register covers the period from 01.01.1980 to 31.12.2006. The University Hospital of North Norway is the only psychiatric hospital covering the two northern-most counties in Norway; Troms and Finnmark. These counties comprise a vast area of approximately 26 000 km^2, with a total of 224 407 inhabitants in 2000. The register has been continuously checked and validated against patient files, and is considered to be complete with no missing values.

Paper I is based on first-ever admitted patients with a minimum of three admissions from January 1st 1980 to December 31st 1995, the case register being the only data source. Paper III is based on the period from January 1st 1980 to December 31st 2006. Some of the analyses are performed only on this case register cohort, while others are based on linkage.

5.1.2 The Norwegian Cause of Death Register (paper III)

All physicians in Norway are required to complete a death certificate, and all death certificates are collected by the Cause of Death Register for coding of information based on International Classification of Diseases (ICD) - currently ICD-10. The Section for Health Statistics at Statistics Norway is the Data Processor for the Cause of Death Register, and the Norwegian Institute of Public Health is the Data Controller. For the period 1951-2010, the cause of death data is available in electronic format from Statistics Norway. The data are usually released with one year delay.

Norway has committed itself to classify and report the cause of death statistics in accordance with the ICD-classification and rules for coding underlying cause of death. The underlying cause of death means 1) the illness or injury that initiated the series of the morbid conditions that led directly to death, or 2) the external circumstances of the accident or act of violence that caused the fatal injury. Beyond the underlying cause of death, complications and contributing factors are coded – up to four in 1969 to 1995 and up to six from 1996.

5.1.3 Data file of psychiatrists' answers

A case description was in 2000 sent to all 980 members of the Norwegian Psychiatric Association, a specialist branch of the Norwegian Medical Association, and to all 163 psychiatrists in the Arkhangel area in Russia. A total of 467 psychiatrists answered, 392 from Norway and 75 from the Arkhangel region in Russia (40 % and 46 % response rate,

respectively). They were asked to participate in a study of diagnostic practice, and to suggest a tentative diagnosis on a written case description of a patient in early phase of a psychosis. All the analyses in the study described in paper II are based on this data file on Norwegian and Russian psychiatrists.

5.2 Methods

5.2.1 Use of case-register

Information used in the analyses was the personal identification number; date of admission; commitment status; date of discharge and diagnosis at discharge. Schizophrenia was defined according to the International Classification of Diseases (ICD-9: 295, ICD-10: F20, F21 and F25). Before 1985, ICD-8 was used, and the diagnoses in this period were converted retrospectively to ICD-9 codes.

In the study presented in paper I, 151 patients (60 women and 91 men) who were admitted for the first time during 1980-1995 were included. They had a total of 1326 admissions. By restricting the cohort to patients admitted at least three times, we secured repeated observations on each patient. 84 first-admission patients were hence excluded.

One of the analyses performed was to assess the latency period before first schizophrenia diagnosis. Diagnoses are formally registered at the day of discharge, the latency period therefore being defined as the mean time from first day of the first admission to the last day of the admission at which the first schizophrenia diagnosis was given. In addition, analyses of diagnostic shifts from first admission until schizophrenia diagnosis was performed, as well as analyses on diagnostic stability after schizophrenia diagnosis. This was done by assessing how many patients kept their diagnosis unchanged, how many had intermediate diagnoses before returning to schizophrenia and how many were re-diagnosed permanently after firstly having received schizophrenia diagnosis.

In paper III, differences in age-adjusted mortality rates between men and women in the in-patient cohort were studied. During the study period there were 22 434 admissions. 5840 persons were admitted, 2724 females and 3116 males. A total of 1111 patients, 38 % of them were women, received at some point a schizophrenia diagnosis. One of the hypotheses tested was whether the relationship between gender and mortality in the cohort persisted during different three follow-up periods with increasing degree of de-institutionalization. We also looked at differences between patient admitted for the first time before or after 1992, to see whether the relationship between gender and mortality depended on when the patients had their first admission. The year 1992 was chosen partly of analytical reasons (to have enough deaths for a meaningful analysis in the last period), partly because a follow-up ending in 1992 has previously been published (13, 14).

Finally, we wanted to investigate if there were any differences in mortality in relation to use of compulsory treatment. According to The Norwegian Act relating to the establishment and provision of mental health care *(the Mental Health Care Act*), compulsory mental health care may be provided in an institution approved for this purpose if a given set of criteria is fulfilled. We divided the cohort into three groups – those who had always been voluntarily admitted, those who had been admitted sometimes voluntarily and sometimes by use of compulsory care, and those who had always been committed by use of compulsory care.

5.2.2 Case simulation study

The design of the study described in paper II approaches behavioural research, as it is a kind of experimental study on physician's decision-making. We wanted to investigate association between patient gender and decision-making among psychiatrists, and to see whether there was a systematically biased interpretation by psychiatrists concerning gender and schizophrenia diagnosis. Our study questions demanded an experimental design and we chose to use a case simulation (a case vignette). On the basis of a discussion among three

experienced clinicians, a case description of a 27-year old patient was designed. The patient had symptoms that could be interpreted as schizophrenia in an early phase, but with room for doubt concerning the diagnosis. The psychiatrists were invited to participate in a study of diagnostic practice based on a case description, and they were specifically informed that there was no "medically correct" answer as it was a study on diagnostic practice as such. The answers were returned anonymously. The psychiatrists were not informed that half of them were introduced to the case vignette describing a male patient, the other half a female. Apart from the patient being described as "he" or "she" the stories were identical. The two gender versions of the vignette were randomly assigned in the male and female group of psychiatrists. They were asked to provide information on their own gender, age, whether they were specialists or in the process of specialising and main area of interests.

The hypothesis tested was whether gender of the patient affected diagnostic decision, and we also wanted to analyze whether gender of clinician, age, experience and area of interest influenced on their diagnostic decision.

5.2.3 Register linkage

In paper III, a linkage between the case register of University Hospital of North Norway and the Norwegian Cause of Death Register was performed, using the unique personal identification number as the identification variable. The personal identification number was also used for obtaining information held by Statistics Norway concerning emigration.

We studied gender differences in SMRs for patients with schizophrenia compared to the general Norwegian population, and as described for the in-patient cohort we wanted to test whether all-cause SMRs changed over three follow-up periods characterized by increasing de-institutionalization, or whether differences were related to first admission before or after 1992. We also divided into natural and unnatural causes of death, further sub-

grouping natural causes into cardiovascular diseases, cancer and others, and unnatural causes into suicide and others. We also looked at the importance of commitment status for difference in all-cause SMRs.

5.2.4 Statistical methods

The statistical methods used in the study are described in the different papers. Means, medians and proportions (%) were used to describe cohort characteristics. Chi-square tests, independent sample t-tests, Wilcoxon test, simple factorial analysis, multiple regression analysis and Cox regression with attained age as the time variable were used to analyse gender differences. Age adjustments of the mortality rates and statistical testing of differences between mortality rates were carried out by applying a Poisson regression model. For comparison with the mortality of the general Norwegian population, indirect age adjustment was used, according to age (5-year groups) and calendar year (5-year groups).

6. Overview of results

6.1 Paper I

Women had a significantly longer latency period than men from first admission until the first diagnosis of schizophrenia was given, both in total amount of time (2.6 years versus 1.6 years) and in number of admissions (3.4 versus 2.3 admissions). 33 % of the women received the diagnosis at their first admission, as opposed to 47 % of the men. The diagnostic pattern before the schizophrenia diagnosis was given was also somewhat different – men received to a higher degree reactive psychoses, while women were diagnosed with personality disorders. Schizophrenia diagnosis was found to be stable after it had been given, with no clear differences between men and women. Diagnostic stability was, however, strongly associated with a longer latency period – that is; higher stability

reflects a higher degree of diagnostic certainty. The impact of the shift from ICD-8 to ICD-9 in 1987 was also investigated, showing that the diagnostic guidelines resulted in shorter latency period even if the criteria were not changed. Nevertheless, the gender difference persisted.

6.2 Paper II

The study showed that a schizophrenia diagnosis was both in Norway and in Russia given significantly more often to the male story than to the female story. The differences persisted both with and without schizotypal disorder included. In the schizophrenia group of diagnoses, the Russians were less likely to put down a diagnosis of schizotypal disorder than the Norwegians. Country, gender of clinician, age of clinician and clinician's main area of interest did not affect the results in a logistic regression, where odds ratio for the male case versus the female case receiving a schizophrenia diagnosis was 1.8 (1.2-2.8).

6.3 Paper III

The 1111 patients were followed for a total of 16 129 person-years. During the total period of 27 years there was a stable bed-to-population ratio of approximately 4 per 10 000 inhabitants.

192 men and 103 women died during the 27 years period. 2.1 % of the men and 1.9 % of the women died during first year of follow-up. In both men and women, 20.4 % of the patients with schizophrenia died of natural causes, a similar proportion of them of cancer (4 %) or cardiovascular diseases (9 %). A larger proportion of the males (7.6 %) than of the females (3.8 %) died of unnatural causes; suicide was the registered cause of death for 5.8 % and 2.1 % of men and women, respectively. Male patients in the cohort had nearly twice the mortality of female patients, the hazard ratio being 1.9 (CI: 1.5, 2.4).

The study showed that men and women had 3.5 and 2.6 times higher total mortality than the general population, respectively (p =0.01 for the difference between genders). The gender differences for each of the examined causes were not statistically significant, but the SMRs were higher for men than for women for both natural and unnatural causes of death. The SMR for cancer was lower than for all natural causes combined, and was for women not significantly different from the cancer mortality in the general population. As expected, very high SMRs were found for suicides; the SMR was 17.0 for men and women combined.

Always voluntarily admitted men had lower all-cause SMR, while the opposite was found in women – always voluntarily admitted women had higher all-cause SMR than those who had been sometimes or always committed by use of compulsory care. All 16 deaths in this group of women had natural causes.

All-cause SMRs were higher for both men and women during the last nine years than the first nine years, and for women admitted for the first time after 1992 there were signs of increasing difference in mortality compared to the general female population. The rise was particularly high for unnatural causes of death (6.6 versus 16.0), and especially for suicide (9.6 versus 50.2). The numbers are, however, very small in this group, and caution must be made in interpretation. As a conclusion, however, the SMR for total mortality of women with schizophrenia is rising and becoming just as high as for men, both for natural and unnatural causes of death.

7. General discussion - methodology

7.1 Internal validity and bias

Internal validity is a description of the degree to which conclusions about *causal* relationships can be made, based on the measures used, research setting and design.

External validity concerns to what extent the (internally valid) results can be applied to other populations, that is; the generalizability of the results.

Bias is any kind of systematic error that affects the result in a way that reduces the internal validity. Bias may be classified in several categories – most usually selection bias, information bias and confounding.

7.2 Completeness of the case register (papers I and III)

All information in the computerized register has been checked against patient files. To our knowledge, the register is complete – that is; all persons that actually have been admitted since 01.01.1980 are included. There are, however, a very small number of missing values in some of the variables. In all, the register comprises 6044 persons, of which 5840 had a valid personal identification number, and 51 variables. Only in 6 of these variables are there any missing values at all, the number of persons with missing values ranging from 0.6 % to 2.9 % of the total 6044 persons. Even so, in a retrospectively validated register there may still be missing values, but the errors these may introduce for gender differences in the analyses are considered negligible.

7.3 Diagnostic reliability in the register (papers I and III)

Diagnoses in the register have been made by clinical judgment and consensus, and not by standardized diagnostic procedures. Many psychiatrists have been responsible for determining the diagnoses, and this may of course have affected diagnostic reliability. There is reason to believe that there has been, especially during the first years of the register, a cautious attitude towards diagnosing patients. It is therefore more likely that a person with the disease will not get the diagnosis than that the opposite happens, especially during the first 15 years. Still, the incidence rate in the age group 15-55 years was 11.1 per 100 000 inhabitants (8.8 for females and 13.3 for males), which is within the described range of

international incidence studies (40). The diagnostic hesitation has changed with time, and there has been a clear trend towards coordination with the rest of Norway. Still, no reliability study has ever been made, and this requires caution when it comes to diagnostic reliability.

7.4 Bias in the case register (paper I and III)

In a study based on case registers selection bias means that the sample studied is not representative of the total population of interest. This can affect both the internal and the external validity of the studies.

In a case register based on in-patients only there may be different subcategories of selection bias that must be considered (52). *Geographical bias* applies to whether the register only comprises people living in one area, in our register this could be the case if most patients admitted to the hospital came from e.g. the city of Tromsø (where the hospital is located) and not from rural areas. It is well known that travelling time to care is of importance when explaining differences in use of health services (80, 81). It may therefore be that patients with long travelling distances (up to 1000 km) or from small, rural communities use the psychiatric hospital to a lower degree. It is unclear to what degree this would affect our results – some studies have found higher prevalence rates of schizophrenia in cities (82), but it must be underlined that Tromsø in this respect is a relatively small city with only 70 000 inhabitants. Also, the psychiatric health services in Troms and Finnmark are exclusively public, and there are well-established cooperation lines from the hospital to the smaller treatment units and outpatient clinics. This cooperation was probably less established during the first years of the register, that is; there might have been a greater loss due to geographical causes during the early years of the register. Still, it is not very likely that this possible geographical bias would affect gender differences found in paper I or III.

Another form of bias could arise from the fact that in some of the smaller municipalities in the two counties there is a majority of Sami inhabitants, and earlier studies on utilization of medical services have shown a lower average consultation rate in Sami than in the general Norwegian population. In a recent study from the same area by Gaski et al (83), however, overall public somatic hospital expenditure in Sami municipalities was above national average. Even if this study does not comprise psychiatry, there are no clear indications that Sami people are admitted to hospital to a lower degree, and even so there is little reason to believe that there has been a gender specific skewness.

Another aspect of selection bias is *treatment bias* - in this setting meaning to which degree only severe cases are admitted to hospital. For every case register where only in-patients are included there is always a risk for exclusion of mild cases, even so in our studies.

Treatment bias may have affected the results in paper I. It might be that men with extensive symptoms is the group most often admitted to hospital, and that women have a longer delay before they are finally admitted. Still, the assumption that men are “more ill” at admission is countered by the fact that the mean total observation time at first admission is not higher for men than for women, and the overall total observation time is significantly higher for women than for men. Sub-typing of the schizophrenia diagnosis also gives a hint that women must have had serious symptoms also before diagnosis was set (paranoid and hebephrenic). A possible treatment bias of women being treated for a longer period outside hospital before admission should lead to a shorter latency period. Hence; an attenuation of the findings would have been more likely.

Also when it comes to paper III, treatment bias may have affected these results. If the register only contains the most seriously ill patients, and more so as the deinstitutionalization developed, it may be that SMR appears to be higher than it would have been if all patients with schizophrenia were included. The time trend showing the

increased SMRs for the whole group of patients in the second period may therefore be biased upward if patients with less symptoms are treated elsewhere than in-hospital. This implication does, however, require lower SMRs in patients with less symptoms, a theoretical association that has not been investigated in our study.

Assessing the finding of higher SMRs for women admitted for the first time after 1992, the results may be biased if a higher degree of deinstitutionalization leads to a higher proportion of relatively well-functioning women never being admitted to the hospital. If that is the case, the time trend of higher SMR may be tautological - as time goes by it is the more severely ill women that are admitted, leading to higher SMRs than the general female population, which again leads us to think that it is the deinstitutionalization that causes the enhanced SMRs. Again, this requires an implication of more symptoms leading to higher SMR. Still, one of our puzzling findings was the inverse relation between SMR and use of coercion for women. This may mean that these relatively well functioning women in fact have higher SMRs, which again may indicate that also never-admitted women with schizophrenia – to the extent to what they actually exist in the catchment area (the counties of Troms and Finnmark) – still may have high SMRs.

Information bias in a register study is associated with loss to follow-up due to death or emigration out of the area, lack of information prior to first entry due to in-migration to the area covered, failed linkage and periods of discontinuity in the register (52). We consider the chance of information bias to be relatively low – in paper III, linkage with the national Cause of Death Register excludes all loss of follow-up due to migration from Troms and Finnmark. Loss of follow-up due to migration from Norway still cannot be excluded, but the numbers are low – 6 out of the 1111 patients with schizophrenia (Paper III) emigrated during 1980 -2006. The use of the personal identification number excludes bias due to failed linkage. There are no discontinuity periods in the register.

The case register contains no information on psychiatric symptomatology or other clinical correlates such as BMI, blood pressure, smoking, drug abuse or other factors that may affect mortality (44, 84 - 87). There may of course be several confounding variables that affect results in both paper I and III. The main topic discussed is, however, the gender differences, and in order to explain them there must be strong correlations between patient gender and possible, unknown confounders.

7.5 Bias in the Cause of Death Register (paper III)

All deaths in Norway are usually certified by a physician, on rare occasions the death certificate may be signed firstly by the police before being confirmed by a physician. The Cause of Death Register is validated against Statistics Norway twice a year, and death certificates are also controlled against other existing information (autopsy reports, the Norwegian Register of Birth, hospital records when needed, the police road accident register etc). "Underlying cause of death" is registered, which means 1) The illness or injury that initiated the series of conditions that led directly to death, or 2) The outer circumstances of the accident or act of violence that caused the fatal injuries (88). A source of uncertainty in the cause of death statistics is, according to Gjertsen (88), partly the cause of death investigation and partly physician reporting of information on the death certificate. Another potential source of error is the classification, coding and input made by medical coders. In practice, classification and coding of underlying cause of death is difficult when multiple causes of death have been reported and several sequences are possible, and it can develop local code cultures that prefers certain diseases than others. Nordic research on the cause of death statistics shows that statistical comparisons can be problematic due to differences in coding, medical culture and working practices, although the classification used is the same (89). In addition, there is always a risk of underreporting suicides, as there may be an overweight of external causes being registered as accidents. Another potential

source of bias is the number of persons dying abroad with no registered cause of death. Some Norwegian citizens die abroad – i.e. 394 persons in 2008 (90). In 90 % of these cases there is no registered cause of death. There is, however, no reason to believe that these examples should affect the gender differences shown in paper III.

7.6 Antipsychotics and mortality

The use of antipsychotic drugs could theoretically be a confounder when it comes to SMR combined for both sexes. During the last years there has been a growing concern that the well-known side-effects of some of the second-generation antipsychotics (increased BMI, increased risk of metabolic syndrome, other possible effect on cardiovascular risk factors) may increase the mortality of patients with schizophrenia. In a review by Smith et al (91) from 2008, there was tentative evidence that the second-generation antipsychotics included in the studies were associated with a small increased risk of diabetes, but the results were difficult to interpret. Other studies the last few years possess ambiguity – Bushe et al (92) concludes that there is some evidence that long-term exposure to antipsychotics increases mortality, but more research is required. This is also the conclusion in a review by Weinmann (93). Tiihonen et al (94), on the other hand, found in their large, register-based study that long-term treatment with antipsychotic drugs is associated with lower mortality compared with no antipsychotic use. Use of clozapine seemed to be associated with a substantially lower mortality than any other antipsychotics, mostly due to lower rate of suicide, while the heterogeneous group of “other” second-generation antipsychotics seemed to be associated with higher all-cause mortality than perphenazine. The methodology and findings in this study have been debated (95). The conclusion so far seems to be that more research is required, as also stated by Kelly (96).

In our study, it is of course possible that use of antipsychotic drugs may have contributed in some way, but it is less likely that the gender difference as such is affected.

7.7 Selection bias among psychiatrists (paper II)

Norwegian Psychiatric Association had 980 members in 2000, comprising 69 % of all Norwegian psychiatrists. Response rate of the study was 40 % in Norway and 46 % in Russia, and this quite low response rate taken into consideration there might be a selection bias. Bias could in principle affect the results in both directions – the psychiatrist not participating could be more or less prone to give a schizophrenia diagnosis given the sex of the patient. Gender distribution in the Norwegian sample was found to be representative of all Norwegian psychiatrists and that of members of the Norwegian Psychiatric Association. Responders were slightly younger (mean age 50.7) than the total population of specialists (mean age 54.9) and members of Norwegian Psychiatric Association (mean age 53.0). The slightly younger age of the participating clinicians may have resulted from the fact that in the total cohort of members there are several who are not longer practicing. Also, it may be that younger clinicians were more interested in participating in research projects. It is, however, difficult to see how the relatively low response rate or the slightly skewed age distribution could bias the results to a significant extent.

It is, due to lack of registration routines at the time, not known to what extent the Russian psychiatrists who took part are representative for all invited psychiatrists.

7.8 Use of case simulation (paper II)

Written case simulations (case vignettes) have been widely used to mimic a clinical situation in studies of medical decision-making, but their validity is not fully established. In psychiatry, case simulations have most often been used for testing of interrater reliability. Effect of gender in case simulations is not easy to find in existing literature, even if there are a few examples including this perspective - Stoppe et al (97) found that a female case vignette was diagnosed more often with (old age) depression in primary care than a male vignette, and

concluded, in line with our conclusions, that gender-related stereotypes and experiences affected the diagnosis.

External validity of case simulations is most often discussed when "true" patients are compared with matching paper patients, as in an article by Borkhoff et al (98) on physician's treatment and referral of total knee arthroplasty. In this study, gender was found to affect the clinicians' decision when presented with a real patient but not so when presented a paper patient. This may imply case simulations to be less sensitive to gender differences – hence; underline the strength of our findings. The results of the study also depend on the quality of the presented case – whether it gives a valid description of a patient where there is reasonable room for doubt. In our opinion, the results indicate that the description was quite accurate – schizophrenia diagnosis was given in about 70 % of the cases. The generalizability and hence the external validity of the results is enhanced by the fact that they are found both in the Russian and in the Norwegian cohort.

8. General discussion - results

The debate on the schizophrenia concept should lead to an open-mindedness towards investigating the boundaries of the syndrome (26, 34) in all senses – gender differences as well as clinical practice, from different angles. The general results in the three studies presented in this thesis strongly support findings in other studies of an existing gender difference in symptomatology, both when it comes to clinicians' interpretation and to outcome (mortality). None of the studies address to which degree men and women are actually *treated* differently. The discussion sections in each paper will not be repeated in this chapter, but a few general lines on the background of the different papers will be drawn.

8.1 Latency period of schizophrenia diagnosis

The mean period from the first admission to first diagnosis of schizophrenia was 2.0 years overall (Paper I), but the latency period was significantly longer for females than for males. A similar gender difference has been found by others (99, 100). Goldacre et al (101) confirmed that when a diagnosis of schizophrenia has been made, it is less likely to be made at the patient's first admission in females than in males. Chen et al (102) did not study latency period per se, but found that males have a higher rate of change from other disorders to schizophrenia than females, whereas females were more likely to have a change in diagnosis from schizophrenia to another disorder. The opposite seems to be the case in our study, but the methods used are different and may not be compared directly.

As described in paper I, Kreitman el (103) outline five elements that characterize the diagnostic process: 1) the patient, 2) the psychiatric interview, 3) the psychiatrist, 4) the analysis and 5) the diagnosis. The focus of the study was the last three elements, which is reflected in the discussion in the paper.

Our study is descriptive, and there are obvious limitations in interpretation of the results when patient issues are not included. The study was performed some years ago, and in light of current research the findings could very well be explained by gender-linked differences in symptomatology, as described in the Background chapter of the thesis (*3.6 Sex and gender differences in schizophrenia*) - independent of whether these differences are a result of neurodevelopmental, biological or general gender factors.

In a study of stability of research diagnoses in a heterogeneous first-admission sample of patients with psychosis, Schwartz et al (104), used DSM IV diagnostic criteria at baseline and after 6 and 24 months. The most important risk factors for changing into schizophrenia diagnosis at 24 months follow-up were more than 3 months of psychosis duration before hospitalization, poorer premorbid adjustment in adolescence, having a longer length of hospitalization, being given antipsychotic medication upon hospital discharge, and having

more negative symptoms at 6-months follow-up. Schwartz et al thereby conclude that changes *to* schizophrenia diagnosis are mostly attributable to the evolution of the illness. Gender differences are not the issue in Schwartz et al's paper, but as both poorer premorbid adjustment in adolescence and more negative symptoms are associated with male gender, this could be important for the gender differences in our study. This view is probably strengthened by the results of Kim et al (38), who investigated diagnostic stability in a group of first-episode psychotic patients. They found schizophrenia diagnosis to be the most consistent, but the rates of change to affective psychosis was significantly higher for women, as well as for patients with better premorbid functioning and shorter duration of untreated psychosis. This may indicate a higher degree of diagnostic uncertainty for women, and that clinical features evolve over some time in the beginning of the disease course.

It has long been recognized that the onset of psychosis is often preceded with symptoms by a period of variable duration, and the pathways to any disorder or diagnosis is heterogeneous (34, 105). An important patient factor that has been emphasized since the mid-1990s is the duration of untreated psychosis (DUP). In a review by Nordentoft et al (106) the average duration of untreated psychosis is said to be around 1-2 years, and as several studies have linked longer duration of untreated psychosis with poorer outcomes this is of course an important research area.

The duration of untreated psychosis (DUP) is not known in our study, but the current knowledge on gender differences in first-episode psychosis is obviously of importance in partly explaining our findings. Gender differences extend to pre-illness characteristics, as described by Cotton et al (107). They found that prior to onset of psychosis, women were more likely to have a history of suicide attempts and depressive symptoms, while men had more marked substance use problems, more severe psychopathology at admission and lower levels of social functioning. As for men; several studies also report more negative

symptoms (108 -110) and substance use (110, 111). Substance abuse in relation to admission could mask the underlying symptoms and thereby prolong the diagnostic delay. In our study (Paper I), there were no significant difference between men and women in percentage distribution of alcohol- and drug-related disorder diagnoses, but the actual use of drugs and/or alcohol in relation to admissions is probably often not reflected in a diagnosis and hence underestimated.

As gender and illness onset is complex also when it comes to first-episode psychosis (that is; also psychoses that might develop into schizophrenia), the patient history before and during first hospital admission could add important information. The patients in the case register may be in different stages in their disease course – some of them have had long duration of untreated psychosis before admission, and some may be admitted quite early in the course. In addition to the gender differences in symptomatology prior to schizophrenia diagnosis, it could be that the women are generally admitted in an earlier phase and therefore have a longer period of diagnostic uncertainty in-hospital. Both Larsen et al (112) and Thorup et al (110) found a longer duration of untreated psychosis in men, this could mean that the men in our study have been psychotic for a longer period, hence; the diagnosis could be more obvious. O'Callaghan et al (113) also concluded that being female, having better premorbid adjustment and fewer negative symptoms were associated with shorter delays in help-seeking behaviour.

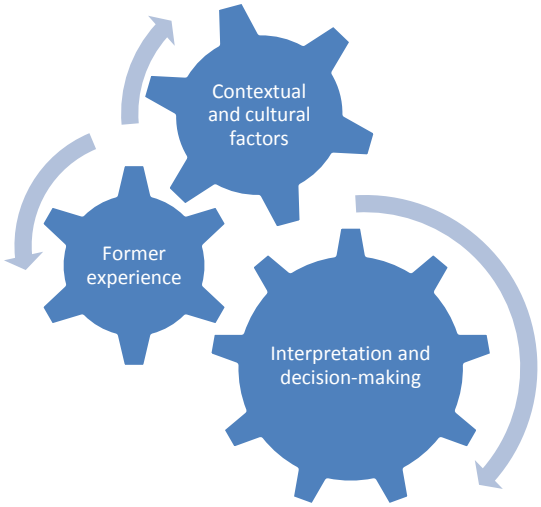
Still, the fact that the mean total period of observation inside hospital before first schizophrenia diagnosis was significantly longer for females than for males, indicate that the symptoms were serious also in women. The presumed serious symptoms may reflect that more women are either treated as outpatients or not treated at all before hospital admission. In addition to diagnostic uncertainty and gender-dependent aspects of disease course, the long observation period after admission may also be caused by poor treatment

response. We do, however, know nothing of the quality of symptoms or treatment given before or after admission, which is of course an obvious weakness of the study when it comes to the patient factor of the diagnostic process.

Nevertheless; the focus of the study was the last three issues in Kreitman et al's description – the psychiatrist, the analysis and the diagnosis. As an additional explanation could be that there is a systematically biased interpretation of symptoms by clinicians, for instance by not recognizing psychotic symptoms in women, a study of the diagnostic practice by clinicians was performed. Results shown in paper II confirm this assumption – to some degree a patient-independent gender bias may contribute to diagnostic delay.

8.2 Clinicians' former experience

When considering differential diagnoses of a patient, the clinician must create a manageable list of relevant diagnoses, and manage to rule-out or rule-in differential diagnoses on the basis of former experience, observation and tests (114). With the experimental design of the second study (paper II), the gender differences have to be explained by the clinicians' former experience, linked to earlier contact with patients and/or to the cultural context, as seen in the figure below.



Clinicians may have observed more men than women with schizophrenia symptoms, and symptoms may have been more severe and more "typical" of schizophrenia at first presentation. Patient gender may thereby influence clinician's decision-making concerning diagnosis at a later stage, as clinicians, more or less consciously, will include their former knowledge and experience concerning prognosis and aetiology when making diagnoses. Women's higher degree of affective symptoms may, hypothetically, contribute to a better ability to verbalize and explain feelings. This can hypothetically make it easier for the clinician to understand and interpret symptoms as non-pathological reactions to stress and life events or as linked to the patient's personality, and make it more difficult to choose the serious, more ''organic'' diagnosis of schizophrenia. As described by Cotton et al (107), women with first-episode psychosis also have a higher degree of traumatic experiences, suicide attempts and depressive episodes. Such experiences could, if expressed by the patient, contribute to this hypothesis. However, this could only be an indirect explanation of the case simulation diagnosis.

Gender differences in interpretation of symptoms are also known from other areas of medicine, as in acute heart disease (115). In a Norwegian study of diagnostic practice in a Pakistani versus a Norwegian population, Steihaug and Rutle (116) found that difference between the sexes was more significant than difference between Pakistani and Norwegian patients— women received more symptom diagnoses and fewer illness diagnoses than men. In the study by Borkhoff et al (98) mentioned in chapter *7.8 Use of case simulation*, gender affected clinicians' decisions; they were more likely to recommend total knee arthroplasty to men than to women with similar symptoms.

Others have advocated the idea that psychiatry represents a value-laden cultural enterprise, and that diagnostic practice may suffer from so-called ''androcentric bias'' (male values and male behaviours are considered healthier and more normal). Physicians may thereby

overlook organic disease in women and consider their symptoms to be due to stress, life events or psychosexual problems. Seeman discusses this view in her book ‘‘Gender and psychopathology’’ (3), but emphasizes that the evidence for this view is ambiguous.

8.3 Mortality and diagnostic practice

Discussion of gender differences in mortality in paper III may be deepened by the results on diagnostic practice. The possible effect of treatment bias in paper III is described in *7. General discussion - methodology*, included the possibility of a higher degree of serious symptoms in female patients in the latter period due to better treatment possibilities and decentralization of services. In Paper I is shown that the latency period decreased gradually after introduction of new guidelines in 1987; this may counteract a possible bias, because of the broadened conceptualization of schizophrenia.

Moreover, schizophrenia is a severe diagnosis that in most cases will lead to a period of hospital treatment at some point. The long follow-up period of the register probably attenuates bias risk; the chances of a patient with psychotic symptoms not being admitted are reduced as time passes. The longer the follow-up, the higher is the chance of being included in the register, even if this will not fully apply to patients eligible for first admission during the latest years of the register follow-up period. As mentioned, psychiatric health care in the area is exclusively public, with well-established structures for cooperation on admission and follow-up. In addition, all involuntary treatment must be initiated in a hospital according to Norwegian legislation. Patients from the area admitted in other parts of Norway or as Norwegian citizens abroad will also be transferred to their “home” hospital.

A possible association between diagnostic practice and cardiovascular mortality may arise on the background of results described in an article by Tabenkin et al (117), where visits by male and female patients at primary care physicians were investigated. After controlling for

visit and patient characteristics, it was found that visits by women had a higher percent of time spent on physical examination, structuring the intervention, patient questions, screening and emotional counselling. Visits by men, on the other hand, involved a higher percent of time spent on procedures and health behaviour counselling. Hence, clinicians' bias in treating men and women with schizophrenia differently could be enhanced when it comes to health behaviour counselling; which is important in prevention of somatic morbidity. Still, further research is required.

In the epidemiological overview by MacGrath et al (40) no difference in SMR between males and females was identified. A somewhat puzzling finding in this review was that the difference in incidence between men and women was not reflected in difference in prevalence – this should have been seen, according to the authors, if men have an earlier age of onset and a worse disease course at earlier stages. The findings of higher SMRs in our and other studies can contribute in explaining this lack of difference in prevalence.

8.4 Internal and external validity

We consider the internal validity in the analyses performed from the case register (Papers I and III) to be acceptable. It may be affected by the possible treatment bias, but it is important to underline that these are studies of in-patients, as most of the studies we compare with also are. Nevertheless, there might still be a group of well-functioning patients being treated without hospital admissions, thereby the validity of the study as a study of all patients in schizophrenia in the two counties Troms and Finnmark can be affected.

All the results, except for the results from the simulation study, are based on the case register of the Department of Psychiatry at the northern-most university hospital in the world. Some of the observations are based on relatively old data (paper I) and follow-up of

patients during a long follow-up, the latter being a necessity in a prospective study. However, we find that the results in many respects are well in accordance with other similar studies. Furthermore, we believe that the results (with some reservations) have external validity for patients with schizophrenia treated under similar, relatively well functional, mental health care systems like in the Nordic countries and some other European countries.

Caution must of course be made in interpreting the results in terms of causality as the results from Paper I and Paper III are from observational epidemiological studies.

9. Clinical implications

1. Women may receive less specific treatment than males, or correct treatment may be given at a later point. Special care must be taken in observing and interpreting the symptoms of women.

2. Clinicians' gender bias should be taken into consideration in studies of diagnostic reliability, as well as in studies addressing gender differences in general.

3. The increasing mortality of patients with schizophrenia should be taken very seriously in further planning of health services, as well as in clinical practice. Prevention of somatic diseases should be considered just as important as prevention of suicides in this group of patients.

4. The indications of rising SMRs for women should warrant extra caution. There might be subgroups of relatively well functioning, but vulnerable women who need better follow-up than given in the existing, deinstitutionalized health care system.

10. Research implications

1. The presented study on mortality is based on a cohort from only two Norwegian counties. The person-identifiable Norwegian Patient Registry established from 2008 contains national cohorts, but has existed too short to provide a sufficient follow-up period. Register based studies on mortality development for patients with schizophrenia in general, and gender differences in particular, should be planned.

2. As there is a delay in giving women schizophrenia diagnosis, but we have no information on the treatment given in this latency period, a closer investigation of treatment given to patients with first admission and psychosis diagnosis would be of interest.

3. As our findings suggest that there may be a subgroup of vulnerable women with higher mortality, studies of gender differences in treatment before hospital admission and follow-up after hospital discharge should be performed.

4. Closer investigation of gender-related stereotypes and the effect of former gender experiences among clinicians are subjects of interest, as it would be useful to create more valid hypotheses on how such differences may influence decision-making.

11. References

1. Stiberg E, Høye A (1998) Finnmark and Troms Psychosis project FINNTROPP 1994-1997. Final report (In Norwegian). University Hospital of North Norway, Tromsø

2. First MB, Spitzer RL, Gibbon M, Williams JBW (1997) Structured Clinical Interview for DSM IV Axis I Disorders (SCID I). Biometric Research, New York

3. Seeman MV (1995) Gender and Psychopathology, American Psychiatric Press, Inc., Washington DC

4. Iacono WG, Beiser M (1992) Where are the women in first episode schizophrenia? Schizophrenia Bull 18:471-480

5. Castle DJ, Wessely S, Murray R (1993) Sex and schizophrenia: effect of diagnostic stringency, and associations with premorbid variables. Br J Psychiatry 162: 659-664

6. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen A (1992) Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organisation ten-country study. Psychol Med Monogr Suppl 20:3-97

7. Hambrecht M, Maurer K, Hafner H, Sartorius N (1992) Transnational stability of gender differences in schizophrenia? Eur Arch Psychiatry Clin Neurosci 242:6–12

8. Eaton WW (1991) Update on the epidemiology of schizophrenia. Epidemiol Rev 13: 320-328

9. Ødegård Ø (1936) Mortality in Norwegian mental hospitals from 1916-1933. Acta Psych Neur Scand II: 323-356

10. Ødegård Ø (1951) Mortality in Norwegian hospitals 1926-1941. Acta Psych Neur Scand 27: 353-367

11. Ødegård Ø (1952) The excess mortality of the insane. Acta Psych Neur Scand 27: 353-367

12. Ødegård Ø (1967) Mortality in Norwegian mental hospitals 1950-1962. Acta Genet Stat Med 17: 137-153

13. Hansen V, Arnesen E, Jacobsen BK (1997) Total mortality in people admitted to a psychiatric hospital. Br J Psychiatry 170: 186-190

14. Hansen V, Jacobsen BK, Arnesen E (2001) Cause-specific mortality in psychiatric patients after deinstitutionalisation. Br J Psychiatry 179**:** 438-443

15. Berrios GE (1996) The history of mental symptoms. University Press, Cambridge, UK

16. Bürgy M (2008) The concept of psychosis: Historical and phenomenological aspects. Schizophr Bull 34: 1200-1210

17. Andreasen NC (1997) The evolving concept of schizophrenia: From Kraepelin to the present and future. Schizophr Res 28: 105-109

18. Raskin DE. Bleuler and schizophrenia (1975) Br J Psychiatry 127: 231-234

19. Craddock N, Owen MJ (2006) The beginning of the end for the Kraepelinian dichotomy. Brit J Psychiatry 186: 364-366

20. Fusar-Poli P, Politi P (2008) Paul Eugen Bleuler and the birth of Schizophrenia (1908). Images in psychiatry. Am J Psychiatry 165: 1407

21. Wing JK, Cooper JE, Sartorius N (1974) The description and classification of psychiatric symptoms: an instructional manual for the PSE and CATEGO systems. Cambridge University Press, London

22. The shorter Oxford English dictionary, 3rd ed (1978) Clarendon Press, Oxford

23. Robins E, Guze SB (1970) Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. Am J Psychiatry 126: 983-987

24. Andreasen NC, Carpenter W (1993) Diagnosis and classification of schizophrenia. Schizophr Bull 19:199 - 214

25. Andreasen NC (1995) The validation of psychiatric diagnoses: new models and approaches (editorial) Am J Psychiatry 152: 161-162

26. Kendell R, Jablensky A (2003) Distinguishing between the validity and utility of psychiatric diagnoses. Am J Psychiatry 160:4-12

27. Parnas J (2011) A disappearing heritage: The clinical core of schizophrenia. Schizophr Bull 37: 1121-1130

28. Carpenter WT junior, Strauss JS (1991) The prediction of outcome in schizophrenia. IV: Eleven-year follow-up of the Washington IPSS cohort. J Nerv Ment Dis 179: 517-525

29. Diagnostic and Statistical Manual of mental disorders, 4th ed (2000). American Psychiatric Association Washington, DC

30. International classification of mental and behavioural disorders, ICD-10 (1992) World Health Organization, Geneva

31. Langfeldt G (1937) The prognosis in schizophrenia and the factors influencing the course of the disease. Melford, London

32. Bergem M, Dahl AA, Guldberg C, Hansen H (1990) Langfeldts schizophreniform psychoses fifty years later. Br J Psychiatry 157: 351–354

33. Palm U, Möller HJ (2011) Reception of Kraepelin's ideas 1900-1960. Psychiatry Clin Neurosci 65: 318-325

34. Keshavan MS, DeLisi L, Seidman L (2011) Early and broadly defined psychosis risk mental states. Schizophr Res 126: 1-10

35. MacDonald AW, Schulz SC (2009) What we know: findings that every theory of schizophrenia should explain. Schizophr Bull 35: 493-508

36. Keshavan MS, Nasrallah HA, Tandon R (2011) Schizophrenia, "Just the Facts" 6. Moving ahead with the schizophrenia concept: from the elephant to the mouse. Schizophr Res 127: 3-13

37. Rahm C, Cullberg J (2007) Diagnostic stability over 3 years in a total group of first-episode psychosis patients. Nord J Psychiatry 61: 189-193

38. Kim JS, Baek JH, Choi JS, Lee D, Kwon JS, Hong KS (2011) Diagnostic stability of first-episode psychosis and predictors of diagnostic shift from non-affective psychosis to bipolar disorder: A retrospective evaluation after recurrence. Psychiatr Res 188: 29-33

39. Schoenbach VJ (rev. 2003) Standardization of rates and ratios. http://www.epidemiolog.net/evolving/Standardization.pdf.

40. McGrath J, Saha S, Chant D, Welham J (2008) Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 30: 67-76

41. Eaton WW, Hall AL, Macdonald R, McKibben J (2007) Case identification in psychiatric epidemiology: A review. Int Rev Psychiatry 19: 497-507

42. Brown S, Inskip H, Barraclough B (2000) Causes of the excess mortality of schizophrenia. Br J Psychiatry 177: 212-217

43. Brown S, Kim M, Mitchell C, Inskip H (2010) Twenty-five year mortality of a community cohort with schizophrenia. Br J Psychiatry 196: 116-121

44. Harris E C, Barraclough B (1998) Excess mortality of mental disorder. Br J Psychiatry 173: 11-53

45. Ösby U, Correia N, Brandt L, Ekbom A, Sparén P (2000) Mortality and causes of death in schizophrenia in Stockholm County, Sweden. Schizophr Res 45: 21-28

46. Saha S, Chant D, McGrath J (2007) A systematic review of mortality in schizophrenia. Is the differential mortality gap worsening over time? Arch Gen Psychiatry 64: 1123 - 1131

47. Brown S (1997) Excess mortality of schizophrenia. A meta-analysis. Br J Psychiatry 171: 502-508

48. Mortensen PB, Juel K (1993) Mortality and causes of death in first admitted schizophrenic patients. Br J Psychiatry 163: 183-189

49. Kringlen E (1967) Heredity and environment in the functional psychoses. Universitetsforlaget, Oslo

50. Onstad S, Skre I, Kringlen E (1991) Twin concordance for DSM-II-R schizophrenia. Acta Psychiatrica Scand 83: 395-401

51. Skre I, Onstad S, Torgersen S, Lygren S, Kringlen E (1993) A twin study of DSM-III-R anxiety disorders. Acta Psychiatr Scand 88: 85-92

52. Tansella M (2000) Do we still need psychiatric case registers? Editorial (invited) Acta Psychiatr Scand 101: 253-255

53. Lunde A, Lundeborg S, Lettenström GS,(??) Thygesen L, Huebner J (1980) The person-number systems of Sweden, Norway, Denmark and Israel. Vital and health statistics: Series 2, Data evaluation and methods research: 84: (PHS) 80-1358. National center for health statistics, US Department of Health and Human Services, Hyatsville Md.

54. Vollset SE, Cappelen I (2007) Register epidemiology. In: Laake et al Epidemiological and clinical research methods (In Norwegian). Gyldendal Akademiske, Oslo

55. Wahlbeck K, Westman J, Nordentoft M, Gissler M, Munk Laursen T (2011) Outcomes of Nordic mental health systems: life expectancy of patients with mental disorders. Br J Psychiatry 199: 453 - 458

56. Morgan VA, Jablensky A (2010) From inventory to benchmark: quality of psychiatric case registers in research. Br J Psychiatry 197: 8-10

57. Wierdsma AI, Sytema S, van Os JJ, Mulder CL (2008) Case registers in psychiatry: do they still have a role for research and service monitoring? Curr Opin Psychiatry 21: 379-384

58. Häfner H, an der Heiden W (1986) The contribution of European registers to research on schizophrenia. Schizophr Bull 12: 26-51

59. Mortensen PB (1995) The untapped potential of case-records and record-linkage studies in psychiatric epidemiology. Epidemiol Rev 17: 205-209

60. Allebeck P (2009) The use of population based registers in psychiatric research. Acta Psychiatr Scand 120: 386-391

61. Deaux K, Major B (1987) Putting gender into context: An interactive model of gender-related behaviour. Psychol Rev 94: 369-389

62. Lewine RR (1994) Sex: An imperfect marker of gender. Schizophr Bull 20:4, 777-779

63. Tartakowsky M (2011) Schizophrenia and Genetics: Research update. http://psychcentral.com/lib/2011/schizophrenia-and-genetics-research-update/all/1/

64. Seeman MV, Lang M (1990) The role of estrogens in schizophrenia gender differences. Schizophr Bull 16: 185-194

65. Häfner H (2003) Gender differences in schizophrenia. Psychoneurendocrinology 28: 17-54

66. Halbreich U, Kahn LS (2003) Review: Hormonal aspects of schizophrenias: an overview. Psychoneuroendochrinology 28: 1-16

67. Leung A, Chue P (2000) Sex differences in schizophrenia, a review of the literature. Acta Psychiatr Scand 101: 3-38

68. Wyatt RJ, Alexander RC, Egan MF, Kirch DG (1988) Schizophrenia, just the facts. What do we know, how well do we know it? Schizophr Res 1: 3-18

69. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D (2004) A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 28: 2-13

70. McGrath J (2005) Myths and plain truth about schizophrenia epidemiology – the NAPE lecture 2004. Acta Psychiatr Scand 11: 4-11

71. Cohen A, Patel V, Thara R, Gureje O (2008) Questioning an axiom: better prognosis for schizophrenia in the developing world? Schizophr Bull 34: 229-244

72. Aleman A, Kahn RS, Selten JP (2003) Sex differences in the risk of schizophrenia: evidence from meta-analysis. Arch Gen Psych 60:565-571

73. Saha S, Chant D, Welham J, McGrath J (2005) A systematic review of the prevalence of schizophrenia. Plos Med 2: e 141

74. Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, Partonen T, Tuulio-Henriksson A, Hintikka J, Kieseppä T, Härkänen T, Koskinen S, Lönnqvist J. (2007) Lifetime prevalence of psychotic and bipolar 1 disorders in a general population. Arch Gen Psychiatry 64: 19-28

75. Faraone SV, Chen WJ, Goldstein JM, Tsuang MT (1994) Gender differerences in age at onset of schizophrenia. Consult Clin Psychol 62: 1017-1025

76. Abel KM, Drake R, Goldstein JM (2010) Sex differences in schizophrenia. Int Rev Psychiatr 22: 417-428

77. Suvisaari JM, Haukka J, Tanskanen A, Lönnqvist JK (1998) Age at onset and outcome in schizophrenia are related to the degree of familial loading. Br J Psychiatry 173: 494-500

78. Morgan VA, Castle DJ, Jablensky AV (2008) Do women express and experience psychosis differently from men? Eodiemiological evidence from the Australian National Study of Low Prevalence (psychotic) disorders. Austr NZ J Psychiatry 42: 74-82

79. Flor-Henry P (1990) Influence of gender in schizophrenia as related to other psychopathological syndromes. Schizophr Bull 16: 211- 227

80. Shannon GW, Bashshur RL, Lovett JE (1986) Distance and the use of mental health services. Milbank Q 64: 302-330

81. Pfeiffer PN, Glass J, Austin K, Valenstein M, McCarthy JF, Zivin K (2011) Impact of distance and facility of initial diagnosis on depression treatment. Health Serv Res 46: 768-786

82. Freeman H (1994) Schizophrenia and city residence. Br J Psychiatry 164 (Suppl 23): 39–50

83. Gaski M, Melhus M, Deraas T, Førde OH (2011) Use of health care in the main area of Sami habitation in Norway – catching up with national expenditure rates. Rural Remote Health 11: 1655 (online)

84. Saku M, Tokudome S, Ikeda M, Kono S, Makimoto K, Uchimura H, Mukai A, Yoshimura T (1995) Mortality in psychiatric patients, with a specific focus on cancer mortality associated with schizophrenia. Int J Epidemiol 24: 366-372

85. Joukamaa M, Heliövaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V (2001) Mental disorders and cause-specific mortality. Br J Psychiatry 179: 498-502

86. Tran E, Rouillon F, Loze J-Y, Casadebaig F, Alain P, Vitry F, Limosin F (2009) Cancer mortality in patients with schizophrenia. Cancer 115: 3555-3562

87. Lawrence DM, Holman CDJ, Jablensky AV, Hobbs MST (2003) Death rate from ischaemic heart disease in western Australian psychiatric patients 1980-1998. Br J Psychiatry 182: 31-36

88. Gjertsen T (2002) The Cause of Death Register – an important source in medical research (In Norwegian). Tidsskr Nor Lægeforen 122: 2551- 2554

89. Johansson LA, Bille H, Ahonen H, Helgadóttir S, Gjertsen F, Lönn Y et al (1999) Statistics of death causes. I: Health statistics for the Nordic countries 1997 (in Danish). NOMESKO 56, Nordisk Medicinalstatistisk Komité, København

90. Nrugham L, Mehlum L (2010) The Norwegian Cause of Death Register: a comment to data quality (In Norwegian). Suicidologi 15: 8-11

91. Smith M, Hopkins D, Peveler RC, Holt RIG, Woodward M, Ismail K (2008) First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analyses. Br J Psychiatry 192: 406-411

92. Bushe CJ, Taylor M, Haukka J (2010) Mortality in schizophrenia: a measurable clinical endpoint. J Psychopharmacol 24 (Suppl 4): 17-25

93. Weinmann S, Read J, Aderhold V (2009) Influence of antipsychotics on mortality in schizophrenia: Systematic review. Schizophr Res 113: 1-11

94. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J (2009) 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort-study (FIN11 study). Lancet 374: 620- 627

95. de Hert M, Correll CU, Cohen D (2010) Do antipsychotic medication reduce or increase mortality in schizophrenia? A critical appraisal of the FIN-11 study. Schizophr Res 117: 68-74

96. Kelly DL, McMahon RP, Liu F, Love RC, Wehring HJ, Shim JC, Warren KR, Conley RR (2010) Cardiovascular disease mortality in patients with chronic schizophrenia treated with Clozapine: A retrospective cohort study. J Clin Psychiatry 71: 304-311

97. Stoppe G, Sandholzer H, Huppertz C, Duwe H, Staedt J (1999) Gender differences in the recognition of depression in old age. Maturitas 32: 205-212

98. Borkhoff CM, Hawker GA, Kreder HJ, Glazier RH, Mahomed NN, Wright JG (2009) Patients' gender affected physicians' clinical decisions when presented with standardized patients but not for matching paper patients. J Clin Epidemiol 62: 527-541

99. Munk-Jørgensen P (1985) The schizophrenia diagnosis in Denmark. A register-based investigation. Acta Psychiatr Scand 72: 266-273

100. Orhagen T, D'Elia G (1992) The "diagnostic history" of schizophrenia. A retrospective study of 84 Swedish inpatients. Psychopathology 25: 41-48

101. Goldacre M, Shiwach R, Yeates D (1994) Estimating incidence and prevalence of treated psychiatric disorders from routine statistics: the example of schizophrenia in Oxfordshire. J Epidemiol Comm Health Care 48: 318-322

102. Chen RY, Swann AC, Burt DB (1996) Stability of diagnosis in schizophrenia. Am J Psychiatry 153: 682-686

103. Kreitman N et al (1961) The reliability of psychiatric assessment: an analysis. J Ment Sci 107: 887-908

104. Schwartz JE, Fennig S, Tanenberg-Karant M, Carlson G, Craig T, Galambos N, Lavelle J, Bromet EJ (2000) Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. Arch Gen Psychiatry 57: 593-600

105. Häfner H, an der Heiden W (1999) The course of schizophrenia in the light of modern follow-up studies: the ABS and WHO studies. Eur Arch Psychiatry Clin Neurosci 249 Suppl 4:14-26

106. Nordentoft M, Jeppesen P, Petersen L, Bertelsen M, Thorup A (2009) The rationale for early intervention in schizophrenia and related disorders. Early Interv Psychiatry 3: 53-57

107. Cotton SM, Lambert M, Schimmelmann BG, Foley DL, Morley KI, McGorry PD, Conus P (2009) Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis. Schizophr Res 114: 17-24

108. Køster A, Lajer M, Lindhardt A, Rosenbaum B (2008) Gender differences in first episode psychosis. Soc Psychiatry Psychiatr Epidemiol 43: 940-946

109. Morgan VA, Castle DJ, Jablensky AV (2008) Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of low prevalence (psychotic) disorder. Aust NZ J Psychiatry 42: 74-82

110. Thorup A, Petersen L, Jeppesen P, Ohlenschloeger J, Christensen T, Krarup G, Jorgensen P, Nordentoft M (2007) Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study. J Nerv Ment Dis 195: 396-405

111. Larsen TK, Melle I, Auestad B, Friis S, Haahr U, Johannessen JO, Opjordsmoen S, Rund BR, Simonsen E, Vaglum P, McGlashan TH (2006) Substance use in first-episode non-affective psychosis. Schizophr Res 88: 55-56

112. Larsen TK, McGlashan T, Moe LC (1996) First-episode schizophrenia: I. Early course parameters. Schizophr Bull 22: 241-256

113. O'Callaghan E, Turner N, Renwick L, Jackson D, Sutton M, Foley SD, McWilliams S, Behan C, Fetherstone A, Kinsella A (2010) First episode psychosis and the trail to secondary care: health-seeking and health-system delays. Soc Psychiat Epidemiol 45: 381-391

114. Feudenreich O, Schulz SC, Goff DC (2009) Initial medical work-up of first-episode psychosis: a conceptual review. Early Interv Psychiatry 3: 10-18

115. Devon HA, Zerwic JJ (2002) Symptoms of acute coronary syndromes: are there gender differences? A review of the literature. Heart Lung 31: 235-245

116. Steihaug S, Rutle O (1997) Seeking of medical advice by Pakistani immigrants (In Norwegian). Tidsskr Nor Lægeforen 117: 2440-2443

117. Tabenkin H, Goodwin M, Zyzanski SJ, Stange K, Medalie JH (2004) Gender differences in time spent during direct observation of doctor-patient encounters. J Women's Health 13: 341-349

Paper 1

Paper 2

Paper 3

Appendix 1

Case description

Background for admission

A 27-year-old woman, who during the last 4–5 weeks has isolated herself and has suffered from increasing mental symptoms. The last 2 weeks she has stayed away from her job as a salesperson, without giving any reason. She has isolated herself at home, her colleagues and parents have tried to contact her by phone several times without success. The day before admission to hospital she came to her parents' house at 4 o'clock in the morning, at that point she seemed anxious and suspicious. She spoke quite incoherently, saying that ''things are connected'', that she was ''being disturbed all the time'' and that two named, earlier class mates ''don't leave me alone''. She also talked about reincarnation and her relationship to religious matters, and accused her parents for not being open-minded. She told them she had not been sleeping for a long time, and that she was afraid that ''something terrible will happen''. Her parents took her to the GP, who recommended admission to psychiatric hospital. The patient wanted herself to be admitted.

Family/social factors

She is the youngest of three siblings. Her parents are married, they say there have been numerous conflicts at home. Mother's sister was once admitted to psychiatric hospital for a longer period, supposedly with a diagnosis of paranoid psychosis. Apart from this there has been no known psychiatric disease in the family. The patient lives in a small flat in her uncle's house. The patient was shy in her childhood. She had some friends, and managed OK at school. During adolescence she stuck to herself, spent a lot of time with computers and music. She did not quite find her place among her friends, whom she claimed had other interests than herself. She could sometimes be quite rejecting if they tried to contact her, and her parents say she could be looked upon as a bit peculiar. She had one close friend she spent a lot of time with, but the contact was broken when the friend moved away. The patient finished high school with average grades. She went 9 months to a folk high school, but quit because she did not like it very much. She thereafter tried to study history of

religions at the University, but finished before her exam. Thereafter she has been unemployed, apart from several minor jobs in shops.
She had a 1-year relationship to a boy the same age as her when she was 20; he finished the relationship. After that she has had little contact with boys. The last couple of years she has been interested in Buddhist religion and culture, and she is in contact with some people with similar interests on the Internet. This interest has lead to conflicts with her parents, who think religious matters occupy her thoughts too much. She has some contact with friends from school, but otherwise she sticks a lot to herself.

Earlier contact with psychiatric care
She has not been admitted to hospital before. After the break with her boyfriend she had some contact with an outpatient clinic, but quit on her own initiative. After the break she experienced similar symptoms as now; the name of her boyfriend was repeated continuously and she had a clear imagination of his face in front of her. The symptoms disappeared after 2–3 weeks. Her GP has been in contact with her twice earlier, both times she has complained about diffuse muscular pain and sleeping problems. Apart from this she has had no other contact with health services.

Psychiatric present state
A 27-year-old woman, slightly strange clothing. She knows time and place. Good formal, reduced emotional contact. She answers questions, but stares at the floor and plucks her clothes. Normal to slightly lowered mood, slightly reduced mimic. Good impulse control. She confirms that the names of two classmates are constantly repeated in her head, she describes it as if her thoughts are ‘‘stuck’’. She is not able to sleep, and she gets ‘‘too many hostile thoughts’’ of these persons. She has no plans of hurting them in any way, but is afraid of her own feelings. She denies hearing voices, says it is her own thoughts she is hearing. She also denies that these persons are able to influence her directly in any way. Her symptoms started gradually after she met them on the street 6 weeks ago, and they did not say hello to her. She has also been thinking a lot about experiences from childhood, and she wonders whether these persons rejected her because she has done something terrible in a former life and that everything is connected in some way. She says she’s almost experiencing that ‘‘all the pieces fit’’, and that everything is becoming ‘‘a whole’’, but she ‘‘misses it just before it’s

completed''. She clamps her hands to her head, explaining that it is difficult to concentrate. She tells that she believes fully in reincarnation, that she is trying to live her life as correctly as possible so that her next life will be better than this one. She claims that she for a long time has been planning to go to India, because she by doing so will come ''home'' and be accepted as she is. She finds her strong, repeated thoughts distressing, and they make her anxious. When asked about visual hallucinations, she says that she for several years has been able to see a ''glowing aura'' around persons with personal strength, and she claims this is an ability she has developed through several years. She communicates a strong interest in religious subjects, but she does not have well defined, religious delusions.

ISBN xxx-xx-xxxx-xxx-x