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Marjo Kiviniemi

MORTALITY, DISABILITY, PSYCHIATRIC TREATMENT AND MEDICATION IN FIRST-ONSET SCHIZOPHRENIA IN FINLAND: THE REGISTER LINKAGE STUDY

UNIVERSITY OF OULU GRADUATE SCHOOL; UNIVERSITY OF OULU, FACULTY OF MEDICINE, INSTITUTE OF CLINICAL MEDICINE, DEPARTMENT OF PSYCHIATRY; OULU UNIVERSITY HOSPITAL; NATIONAL INSTITUTE FOR HEALTH AND WELFARE, CENTRE FOR HEALTH AND ECONOMICS; CITY OF OULU, SOCIAL AND HEALTH SERVICES



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MARJO KIVINIEMI

### MORTALITY, DISABILITY, PSYCHIATRIC TREATMENT AND MEDICATION IN FIRST-ONSET SCHIZOPHRENIA IN FINLAND: THE REGISTER LINKAGE STUDY

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in the OP auditorium (L10), Linnanmaa, on 21 November 2014, at 12 noon

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#### Abstract

The focus of this study was to examine mortality, disability, psychiatric treatment and medication utilizing register-based five-year follow-up data on all first-onset schizophrenia patients between the years 1995 to 2003 in Finland. The data were obtained from the Finnish Hospital Discharge Register, the national Finnish Causes of Death Register, and registers of pensions and reimbursed medicines.

People with first-onset schizophrenia had a 4.45-fold higher mortality rate than the general population. Mortality was significantly elevated in all age groups. The most prominent single unnatural cause of death was suicide and the most common natural cause of death was circulatory diseases.

Half of all first-onset schizophrenia patients retired on disability pension within the five-year follow-up period. Men retired at an earlier age and more commonly than women. Regional differences in mortality and disability retirement were evident.

Patients first identified as outpatients had better outcomes than patients first identified following hospitalization. In total, 40% of outpatient-treated patients and 74% of hospital-treated patients had experienced a relapse during follow-up period.

The use of second generation antipsychotics (SGAs) was associated with reduced risk of allcause mortality, while clozapine was associated with lower suicide risk. First generation antipsychotics (FGAs) were associated with increased all-cause mortality and, particularly chlorprothixene, with increased suicide mortality. An increased likelihood of cardiovascular death was found among users of levomepromazine. In antidepressants, use of mirtazapine was associated with increased risk of suicide.

In this study, the results and outcomes of first-onset schizophrenia patient treatment were analysed using register-based data. The results indicate that the outcome of first-onset schizophrenia is not good enough. Regional differences were seen in mortality and treatment practices. In clinical work more attention should be paid to health promotion and somatic screening, but also treatment of depressive symptoms. The results indicate that more effective treatments and rehabilitation are needed along with improved equality of treatment practices between hospital districts.

*Keywords:* antipsychotics, disability, mortality, psychiatric treatment, regional differences, schizophrenia

#### Kiviniemi, Marjo, Rekisteritutkimus uusien skitsofreniapotilaiden kuolleisuudesta, työkyvyttömyydestä, sairaalahoidosta ja lääkehoidosta Suomessa.

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#### Tiivistelmä

Tavoitteena oli tutkia skitsofreniaan sairastuneiden kuolleisuutta, työkyvyttömyyttä ja sairaalahoitoa sekä selvittää lääkehoidon yhteyttä kuolleisuuteen. Tutkimusaineistona olivat hoitoilmoitus-, kuolinsyyrekisteri-, eläkerekisteri- ja lääkekorvattavuustiedot. Tutkimusjoukkona olivat vuosien 1995-2003 aikana skitsofreniaan sairastuneet henkilöt. Seuranta-aika oli 5 vuotta.

Skitsofreniaa sairastavien kuolleisuus oli 4.4 -kertainen normaaliväestöön verrattuna. Kuolleisuus oli korkeaa kaikissa ikäryhmissä sairastumisiästä riippumatta. Yleisin kuolinsyy oli itsemurha. Yleisin luonnollinen kuolinsyy olivat sydän- ja verenkiertoelinten sairaudet.

Skitsofreniaan sairastuneista puolet jäi työkyvyttömyyseläkkeelle viiden vuoden seurannan aikana. Miehet eläköityivät nuorempina ja useammin kuin naiset. Kuolleisuudessa ja eläkkeelle siirtymisessä oli havaittavissa alueellista vaihtelua. Avohoidossa hoidetuilla vasta skitsofreniaan sairastuneilla oli parempi ennuste kuin sairaalahoitoon joutuneilla. Heidän kuolleisuutensa sekä sairaalahoitopäivien, relapsien ja vastentahtoisen hoidon määrät olivat alhaisemmat kuin sairaalassa hoidetuilla.

Toisen polven antipsykoottien käyttö oli yhteydessä alentuneeseen kuolleisuuteen ja ensimmäisen polven antipsykootit kohonneeseen kuolemanriskiin. Klotsapiinin käyttö oli yhteydessä alhaisempaan itsemurhariskiin, kun taas masennuslääkkeistä mirtatsepiinin käyttö liittyi kohonneeseen itsemurhariskiin.

Skitsofrenian hoidon kehittymisestä huolimatta sairauden ennuste on edelleen huono. Skitsofreniaa sairastavilla on yhä korkeampi kuolleisuusriski kuin muulla väestöllä. Hoitomenetelmien kehittymisestä huolimatta puolet sairastuneista on työkyvyttömyyseläkkeellä viiden vuoden kuluessa sairastumisesta. Sairauden vakavuutta osoittaa myös se, että iso osa skitsofreniaan sairastuneista tarvitsee useamman sairaalahoitojakson ja tahdosta riippumatonta hoitoa. Lisäksi useat tarvitsevat tuettua asumispalvelua.

Skitsofrenian somaattisten sairauksien ja masennusoireiden arviointi vaatii edelleen huomioita. Hoitoon ja kuntoutukseen pitää panostaa ja taata, että skitsofrenian hoito olisi yhtä laadukasta koko Suomessa. Potilaat ovat eriarvoisessa asemassa, mikäli hoitokäytännöt ja mahdollisuus saada kuntoutusta vaihtelevat asuinpaikasta riippuen.

*Asiasanat:* alueelliset eroavaisuudet, antipsykootit, kuolleisuus, sairaalahoito, skitsofrenia, työkyvyttömyys

To my father

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Kempele, October 2014

Marjo Kiviniemi

# Abbreviations

APA	American Psychiatric Association
BMI	Body Mass Index
CI	Confidence Interval
DSM	Diagnosis and Statistical Manual of Mental Disorders
DSM-III-R	Diagnosis and Statistical Manual of Mental Disorders. 3 <sup>rd</sup> edition,
	revised
DUI	Duration of untreated illness
DUP	Duration of untreated psychoses
Exp	Expected number
FCP	Finnish Centre for Pensions
FGA	First-generation antipsychotic
FHDR	Finnish Hospital Discharge Register
GAF	Global Assessment of Functioning
HP	Hospitalized patients
ICD	Manual of International Statistical Classification of Diseases and
	Causes of Death
ICD-10	Manual of International Statistical Classification of Diseases and
	Causes of Death, 10 <sup>th</sup> edition
NFBC	Northern Finland Birth Cohort
Obs	Observed number
OR	Odds ratio
OTP	Outpatient-treated patients
PERFECT	PERFormance, Effectiveness and Cost of Treatment episodes project
PYLL	Potential Years of Life Lost
RR	Relative Risk
SD	Standard Deviation
SGA	Second-generation antipsychotic
SII	Social Insurance Institution
SMR	Standardized mortality ratio
THL	National Institute for Health and Welfare
WHO	World Health Organization

# List of original publications

This dissertation is based on the following four original publications, which are referred to in the text by the Roman numerals I–IV.

- I Kiviniemi M, Suvisaari J, Pirkola S, Häkkinen U, Isohanni M & Hakko H (2010) Regional differences in five-year mortality after a first episode of schizophrenia in Finland. Psychiatric Services 61(3):272–279.
- II Kiviniemi M, Suvisaari J, Pirkola S, Läksy K, Häkkinen U, Isohanni M & Hakko H (2011) Five-year follow-up study of disability pension rates in first-onset schizophrenia with special focus on regional differences and mortality. General Hospital Psychiatry 33:509–517.
- III Kiviniemi M, Suvisaari J, Isohanni M, Saarento O, Häkkinen U, Pirkola S & Hakko H (2013) The characteristics and outcomes of hospitalized and outpatient-treated firstonset schizophrenia patients: a five-year register linkage study. The International Journal of Clinical Practice 67 (11): 1105–1112.
- IV Kiviniemi M, Suvisaari J, Koivumaa-Honkanen H, Häkkinen U, Isohanni M & Hakko H. (2013). Antipsychotics and mortality in first-onset schizophrenia: prospective Finnish register study with 5-year follow-up. Schizophrenia Research 150(1):274–80.

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### 1 Introduction

Schizophrenia is a severe mental disorder characterized by abnormalities in the perception or expression of reality. Common clinical symptoms include delusions, hallucinations and disorganized thinking (WHO 2012). In Finland, lifetime prevalence of schizophrenia is 0.87% (Perälä *et al.* 2007). The prevalence is subject to regional variation, being higher in Northern Finland (1.84%) compared to the regions of Eastern (1.07%), Southern (0.92%), Western (0.78%) and South-Western Finland (0.63%) (Perälä *et al.* 2008).

Schizophrenia varies in severity from person to person. Severity of schizophrenia can be seen among declining functional ability, diminishing social relationships, recurrent hospitalization, premature retirement and increased mortality. Schizophrenia patients have an approximately 20% shorter life expectancy compared to the general population (Hennekens *et al.* 2005). In Finland, life expectancy in men is 15.5 years shorter and in women 11 years shorter than general population (Nordentoft *et al.* 2013).

Schizophrenia often leads to a progressive decline in cognitive and psychosocial functioning and consequent work disability (Minatogawa-Chang *et al.* 2009, Rannikko *et al.* 2012, Rossler *et al.* 2005). Nearly 60% of schizophrenic patients in Finland are pensioned on average 10 years after onset of the disorder (Miettunen *et al.* 2007). Negative symptoms, early onset and long duration of untreated psychosis are predictors of disability due to schizophrenia (Alptekin *et al.* 2005). Disability pension and unemployed status are associated with weakened social competence, decreased quality of life, economic losses, and increased need for health services (Klazinga *et al.* 2001, Kouzis & Eaton 2000, Marwaha & Johnson 2004).

Treatment of schizophrenia has changed in recent decades. After an era of rapid deinstitutionalization, patients with schizophrenia are being increasingly diagnosed and treated in exclusively outpatient settings. There are still many patients who need hospital treatment for acute psychoses, but in general, the length of hospital treatment periods have shortened. (Nenonen *et al.* 2001, Pylkkänen 2012).

In recent decades, second-generation antipsychotics have become the firstline treatment of choice for first-onset schizophrenia (Buchanan *et al.* 2010). At the same time, the role of first and second-generation antipsychotic medication in excess mortality has gained increasing interest. The use of any antipsychotics is associated with lower mortality in people with schizophrenia (Tiihonen *et al.*  2006, Tiihonen *et al.* 2011), in particular suicide mortality (Haukka *et al.* 2008). However, taking more than one antipsychotic concurrently is associated with increased risk of premature death (Joukamaa *et al.* 2006, Waddington *et al.* 1998). Excess mortality has been particularly associated with the use of first generation antipsychotics (Cullen *et al.* 2012, Montout *et al.* 2002, Tenback *et al.* 2012).

The focus of this doctoral dissertation is on the mortality, disability pension, psychiatric treatment and medication of first-onset schizophrenia patients in Finland. The aim was to analyse these four aspects by utilizing the Finnish national registers. The analysis comprised the following four stages. Firstly, the regional mortality of first-onset schizophrenia patients was compared with that of the general population. Secondly, the outcome of schizophrenia treatment was evaluated using the disability pension rate as an indicator. Thirdly, outcomes between hospitalized and outpatient-treated first-onset patients were compared. And fourthly, the impact of the most commonly used first- and second-generation antipsychotics on the mortality of patients with first-onset schizophrenia was assessed. Mortality, disability pension, psychiatric treatment and medication were chosen as focus areas because information on these outcome indicators are measurable from the Finnish national registers and they can be consider to illustrate the effectiveness of the services. Special focus was placed on regional differences in mortality and disability at the hospital district level in Finland.

## 2 Literature review

The literature review content reflects the themes of the original publications, from schizophrenia as a disease to mortality, disability pension, hospital treatment and medication among first-onset schizophrenia patients.

#### 2.1 Schizophrenia

As summarized by WHO, schizophrenic disorders are characterized in general by fundamental and characteristic distortions of thinking and perception, and affects that are inappropriate or blunted. Clear consciousness and intellectual capacity are usually maintained, although certain cognitive deficits may evolve in the course of time. The psychopathological phenomena of schizophrenic disorders include thought echo; thought insertion or withdrawal; thought broadcasting; delusional perception and delusions of control; influence or passivity; hallucinatory voices commenting or discussing the patient in the third person; thought disorders and negative symptoms. (WHO 2012).

Schizophrenia is a severe psychiatric disorder. Onset of the illness usually occurs in young adulthood, a time when individuals are typically beginning a productive career. People with schizophrenia are typically unable to continue in employment or education (Schultz & Andreasen 1999). Schizophrenia often leads to a progressive decline in cognitive and psychosocial functioning and consequent work disability (Rossler *et al.* 2005), but symptomatic and functional remission is also possible. A systematic review of over 50 studies found that 13.5% of patients of schizophrenia met the criteria for recovery (Jääskeläinen *et al.* 2013). In a Danish study, 14% of people in first-episode psychosis met the criteria for symptomatic and psychosocial recovery at 10 years (Austin *et al.* 2013).

#### 2.1.1 Diagnosis and symptoms

There are two main diagnostic classification systems for mental disorders: the American Psychiatric Association's (APA) Diagnosis and Statistical Manual for Mental Disorders (DSM) (APA 1994) and the World Health Organization's (WHO) International Classification of Diseases and Causes of Death (ICD) (WHO 2012). During 1987–1995 in Finland, the ICD 9th Revision (ICD-9) with DSM-III-R criteria, called the Finnish Classification of Diseases 1987, was used (WHO 1993). Since 1<sup>st</sup> January 1996, the ICD-10 has been the official diagnostic

classification system (WHO 2012). Major diagnostic criteria for schizophrenia based on these two diagnosis classification systems are presented in Table 1.

Diagnosis	Codes	Characteristic symptoms		
classification		At minimum one of the following	Or two or more symptoms of the following	Duration
system		symptoms		
Finnish	295 Schizophrenia	Delusions, hallucinations	Social withdrawal	A period of 6
Classification	2951 Schizophrenia hebephrenica	Catatonic behaviour	Lowering of social performance	months or more
of Diseases	2952 Schizophrenia catatonica	Disorientation of thinking	Bizarre behaviour	
1987	2953 Schizophrenia paranoica	Flat affect or inappropriate affect	Reduced personal hygiene and self-care	
(years 1987–	2954A Psychosis		Flat affect or inappropriate affect	
1995)	schizophreniformis		Speech incoherent, rambling or impoverished	
	2956 Schizophrenia residualis		Delusion or magical thinking	
	2957A Psychosis schizo-affectiva		Hallucinations	
	2969 Schizophrenia NUD		Lack of initiative or loss of interest	
	(unspecified)			
ICD-10 (since	F20 Schizophrenia	Thought echo, thought insertion or	Persistent hallucinations;	A period of 1
1996–)	F20.0 Paranoid schizophreia	withdrawal or thought broadcasting;	Breaks or interpolations in train of thought	month or more
	F20.1 Hebephrenic schizophrenia	Delusions of control, influence, or	resulting in incoherence, irrelevant speech or	
	F20.2 Catatonic schizophrenia	passivity, clearly referred to body or	neologisms;	
	F20.3 Undifferentiated	limb movements or specific	Catatonic behaviour	
	schizophrenia	thoughts, actions, or sensations;	"Negative" symptoms such as marked apathy,	
	F20.4 Post schizophrenic depression	delusional perception;	paucity of speech, and blunting	
	F20.5 Residual schizophrenia	Hallucinatory voices;	A significant and consistent change in the	
	F20.6 Simple schizophrenia	Persistent delusions of other kinds	overall quality of some aspects of personal	
	F20.8 Other schizophrenia	that are culturally inappropriate and	behaviour, manifest as loss of interest,	
	F20.9 Schizophrenia, unspecified	completely impossible	aimlessness, idleness, a self-absorbed	
			attitude, and social withdrawal.	

Symptoms of schizophrenia are categorized as either positive or negative. Positive symptoms include prominent delusions, hallucinations, positive formal thought disorder, and persistently bizarre behaviour. Negative symptoms include affective flattening, alogia, avolition, anhedonia, and attentional impairment. (Andreasen & Olsen 1982).

Schizoaffective disorder (ICD-9 with DSM-III-R: 2957A, ICD-10: F25) is an episodic disorder in which both affective and schizophrenic symptoms are prominent but symptoms do not justify a diagnosis of either schizophrenia or depressive or manic episodes. In DSM-III-R, schizoaffective disorder is classified as a sub-type of schizophrenia. In ICD-10 it is classified separately under the category Schizophrenia, schizotypal and delusional disorders (F20-F29). (WHO 1993).

In previous studies in which diagnoses are based on DSM coding systems, schizoaffective disorder has always been included in the sample of patients with schizophrenia (Allebeck & Wistedt 1986, Caron *et al.* 2005, Enger *et al.* 2004, Hannerz *et al.* 2001, Heilä *et al.* 2005, Lindenmayer *et al.* 2003, Meltzer *et al.* 2004b). In addition, also in later studies schizoaffective disorder is often included in the sample of patients with schizophrenia (Ascher-Svanum *et al.* 2010, Boden *et al.* 2011, Boter *et al.* 2010, Capasso *et al.* 2008, Cougnard *et al.* 2007, Craig *et al.* 2006, Katona *et al.* 2014, Reichert *et al.* 2008, Tiihonen *et al.* 2006), which facilitates the comparison of results between studies.

#### 2.1.2 First-onset schizophrenia

First-onset of illness in medicine typically means the first appearance of the signs or symptoms of an illness (Shiel & Stöppler c2008). First onset of schizophrenia can be described by the following two definitions: first sign of disorder, and first psychotic symptom. The first sign of disorder is the beginning of the prepsychotic prodromal stage and the first psychotic symptom is the beginning of the duration of untreated psychosis (DUP).

The prepsychotic prodromal stage is defined as the time period between first sign of disorder and first psychotic symptoms. The mean duration of the prepsychotic prodromal stage (first negative or non-specific sign of mental disorder) in schizophrenia lasts approximately five years. The onset of first positive symptoms indicates the initiation of a psychotic prophase, which lasts 1.3 years. (Häfner & Nowotny 1995, Häfner & Maurer 2006). The first-onset of schizophrenia is often a period of diagnostic uncertainty and the first sign of symptoms could come months or years before the first negative or positive symptoms. The time between

first sign and first hospital admission is shown to be about six years. (Häfner 1998, Häfner & Maurer 2006, Maurer & Häfner 1995).

The time between the first psychotic symptoms and the initiation of adequate psychiatric treatment is called the duration of untreated psychosis (DUP). Adequate psychiatric treatment is, for example, medication or psychiatric hospitalization. (Marshall *et al.* 2005, Penttilä *et al.* 2014).

In the first-onset schizophrenia studies, first-onset is usually defined as the first contact for psychosis or first psychiatric hospitalization (Heilä *et al.* 2005, Laursen *et al.* 2007, Mortensen & Juel 1993, Ösby *et al.* 2000). First onset of schizophrenia in an individual generally occurs in late adolescence or early adulthood. Men have an earlier onset of schizophrenia than women. Onset is typically at age 18–25 years in men and 25–35 years in women. (Castle *et al.* 1993, Häfner *et al.* 1998a, Leung & Chue 2000, Maurer & Häfner 1995, Ochoa *et al.* 2012).

#### 2.2 Mortality among patients with schizophrenia

The disease severity of schizophrenia is reflected in the high mortality of patients. Patients with schizophrenia have an increased risk of premature death (Brown *et al.* 2000, Chesney *et al.* 2014, Hannerz *et al.* 2001, Joukamaa *et al.* 2001, Kredentser *et al.* 2014, Laursen *et al.* 2013a, Saha *et al.* 2007, Ösby *et al.* 2000) and approximately 20% reduced life expectancy compared with the general population (Hennekens *et al.* 2005, Laursen *et al.* 2013a). In Finland, the life expectancy for schizophrenia-like psychoses is approximately 11 years less for women and 16 years less for men compared to the general population (Nordentoft *et al.* 2013).

Patients with schizophrenia have increased risk of death from both natural and unnatural death causes (Brown *et al.* 2000, Dutta *et al.* 2011, Saha *et al.* 2007). Recent evidence has indicated that the mortality gap compared with the general population has increased (Dutta *et al.* 2011, Hoang *et al.* 2011, Hoye *et al.* 2011, Saha *et al.* 2007). One Finnish study has shown that the life expectancy of patients with schizophrenia has remained lower than the general Finnish population while the use of second-generation antipsychotics has increased (Tiihonen *et al.* 2009).

In previous studies, schizophrenia patients' risk of premature death from all causes has varied from 1.8 and 3-fold compared to the general population or controls (Black 1998, Brown *et al.* 2000, Chesney *et al.* 2014, Dutta *et al.* 2011, Kredentser *et al.* 2014, Saha *et al.* 2007). In the Finnish 17-year follow-up study of persons aged 30 and over, the age and gender adjusted relative mortality risk was

2.8 among patients with schizophrenia compared with the general population. Relative mortality risk was 2.25 after adjusting for somatic diseases, blood pressure, cholesterol, body mass index, smoking, exercise, alcohol use and education. (Joukamaa *et al.* 2006). In a Swedish study, 10-year mortality rate for patients with schizophrenia was twice as high as the general population (Fors *et al.* 2007).

#### 2.2.1 Natural causes of death

Of all deaths of schizophrenia patients, the proportion attributed to natural causes is reported to be 72–84% (Capasso *et al.* 2008, Dutta *et al.* 2011, Harris & Barraclough 1998, Hiroeh *et al.* 2001). The most common single natural causes of death are shown to be cardiovascular or respiratory diseases and cancers (Brown *et al.* 2000, Capasso *et al.* 2008, Dutta *et al.* 2011, Harris & Barraclough 1998, Joukamaa *et al.* 2001, Saha *et al.* 2007). Schizophrenia patients' mortality risk due to natural causes is reported to vary from 1.84 to 2.41 compared to the general population (Black 1998, Brown *et al.* 2000, Saha *et al.* 2007). Men with schizophrenia are reported to have a higher risk of premature mortality due to natural causes of death than women with schizophrenia (Brown *et al.* 2000, Dutta *et al.* 2001, Fors *et al.* 2007, Harris & Barraclough 1998, Ösby *et al.* 2000).

Excess mortality of schizophrenia patients is commonly explained by unhealthy lifestyle, such as smoking, alcohol abuse and obesity (Brown *et al.* 1999, Brown & Mitchell 2012, Goff *et al.* 2005) and by medication side effects, which can cause weight gain and cardiovascular diseases (Daumit *et al.* 2008, Green *et al.* 2000, Hennessy *et al.* 2002, Koponen *et al.* 2002, Koponen *et al.* 2008, Murray-Thomas *et al.* 2013, Sernyak *et al.* 2002, Volavka *et al.* 2002). There is also evidence that higher prescribed doses of antipsychotics (Osborn *et al.* 2007) or long-term exposure to antipsychotics increase the mortality of patients with schizophrenia (Weinmann *et al.* 2009).

Untreated or undiagnosed physical illnesses of psychiatric patients are suggested to be related to premature mortality (Druss *et al.* 2000, Druss *et al.* 2001, Laursen *et al.* 2013, Lawrence *et al.* 2003). For example, schizophrenia patients' metabolic disorders are often untreated (Nasrallah *et al.* 2006). In general, the quality of somatic treatment of psychiatric patients could also be poorer than the general population (Druss *et al.* 2000, Druss *et al.* 2001, Laursen & Nordentoft 2011, Lawrence *et al.* 2003) and individuals with schizophrenia are rarely treated for their physical illness in its early, less severe phases (Muck-Jorgensen *et al.* 2000). Active psychoses may be an independent predictor of death from natural causes because psychoses may interfere with the patient's ability to recognize and describe symptoms of illness, keep appointments and adhere to treatment (Brown & Mitchell 2012).

The most common single natural cause of death in schizophrenia patients is cardiovascular disease (Brown *et al.* 2000, Capasso *et al.* 2008, Dutta *et al.* 2011, Harris & Barraclough 1998, Joukamaa *et al.* 2001, Saha *et al.* 2007) due to high prevalence of metabolic syndrome and dyslipidaemia (Joshi *et al.* 2013). Compared to the general population, patients with schizophrenia have a 1.4–2.8 fold risk of cardiovascular death, and the risk is higher in younger schizophrenia populations (Dutta *et al.* 2011, Fors *et al.* 2007, Kredentser *et al.* 2014, Osborn *et al.* 2007, Saha *et al.* 2007). Life expectancy is approximately 17.1 years shorter for men and 15.6 years shorter for women in schizophrenia with circulatory system disease (Laursen *et al.* 2013b).

Risk of death due to respiratory diseases is also notably higher than the general population at 2.0-3.5 –fold (Brown *et al.* 2000, Dutta *et al.* 2011, Kredentser *et al.* 2014, Saha *et al.* 2007, Ösby *et al.* 2000). Although risk of cancer has been shown to be lower among persons diagnosed with schizophrenia (Cohen *et al.* 2002), the relative risk of death due to neoplastic diseases has been shown in a Swedish study to be 1.2-fold (Fors *et al.* 2007) and in another systematic review 1.33-fold (Saha *et al.* 2007) compared to the general population. In an English study, schizophrenia patients had an 11.7-fold risk of endocrine disease (Brown *et al.* 2000), although in systematic reviews the risk was claimed to be lower (SMR 2.3–4) (Harris & Barraclough 1998, Saha *et al.* 2007).

Mortality risk assessment approaches vary greatly. Comparison of risk estimates between different studies must therefore be done with great caution, since the characteristics of the patient sample, and follow-up times in relation to mortality can vary considerably.

#### 2.2.2 Unnatural causes of death

Unnatural deaths are considered to include deaths due to suicide, accidents or homicide. Finland has an annual suicide rate of 16 per 100,000 population. In the 2010s, the suicide mortality per 100,000 inhabitants has been highest in the regions of North Karelia, Kainuu, Central Finland, Lapland, Kanta-Häme and Etelä-Savo, and lowest in the regions of Ostrobothnia and Uusimaa. (SOTKAnet 2014 by THL).

Among schizophrenia patients the risk of death from unnatural causes is as high as 8.1-fold compared to the general population (Saha *et al.* 2007). In the Swedish 10-year mortality study of persons with schizophrenia, the relative risk of death from unnatural causes was 4.3-fold (Fors *et al.* 2007).

Suicide is the most common single unnatural cause of death in patients with schizophrenia (Brown *et al.* 2000, Craig *et al.* 2006, Dutta *et al.* 2011, Harris & Barraclough 1998, Rantanen *et al.* 2009) and it usually occurs close to onset of the disease (Alaräisänen *et al.* 2009, Bertelsen *et al.* 2007, Nordentoft *et al.* 2004a, Palmer *et al.* 2005, Qin & Nordentoft 2005). Overall, the lifetime suicide risk in schizophrenia is estimated to be approximately 5% (Hor & Taylor 2010, Palmer *et al.* 2005). Compared to the general population, the risk of suicide among schizophrenia patients has been reported to vary from 8.7 to 16-fold (Kredentser *et al.* 2014, Limosin *et al.* 2007, Saha *et al.* 2007).

Sociodemographic risk factors for suicide of patients with schizophrenia are related to young age, male gender, and a high level of education, while illnessrelated risk factors are reported to be number of prior suicide attempts, depressive symptoms, active hallucinations and delusions. A family history of suicide and comorbid substance misuse are positively associated with increased likelihood of suicide. (Hor & Taylor 2010, Sanchez-Gistau et al. 2013). Suicide prevention has conventionally relied on identifying the individual's risks with successive treatment of comorbid depression, substance misuse and psychotic symptoms (Challis et al. 2013, Hor & Taylor 2010). According to Buchanan and colleagues, schizophrenia patients who exhibit marked and persistent suicidal thoughts or behaviours should be considered for medication with clozapine (Buchanan et al. 2010). Clozapine treatment is associated with a three-fold overall reduction in risk of suicidal behaviour compared to other antipsychotics (Hennen & Baldessarini 2005). Pharmacotherapy used in suicide prevention is, however, problematic. Clozapine is not a first-choice medication and does not offer a general solution to suicidality in schizophrenia, especially among first-onset patients (Filakovic & Eric 2013).

Patients with schizophrenia also have a 2.5-fold risk of accidental death (Crump *et al.* 2013a, Saha *et al.* 2007). Risk of unspecified violence was in men 11.7-fold and in women 9.9-fold compared to the general population (Ösby *et al.* 2000). In a Danish study, the risk of death by homicide was 7.4-fold in male and 3.4-fold in female schizophrenia patients (Hiroeh *et al.* 2001). The results of a recent Swedish study showed the homicide risk to be 1.8-fold among patients with schizophrenia compared to the general population (Crump *et al.* 2013b).

#### 2.3 Disability pension

In Finland, the granting of disability pension is a multi-phased process. Disability pension can be granted to persons aged 16-62 years. Disability is determined based on a medical certificate on the state of health of the patient. The disability pension process generally begins with a physician's estimate of a decrease in working ability of at least 3/5 of the individual's original capacity. The illness must be such that it deprives the patient of their work capacity totally or partially for at least one year. The authorized pension provider determines whether the applicant's work capacity has decreased so much that the applicant is entitled to a full disability pension, or whether a cash rehabilitation benefit or a partial disability pension is appropriate. The pension provider may also reject the application. (FCP 2014). In Finland, approximately 25% of all disability pension applications are rejected (Blomgren & Virta 2012) and 9% of disability pension applications for schizophrenia are rejected (Gould & Nyman 2012). When making a pension decision, the applicant's age, previous work experience, education, family relations and place of residence are taken into account, as well as their ability for suitable employment despite the illness. The decision regarding permanent disability pension is usually preceded by one or two temporary reimbursement periods, which usually means that the incapacity for work has lasted one year. (FCP 2014).

In 2012, 32% of all disability pensions granted in Finland were on the grounds of mental or behavioural disorders. Of all mental and behavioural disorders, the most common grounds for disability pension were mood disorders (19.4%) followed by schizophrenia, schizotypal and delusional disorders (5.1%). In the 16 to 44 age group, mood disorders was the most common and schizophrenia, schizotypal and delusional disorders the second most common reason for disability pension. About 1,280 people are granted disability pension for schizophrenia, schizotypal and delusional disorders per year in Finland. (Nyman *et al.* 2012).

#### 2.3.1 Disability pension in schizophrenia

Schizophrenia often leads to a progressive decline in cognitive and psychosocial functioning and consequent work disability (Rossler *et al.* 2005). Nearly 60% of schizophrenic patients in Finland are pensioned on average 10 years after the onset of disease and 20% work at least part-time (Miettunen *et al.* 2007). Schizo-

phrenia patients are 4.5 times more likely to be disabled and to receive disability payments than persons without the disorder (Kouzis & Eaton 2000). Negative symptoms, early onset and long duration of untreated psychosis are common predictors of disability (Alptekin *et al.* 2005). Other predisposing factors for early retirement of patients with schizophrenia are the severity of symptoms, low functional level and need for assistance or care in everyday life, older age at first diagnosis of schizophrenia, and antipsychotic treatment with typical antipsychotics (Schnabel *et al.* 2008).

Generally, disability pension and unemployed status are associated with weakened social competence and decreased quality of life. Unemployment also brings economic losses and increased need for health services among persons with mental disorder. (Klazinga *et al.* 2001, Kouzis & Eaton 2000, Marwaha & Johnson 2004). Conversely, being employed is associated with better quality of life and self-esteem of schizophrenia patients (Caron *et al.* 2005, Eklund *et al.* 2001, Marwaha & Johnson 2004, Priebe *et al.* 1998). The undesirable fact, however, is that of those having a serious mental illness, persons with schizophrenia are the least likely to be employed (Mechanic *et al.* 2002). A cross-sectional survey of 27 countries shows that people with schizophrenia commonly experience negative discrimination in many domains of life, including finding and keeping a job (Thornicroft *et al.* 2009).

In general, higher age ( $\geq$  45 years), being a woman, being unmarried, being unemployed, having poor or moderate self-rated health, being under- or overweight, having former tobacco use and being an abstainer from alcohol seem to be predictors of disability pension due to mental diagnoses (Samuelsson *et al.* 2012, Samuelsson *et al.* 2013).

#### 2.4 Treatment of schizophrenia

Schizophrenia is disease that often requires life-time treatment. The disease affects the patient's ability to function in multiple ways, and thus treatment must be designed according to each patient's individual needs and schizophrenia symptoms. The treatment of schizophrenia usually includes antipsychotic treatment and, depending on the comorbidity and symptoms, antidepressant and/or anxiolytics treatment. Comorbidities often require monitoring and treatment of somatic health, and psychosocial interventions for alcohol and substance use disorders.

Patients typically receive treatment through outpatient services. Outpatient treatment may include, for example, supportive psychotherapy, psychoeducation,

supported employment, work rehabilitation, cognitive behavioural therapy or social skill training. Patients who have ongoing contact with their families and relatives are also offered family intervention. The benefits of family intervention are nowadays widely acknowledged in clinical practice and include increased medication adherence, reduced symptoms, and reduced level of perceived stress for patients (Buchanan *et al.* 2010, Dixon *et al.* 2010, Xia *et al.* 2011). Different countries have drawn up national guidelines for the treatment and management of schizophrenia, including recommendations for medical treatment and psychosocial interventions (Buchanan *et al.* 2010, Dixon *et al.* 2010, Gaebel *et al.* 2005). In Finland, the so-called Current Care Guidelines for schizophrenia were published in 2001 by the Finnish Medical Society Duodecim and the Finnish Psychiatric Association (http://www.kaypahoito.fi/web/english/home).

Patients with schizophrenia often need hospital treatment in acute psychoses. However, since schizophrenia is often a disabling and severe disease, many patients may need long-term housing and residential support after discharge from hospital treatment.

#### 2.4.1 Relapse

Relapse means the return of signs and symptoms of a disease after remission (Medical Dictionary 2014). The operational definition of relapse in schizophrenia, however, varies greatly between studies. The most commonly used definition of relapse is admission to a psychiatric hospital or worsening symptoms of schizophrenia, especially exacerbation of positive symptoms (Alvarez-Jimenez *et al.* 2012, Gleeson *et al.* 2010, Nuechterlein *et al.* 2006, Olivares *et al.* 2013).

Regardless of the applied definition of relapse, the risk of relapse is high in schizophrenia following the first admission or episode, with relapse rates tending to increase steadily during the follow-up years. One-year follow-up studies have shown relapse rates to vary between 19–21% (Caseiro *et al.* 2012, Chen *et al.* 2005, Gleeson *et al.* 2005, Nuechterlein *et al.* 2006), while five-year follow-up studies have shown a rate of relapse of between 70–82% (Mc Creadie *et al.* 1992, Robinson *et al.* 1999). In a twenty-year longitudinal follow-up study, more than 80% of the cohort experienced relapses (Thara 2004).

Non-adherence to medication is shown to be major predictor of relapse (Alvarez-Jimenez *et al.* 2012, Caseiro *et al.* 2012, Robinson *et al.* 1999). The risk of first and second relapse was almost five times greater when not taking medication (Robinson *et al.* 1999). Other predictors of relapse are reported to be increasing symptoms, trouble sleeping, symptoms of disorganization, mood changes (Bouhlel *et al.* 2012), depressive symptoms, side effects, a worse attitude to treatment and not having a job (Schennach *et al.* 2012). Persistent substance use, carers' critical comments, and poorer premorbid adjustment, stress and prominent paranoid symptoms are also associated with relapse (Alvarez-Jimenez *et al.* 2012, Olivares *et al.* 2013, Xiang *et al.* 2011).

On the other hand, factors that reduce relapse risk in addition to antipsychotic treatment include psychoeducation and cognitive behavioural therapy. However, during these interventions schizophrenia patients are usually already users of antipsychotic treatment (Olivares *et al.* 2013). Correspondingly, higher quality of life measurements predict lower rates of relapse (Boyer *et al.* 2013).

#### 2.5 Medication in schizophrenia

Mainstream medical treatment for schizophrenia includes the use of antipsychotics, which, depending on the symptoms and comorbidities, are used along with other psychotropic medications such as antidepressants or anxiolytics. Antipsychotics have been categorized into two main groups, namely first-generation antipsychotics (FGAs, i.e. typical antipsychotics) and second-generation antipsychotics (SGAs, i.e. atypical antipsychotics) (Chien & Yip 2013).

#### 2.5.1 Antipsychotic treatment

The first antipsychotic, chlorpromazine, developed in the 1950s, was the first medicine discovered that relieved the symptoms of schizophrenia. The discovery paved the way for the next three decades of development of first-generation antipsychotics (FGAs) for the treatment of psychotic diseases. During the 1990s a new wave of antipsychotics – second-generation antipsychotics (SGAs) – were developed with the goal of achieving greater efficiency and fewer side-effects than FGAs. (Jasovic-Gasic *et al.* 2012, Meyer & Simpson 1997). Despite these advances in antipsychotic medication, the proportion of patients in recovery has not, however, increased (Jääskeläinen *et al.* 2013). Because the exact causes and disease-modifying factors of schizophrenia remain unknown, our ability to enhance medications remains severely limited.

SGAs and FGAs are both effective for reducing psychotic symptoms. There is no clear evidence for differences in efficacy between first generation and second-generation antipsychotics, but some SGAs (mainly clozapine) might have some advantages in overall efficacy and in relapse prevention. When prescribing antipsychotics, the different side-effect profiles of SGAs and FGAs must be taken into account. (Hasan *et al.* 2012). Treatment with second-generation antipsychotics is associated with weight gain and first generation antipsychotics with a greater incidence of extrapyramidal side-effects (Crossley *et al.* 2010, Geddes *et al.* 2000).

First-onset schizophrenia patients exhibit increased treatment responsiveness and sensitivity to side-effects compared to patients with multi-episode schizophrenia. Therefore, antipsychotic treatment should be started with lower doses of antipsychotics. (Buchanan *et al.* 2010). The choice of antipsychotic treatment should be based on the drug's profile of adverse effects and each patient's individual risk of developing side-effects (Hasan *et al.* 2012). Recent studies have also suggested that certain side-effects may have long-term adverse effects in patients. Especially high doses of antipsychotics might be related to brain volume loss (Fusar-Poli *et al.* 2013, Veijola *et al.* 2014) and cognitive decline (Husa *et al.* 2014, Torniainen *et al.* 2012).

Nonadherence to prescribed antipsychotic medication is common. The mean rate of nonadherence among schizophrenia patients is between 41–49% (Lacro *et al.* 2002). Nonadherence of antipsychotics has a negative impact on the course of illness, as reflected in rate of relapse, rehospitalization, time to remission and attempted suicide (Higashi *et al.* 2013, Leucht & Heres 2006).

New data on the long-term harms and effects of antipsychotics may influence and lead practitioners to more often consider lower doses and even discontinuation of medication. Current treatment guidelines are undifferentiated and vague in regards to dose tapering and discontinuation, and to recommended psychosocial interventions. (Gaebel *et al.* 2005).

#### 2.5.2 Antidepressant treatment

Depressive symptoms can occur in all phases of schizophrenia. They can interfere with role functioning and negatively impact quality of life (Buchanan *et al.* 2010). Depressive symptoms have been shown to occur in a mean of 33% of first-admission patients with psychotic symptoms, 38% of acute relapse and 29% of patients with chronic stable schizophrenia (Siris *et al.* 2001). Depressive symptoms can be a negative symptom of schizophrenia, a side-effect of antipsychotic medication or substance use (Lehman *et al.* 2004), or a symptom of comorbid depression (Buckley *et al.* 2009).

The most important groups of antidepressants are: first-generation antidepressants (tricyclic antidepressants), second-generation antidepressants (SSRI=Selective Serotonin Reuptake Inhibitor), and other antidepressants. First-generation antidepressants were developed in the 1950s and 60s. Second-generation antidepressants, developed in the 1980s, include, for example, cital-opram and fluoxetine. Other antidepressants were developed in the 1990s and later, including, for example, mirtazapine and venlafaxine. (Bauer *et al.* 2013).

First-generation antidepressants are known to be effective against major depression. They do not differ among themselves in terms of efficacy, but do exhibit different side-effect profiles. The most frequent side-effects are anticholinergic, cardiovascular, antihistaminergic and neurological side-effects. (Bauer *et al.* 2013).

Second-generation antidepressants have demonstrated superior efficacy compared to placebos, but no overall difference in efficacy between first- and secondgeneration antidepressants has been shown (Anderson 2000, Bauer *et al.* 2013). There is little or no reliable difference in effectiveness between second-generation antidepressants (Allan *et al.* 2011). In general, second-generation antidepressants are better tolerated and safer to use than first-generation antidepressants. The most frequent side-effects are gastrointestinal, activation/restlessness, sexual dysfunction and neurological. (Bauer *et al.* 2013).

Of the other antidepressants, mirtazapine has a faster onset action than second-generation antidepressants. The main side-effects of mirtazapine include weight gain and increase in appetite, but it is less likely to cause nausea or sexual dysfunction (Bet *et al.* 2013, Watanabe *et al.* 2011). Mirtazapine and venlafaxine are equally effective against major depression (Fang *et al.* 2010). Venlafaxine side-effects include profuse sweating and weight gain (Bet *et al.* 2013).

An antidepressant treatment plan should be developed on the basis of the patient history, experiences of previous treatments, clinical subtype, severity of illness and risk of suicide. Antidepressants are the first-line treatment for major depression, but antidepressant treatment might also be indicated in mild depression episodes. (Bauer *et al.* 2013). Antidepressive medication, especially citalopram, can also be beneficial in improving negative symptoms of schizophrenia (Vahia *et al.* 2013).
#### 2.5.3 Medication and mortality

The use of any antipsychotics is associated with lower mortality compared with non-use of antipsychotics (Tiihonen *et al.* 2006, Tiihonen *et al.* 2011). However, the study of Joukamaa *et al.* showed that the risk of dying increased if partisipants were taking more than one antipsychotic drug (Joukamaa *et al.* 2006). Opposite findings indicate that antipsychotic polypharmacy is not associated with increased mortality from natural causes when compared to monotherapy (Baandrup *et al.* 2010). The same result was reported by Tiihonen *et al.* (2012). In the Finnish study, the prevalence of antipsychotic polypharmacy in patients with schizophrenia was 46.2%. Antipsychotic polypharmacy was associated with long hospitalizations and long duration of illness. (Suokas *et al.* 2013).

In previous studies, people with schizophrenia appeared to have an elevated risk of death from cardiovascular disease compared to the general population, and patients receiving a high dose of antipsychotics were at even greater risk (Murray-Thomas et al. 2013, Osborn et al. 2007). Users of typical antipsychotics had a higher risk of myocardial infarction and sudden cardiac death (Enger et al. 2004, Koponen et al. 2008, Murray-Thomas et al. 2013). In a large cohort study by Ray and colleagues, patients using antipsychotics in doses of more than 100 mg of thioridazine or equivalent had a 2.4-fold increase in the rate of sudden cardiac death. The relative and absolute rates were increased among moderate-dose antipsychotics users who also had severe cardiovascular disease. (Ray et al. 2001). In later studies, thioridazine was exclusively associated with sudden cardiac death (Reilly et al. 2000, Reilly et al. 2002, Stöllberger et al. 2005) and was subsequently withdrawn from the market in 2005. The results of the CATIE schizophrenia study indicate that the impact on 10-year coronary heart disease risk differs significantly between antipsychotics, with olanzapine producing the largest elevation in coronary heart disease risk (Daumit et al. 2008). One reason for this is that SGAs, especially olanzapine and quetiapine, increase Body Mass Index (BMI), serum triglycerides, and cholesterol (O'Donoghue et al. 2013).

Suicide is one of the main causes of premature death among schizophrenia patients (Alaräisänen *et al.* 2009, Brown *et al.* 2000, O'Connor *et al.* 2014, Saha *et al.* 2007). The use of antipsychotic medication is associated with lower suicide mortality (Haukka *et al.* 2008), while patients not taking any antipsychotics have been shown to have a 37-fold risk of suicide compared to users of antipsychotics (Tiihonen *et al.* 2006).

Second-generation antipsychotics may have an antisuicide effect, but the effect seems differ between antipsychotics. Risperidone and olanzapine, in particular, may be protective against suicidality (Barak *et al.* 2004, Reutfors *et al.* 2013). Clozapine treatment is also known to prevent suicide attempts and, thus it is associated with fewer deaths due to suicide (Hennen & Baldessarini 2005, Jagodic *et al.* 2013, Meltzer *et al.* 2003, Reutfors *et al.* 2013, Ringbäck Weitoft *et al.* 2014, Sernyak *et al.* 2001). In two studies, rates of suicide or suicide attempt did not differ when comparing patients with risperidone, quetiapine or olanzapine treatment with those receiving placebo treatment (Khan *et al.* 2001, Storosum *et al.* 2003). In other studies olanzapine has been associated with reduced risk of suicide (Haukka *et al.* 2008, Ringbäck Weitoft *et al.* 2014). In the FGA group, suicide risk was 2.2-fold in users of thioxanthenes (Montout *et al.* 2002).

Depression is a major risk factor for suicidal behaviour in schizophrenia individuals (Harkavy-Friedman *et al.* 1999). In a Finnish study, no significant decrease in mortality was observed during current use of antidepressants of schizophrenia patients (Haukka *et al.* 2008). In another Finnish study, fluoxetine use was associated with the lowest risk (RR 0.5) and venlafaxine hydrochloride use with the highest risk (RR 1.6) of suicide. Among subjects who had never used antidepressants, the current use of medication was associated with a markedly increased risk of attempted suicide, but also with a markedly decreased risk of completed suicide and mortality. (Tiihonen *et al.* 2006). Furthermore, use of citalopram is reported to decrease all-cause and suicide mortality (Haukka *et al.* 2008).

#### 2.6 Regional differences in Finland

#### 2.6.1 Prevalence of schizophrenia

In the Psychoses in Finland study (substudy of the Health 2000 survey), the lifetime prevalence of all psychotic disorders was 3.48%. The most common psychotic disorder was schizophrenia, with a lifetime prevalence of 1%. Large regional variation in the prevalence of psychotic disorders was observed throughout Finland. Prevalence was three times higher in Northern Finland than in South-Western Finland. The regional variation was explained by the effect of place of birth, not current residence. The highest likelihood of having a psychotic disorder was found among people who had been born in Northern (OR 3.3) or Eastern (OR 2.97) Finland, and the likelihood was lowest among those born in South-Western (OR 1) Finland (Suvisaari *et al.* 2012). These findings are similar to an earlier Finnish study, which showed the lifetime prevalence of schizophrenia to be higher, according to place of residence, in Northern Finland (1.84%) compared to Eastern (1.07%), Southern (0.92%), Western (0.78%) and South-Western (0.63%) Finland (Perälä *et al.* 2008).

#### 2.6.2 Mental health services

In Finland, the process of deinstitutionalization started in the 1980s. The aim of the transformation was to shift the focus from institutional care towards outpatient care of psychiatric patients. While in the 1980s mental hospital beds numbered 3.9 per thousand inhabitants, by the 2000s the figure had reached 0.76 per thousand inhabitants. As hospital patients were discharged, resources were transferred from hospitals to community care. (Pylkkänen 2012). The number of psychiatric hospital beds continued to decrease across all hospital districts, while outpatient service resources increased and diversified. Today, outpatient services also include increasing numbers of third sector and private sector actors (Nielsen 2007) (http://uusi.sotkanet.fi/portal/page/portal/etusivu).

Deinstitutionalization has had four notable outcomes: 1) the number of patients in inpatient care has not reduced, 2) the length of psychiatric treatment has shortened, 3) mental health outpatient visits have increased, and 4) the amount of psychiatric housing services and support housing has increased significantly, with municipalities and the private sector increasing the supply of services. (http://uusi.sotkanet.fi/portal/page/portal/etusivu).

This shift in focus from psychiatry hospitals to outpatient mental health care has not occurred equally across all hospital districts in Finland. Many areas are suffering from a lack of psychiatrists and nurses and other key resources. In addition, in many regions distances to services are long.

Differences in treatment availability and use of services are reflected in several characteristics of the hospital districts (Table 2). Outpatient visits per 1,000 inhabitants vary from 77 to 381, being lowest in Lapland and highest in South-Western Finland. In Lapland, population density is low and the distances to services are long, which may have impacted the supply of services. (SOTKAnet 2014).

The Länsi-Pohja hospital district had the lowest length of hospital treatment (SOTKAnet 2014). The Länsi-Pohja hospital district is well-known for the com-

munity-based open dialogue approach implemented at the Keropudas hospital. The model aims at treating psychotic patients in their homes. The treatment involves the patient's social network, especially family members, and starts within 24 hours after contact. Responsibility for the entire treatment process rests with the same team in both inpatient and outpatient settings. This approach reduces hospitalization and the use of medication among patients with early psychosis. (Seikkula *et al.* 2006, Seikkula *et al.* 2011).

Higher rates of involuntary care were reported in North Karelia hospital district. The lowest rate of involuntary care was reported in the Kanta-Häme, Itä-Savo and Kainuu hospital districts. (SOTKAnet 2014).

As the number of psychiatric hospital beds has decreased, the number of clients in psychiatric rehabilitation homes has correspondingly increased. Client growth in psychiatric rehabilitation homes can be observed in all hospital districts between 1998 and 2008.

				•						
Hospital distric	t Mental	Change in	Hospital	Change in	Average	Change in	Involuntary	Change in	Clients in	Change in
	health	outpatient	days/1000	hospital	length of	length of	care/1000	involuntary	psychiatric	number of
	outpatient	visits/1000	inhabitants	days/1000	hospital	hospital	persons of	care/persons	rehabilitation	clients in
	visits/1000	inhabitants <sup>2</sup>		inhabitants <sup>2</sup>	treatment	treatment <sup>2</sup>	same age	of same age <sup>2</sup>	homes/1000	psychiatric
	inhabitants <sup>1</sup>						(age 18 or		inhabitants <sup>3</sup>	rehabilitation
							over)			homes <sup>2</sup>
Helsinki and	317	+25	373	-94	36	-9	1.1	0	0,69	+1418
Uusimaa										
Southwest	381	+104	332	-65	41	-33	1.2	+0.3	0,76	+463
Finland										
Satakunta	301	+249	333	-63	48	-28	1.1	9.0+	0,75	+172
Kanta-Häme	317	+63	358	-28	30	0	0.9	-0.3	0,69	+116
Pirkanmaa	177	-65	354	-160	40	-18	1.1	0	1,08	+472
Päijät-Häme	211	+59	314	-29	39	+	1.2	-0.3	0,98	+320
Kymenlaakso	204	-165	381	-122	55	7+7	1.5	-0.4	0,97	+331
South Karelia	127	+126	317	-129	50	-59	1.2	-0.2	1,2	+93
Etelä-Savo	206	-119	430	-185	42	-26	1.6	0	1,18	+124
ltä-Savo	197	+14	325	+32	49	-62	0.9	-0.3	0,91	+25
North Karelia	237	+25	328	4-	37	+17	1.7	9.0+	0,9	+180
Pohjois-Savo	318	+130	372	-65	32	-13	1.4	+0.2	1,06	+221
Central Finland	100 H	+105	359	-208	49	-15	1.0	-0.3	1,1	+269
South	252	+123	361	-92	42	-24	1.0	-0.2	1,24	+176
Ostrohothnia										

Table 2. Numbers of mental health services in Finland by hospital district.

39

40	Hospital distric	:t Mental	Change in	Hospital	Change in	Average	Change in	Involuntary	Change in	Clients in	Change in
		health	outpatient	days/1000	hospital	length of	length of	care/1000	involuntary	psychiatric	number of
		outpatient	visits/1000	inhabitants	days/1000	hospital	hospital	persons of	care/persons	rehabilitation	clients in
		visits/1000	inhabitants <sup>2</sup>		inhabitants <sup>2</sup>	treatment	treatment <sup>2</sup>	same age	of same age <sup>2</sup>	homes/1000	psychiatric
		inhabitants <sup>1</sup>						(age 18 or		inhabitants <sup>3</sup>	rehabilitation
								over)			homes <sup>2</sup>
	Vaasa	330	-19	364	-188	68	-23	1.1	+0.1	0,43	+71
	Central	281	+68	323	-45	39	+10	1.1	+0.1	1,07	+39
	Ostrobothnia										
	North	186	6+	343	-33	36	8-	1.2	+0.3	1,1	+371
	Ostrobothnia										
	Kainuu	140	+106	457	-50	45	-15	0.9	-0.1	1,08	+12
	Länsi-Pohja	238	-22	332	+54	29	+17	1.3	+0.1	0,93	+29
	Lapland	77	+38	340	+35	46	-25	1.7	+0.3	0,8	+70
	Finland	230	+43	350	-75	43	-15	1.2	0	0,87	+249
	Data on outpa	tient visits, hos	spital days and l	engths, medic	ines and involu	intary care o	btained via So	otkaNet by TF	HL (used figures	were averages	of 1998–2008
	data). Include:	s outpatient vis	sits in specialize	d medical cart	e and primary c	are among ¿	adults during (	1998–2008. *(	Change during 1	1998–2008. <sup>v</sup> Inc	licator gives the
	number of clie	nts in psychiati	ric rehabilitation	homes at enc	1 of year. Psych	iatric rehabi	litation homes	: housing ser	vices for people	with mental he	alth problems

#### 2.6.3 Use of antipsychotics across hospital districts

The number of antipsychotic drug prescriptions varied between hospital districts (Figure 1). The highest numbers of prescriptions were recorded in the Kainuu, North Karelia, Etelä-Savo and Central Ostrobothnia hospital districts, of which Kainuu, North Karelia and Etelä-Savo also have high morbidity of psychoses. The lowest numbers of prescriptions are in Southwest Finland, which also has the lowest psychosis morbidity. Exceptions are the hospital districts of Pohjois-Savo and North Ostrobothnia where psychosis morbidity is high, but the number of prescriptions of antipsychotics is low. The density of physicians and psychiatrists varies across hospital districts, and is not taken into account in the calculations of Figures 1–2.



### Fig. 1. Average number of antipsychotic drug (N05A) prescriptions per physician by hospital district in Finland in 2008.

Information obtained from Kelasto-report by SII (http://www.kela.fi/web/en/statistical-database-kelasto).

#### 2.6.4 Use of antidepressants across hospital districts

Figure 2 shows the average number of antidepressant prescriptions per physician for the year 2008. The highest number of prescriptions were recorded in the South Ostrobothnia, North Karelia, Kainuu and Itä-Savo hospital districts. The lowest rates were in the Helsinki and Uusimaa, Southwest Finland and North Ostrobothnia hospital districts.



Fig. 2. Average number of antidepressant drug (N06A) prescriptions per physician by hospital district in Finland in 2008.

Information obtained from Kelasto-report by SII (http://www.kela.fi/web/en/statistical-database-kelasto).

#### 2.7 Summary of the literature

The mortality of schizophrenia has been extensively studied and its excess mortality is well known. Earlier studies have shown that the life expectancy of schizophrenia patients is shorter than the general population and that they have increased risk of death from both natural and unnatural causes. Schizophrenia patients' premature mortality is explained by medication side-effects, unhealthy lifestyle, obesity, and comorbid diseases. Despite extensive research, the publication of national treatment guidelines, and heightened awareness of the issue, the mortality rate for people with schizophrenia remains markedly higher than the general population.

Schizophrenia is a disorder that often leads to progressive decline in cognitive and psychosocial functioning. The severity of the symptoms and decline in functioning ability leads to inability to work, with many patients being granted disability retirement within just a few years of onset. People with schizophrenia are 4.5 times more likely to be disabled than persons without the disorder.

The focus of mental health services has shifted to outpatient services and the number of hospital days has decreased. However, the number of patients in inpatient care has not decreased. It is also known that relapse rates are high, with most schizophrenia patients experiencing relapse. The relationship between antipsychotics and mortality has gained increasing interest. While the use of any antipsychotics has been shown to be associated with lower mortality in schizophrenia, different studies have produced varying results as regards which antipsychotics raise or lower premature mortality and in what settings. Excess mortality has been associated in many studies with lower rates of suicide and attempted suicide.

Although Finland is a relatively small country, regional differences in the prevalence of psychoses and in treatment practices are evident. The prevalence of psychoses is highest in Eastern and Northern Finland, and lowest in Southwest Finland. Regions with the highest prevalence also have the highest numbers of prescriptions of antipsychotics and antidepressants. Some hospital districts have a high prevalence of psychoses but a low rate of prescription of antipsychotics.

In general, psychiatric hospital days have decreased and outpatient visits have increased between 1998 and 2008, but it some hospital districts this trend has been less evident. The provision of psychiatric housing services and support housing has, however, increased across all hospital districts.

#### 3 Aims of the study

The purpose of the present study was to investigate first-onset schizophrenia patient mortality, disability pension rates, psychiatric treatment and medication by using Finnish health care register data. Hereafter, the Roman numerals I–IV refer to the original publications.

- 1. Analyse the gender-specific mortality of patients with first-onset schizophrenic illness over a five-year follow-up period (I).
- 2. Evaluate the rate and regional determinants of disability pension (II).
- 3. Investigate the course and outcome of schizophrenia in two groups with firstonset schizophrenia: first-onset hospitalized patients (HP) and first-onset outpatient-treated patients (OTP) (III).
- 4. Study the relationship between antipsychotic medication and mortality among first-onset schizophrenia patients (IV).

#### 4 Material and methods

#### 4.1 Data collection

Data was collected by the National Institute for Health and Welfare (THL) for the purposes of the PERFormance, Effectiveness, and Cost of Treatment episodes (PERFECT) project (http://www.thl.fi/fi/tutkimus-ja-asiantuntijatyo/hankkeet-ja-ohjelmat/perfect), a collaborative project between THL, the university hospital districts, and the Social Insurance Institution (SII) of Finland. The data for this study is based on the schizophrenia subproject of the PERFECT project, in which the main responsibility for research was granted to the Northern Ostrobothnia Hospital District (Karvonen *et al.* 2008).

The data collection and linkage between Finnish national registers was carried out by THL. Personal data was encrypted before release to the research groups. Only relevant information required by the PERFECT project was extracted from the national registers.

#### 4.2 Registers

The data for the schizophrenia subproject was based on the following national registers: the Finnish Hospital Discharge Register (FHDR) provided by THL, the Finnish Causes of Death Register (FCDR) provided by Statistics Finland, registers of disability pensions and reimbursed medicines provided by the Social Insurance Institution (SII) and the Disability Pension Register provided by the Finnish Centre for Pensions (FCP). The data in these registers were linked by a unique personal identification number assigned to each Finnish citizen.

The FHDR contains data on all admissions to Finnish psychiatric and somatic inpatient facilities since 1969. The information in the FHDR includes, for example, personal and hospital identification codes, age, gender, length of stay and primary diagnosis at discharge together with several subsidiary diagnoses. In addition to mental and general hospitals the FHDR also includes in-patient treatments in local health centres and private hospitals nationwide. The validity of the FHDR diagnoses has been shown to be acceptable for large-scale register studies (Pihlajamaa *et al.* 2008), also in psychoses and schizophrenia (Isohanni *et al.* 1997, Moilanen *et al.* 2003, Sund 2012).

The Finnish Causes of Death Register contains information based on death certificates issued by physicians. In Finland, all deaths are determined by physicians. Furthermore, a forensic medical examination is called for if the cause of death is uncertain or suspected to be caused by suicide. Finnish death certification practices have been shown to be reliable for research purposes (Lahti & Penttilä 2001).

The registers of the SII cover information on all disability pensions since 1962 and information on patients with diseases entitling special medication reimbursement since 1964. The FCP includes information on earnings-related pensions since 1962.

#### 4.3 Subjects of the study

The study population consisted of all first-onset patients of schizophrenia and schizoaffective disorders occurring between January 1<sup>st</sup>, 1995 and December 31<sup>st</sup>, 2003 (ICD-9 code 295, ICD-10 codes F20 and F25), as shown in Table 3. Although the text mentions only schizophrenia, schizoaffective disorder is also included in the study population.

Three different approaches were used to identify the study participants:

- Data included all first-admission patients with diagnoses of schizophrenia. Onset of illness was defined as the date of the beginning of the first hospitalization (ICD-9: 295, ICD-10: F20, F25) as stated in the Finnish Hospital Discharge Register (FHDR).
- 2. The Finnish disability and pension registers (SII, FCP) were scanned to identify schizophrenia patients (ICD-9: 295, ICD-10: F20, F25) who had not been hospitalized due to schizophrenia or psychoses before disability pension was granted. The onset of schizophrenia was defined as one year before the granting of disability pension due to schizophrenia (detailed explanation below).
- 3. Data included patients admitted to psychiatric hospital due to psychosis (ICD-9:297–299, ICD-19:F22, F23, F24, F28, F29) who later received diagnosis of schizophrenia in FHDR or disability pension for schizophrenia. Onset of schizophrenia of these patients was defined as the date of the beginning of the first hospitalization for psychosis.

For each eligible patient the follow-up time was five years after onset of schizophrenia.

The information on schizophrenia diagnosis was extracted from the primary diagnosis at discharge as recorded in the FHDR. This minimizes the risk of false positive cases. If a chronic schizophrenia patient is admitted to hospital due to somatic illness, it is common practice in Finland to record the somatic disease as the primary diagnosis and schizophrenia as a subsidiary diagnosis.

Participants who were identified from the register of pensions had gone through an illness evaluation process in outpatient services, lasting approximately 1 year, prior to being granted a disability pension. Their first-onset age is estimated at one year younger than the date when disability pension was granted. The follow-up period for this subgroup was started from the date of granting disability pension for schizophrenia because outpatient registers were not available at the time of data collection.

Patients over 65 years of age were excluded from the study. In addition, foreign citizens and Province of Åland residents were excluded because they might have had previous hospital admissions abroad.

#### 4.3.1 Study subjects of original publications

The study subjects of each original publication are described below, and a summary is presented in Table 3. The research data was updated with more recent data after the first original publication.

*Original publication I:* The study population consisted of all patients whose onset of schizophrenia occurred between 1 January 1995 and 31 December 2001 (n=7,591, mean age 33.5 years, men 58%).

All three approaches (see paragraph 4.3: subjects of the study) were used to identify the study subjects. The data of first-admission due to schizophrenia contained information from 3616 patients. Registers of pensions contained information from 622 patients, and the data of hospitalized patients due to psychoses and later diagnoses of schizophrenia contained information from 3353 patients.

*Original publication II:* The study population consisted of all 16- to 65-yearold patients whose onset of schizophrenia occurred between 1 January 1998 and 31 December 2001 (n=3875, mean age 32.4 years, men 58.7%). The data of this study covered only those subjects who were identified through the FHDR register.

The data of all first-admission patients with schizophrenia as a primary diagnosis contained information from 1809 patients. The data of patients who were admitted to psychiatric hospital due to other psychoses and who later received diagnosis of schizophrenia contained information from 2066 patients. All study participants were of eligible age for disability pension. None of the participants had a disability pension due to schizophrenia at the beginning of their first hospitalization for schizophrenia or psychosis.

*Original publication III.* The study population consisted of all 16- to 65-yearold patients whose onset of schizophrenia occurred between 1 January 1998 and 31 December 2003 (n=7087, mean age 33.5, men 57.8%).

Three approaches were used to identify the study participants. The data of first-admission due to schizophrenia contained information from 2878 patients. Registers of pensions contained information from 1220 patients, and data of hospitalized patients due to psychoses and later diagnoses of schizophrenia contained information from 2989 patients.

*Original publication IV:* The study population included patients presenting with first-onset schizophrenia between 1 January 1998 and 31 December 2003 (n=6987, mean age 33.8, men 58.8%).

The three different methods were used to identify the study subjects. The data of first-admission due to schizophrenia contained information from 2994 patients. Registers of pensions contained information from 1048 patients, and data of hospitalized patients due to psychoses and later diagnoses of schizophrenia contained information from 2945 patients.

Original	Participants	First-onset time	Registers	Outcomes
publicatior				
_	N=7591, first-admission patients with schizophrenia, or	1 January 1995–	FHDR, national causes of	Standardized mortality ratios
	patient with first hospitalization due to psychosis and	31 December 2001.	death register, registers of	(SMRs), potential years of life
	later diagnosis of schizophrenia, or status of disability	5-year follow-up.	disability pensions, reimbursed	lost (PYLL) per 100,000
	pension for schizophrenia. Age 8 to 65 years.		medicines (SII)	population, regional mortality.
=	N=3875, first-admission patients with schizophrenia.	1 January 1998–	FHDR, national causes of	Retirement percentage,
	Age 16 to 65 years.	21 December 2001.	death register, registers of	mortality among patients with
		5-year follow-up.	pensions (SII, FCP),	and without disability pension,
			reimbursed medicines (SII)	regional retirement percentage.
≡	N=7087, first-admission patients with schizophrenia or	1 January 1998–	FHDR, national causes of	Mortality, psychiatric hospital
	patient with first hospitalization due to psychosis and	31 December 2003.	death register, registers of	utilization, relapse rate,
	later diagnosis of schizophrenia or status of disability	5-year follow-up.	pensions (SII, FCP),	occupational functioning.
	pension for schizophrenia. Age 16 to 65 years.		reimbursed medicines (SII)	
≥	N=6987, first-admission patients with schizophrenia or	1 January 1998–	FHDR, national causes of	Use of antipsychotics and
	patient with first hospitalization due to psychosis and	31 December 2003.	death register, registers of	antidepressants, mortality.
	later diagnosis of schizophrenia or status of disability	5-year follow-up.	pensions (SII, FCP),	
	pension for schizophrenia. Age 16 to 65 years.		reimbursed medicines (SII)	
Patients of	schizophrenia also include patients with schizoaffective d	isorders (ICD-9 code 295	, ICD-10 codes F20 and F25).	

Table 3. Study design in the original papers.

#### 4.4 Assessment of Cause of Death (I–IV)

The Finnish Cause of Death Register contains all causes of death according to the ICD-9 (up to 1995) and ICD-10 (from 1996). It has been shown to be a reliable source of information. All deaths are usually diagnosed by physicians, and a forensic medical examination is called for if the cause of a death is uncertain or suspected to be caused by suicide. The Finnish death certificate form, death certification practices and cause of death validation procedures have been shown to serve the coding of causes of death for mortality statistics appropriately (Lahti & Penttilä 2001, Lahti 2005).

The causes of death classification was based on the categorization used in official statistics provided by Statistics Finland. For the purpose of this study, the causes of death were further categorized according to natural and unnatural deaths. Unnatural causes of death include codes for suicide (ICD-9 codes E950– E959B, E959X, ICD-10 codes X60–X84, Y870), accident (ICD-9 E800–E929, E970–E990, ICD-10 V01–X59, Y10–Y86, Y872, Y88–89) and homicide (ICD-9 E960–969, ICD-10 X85–Y09, Y871). All other codes were defined to be natural causes of death.

#### 4.5 Disability pension for schizophrenia (II)

Disability pension status, based on the information of the SII and FCP, was defined to be present if a patient had received disability pension during the five-year follow-up period from onset of schizophrenia. Disability pension was coded as present if the patient had a full or part-time pension or cash rehabilitation benefit status for schizophrenia. Cash rehabilitation benefit status is also included, because this temporary reimbursement period often leads to a decision about permanent disability pension status.

#### 4.6 Mental health care in hospital districts (I, II)

In Finland, psychiatric specialist-level care is provided by 21 hospital districts. The Finnish Act on Specialized Medical Care (1st Dec, 1989/1062) requires that every municipality must belong to one of these hospital districts. The Mental Health Act (1116/1990) and Mental Health Decree (1247/1990) provide the main guidelines for mental health work. Each municipality shall see to it that persons

domiciled in that municipality receive the necessary specialized medical care. Mental health services are organized primarily as non-institutional care, but they vary between different municipalities (http://www.finlex.fi/en/). In this study, hospital district is used to indicate the place of residence of the study subjects. One hospital district – the autonomous Province of Åland – was excluded from this study because its residents could have had hospital admissions abroad.

#### 4.7 Hospitalized patients group (III)

Hospitalized patients (HP) were defined as those first-onset patients who were identified through the Finnish Hospital Discharge Register (FHDR). The group includes first-admission patients with a primary diagnosis for schizophrenia, and patients who were first admitted to psychiatric hospital because of psychotic disorders but later had hospital admission or disability pension due to schizophrenia.

#### 4.8 Outpatient-treated patient group (III)

Outpatient-treated schizophrenia patients (OTP) were defined as those patients who were identified through registers of pensions (SII, FCP). The group includes non-hospitalized first-onset patients who had never been hospitalized previously due to schizophrenia but who had been granted a disability pension for schizophrenia.

#### 4.9 Definition of relapse (III)

Relapse is broadly defined as the 'next psychiatric hospital admission'. This is the only accurate and measurable definition when using health care registers as a data source. Specifically, in the hospitalized patient (HP) group a relapse was defined as the next psychiatric hospital admission following first (index) hospitalization due to schizophrenia or psychosis. In the outpatient-treated (OTP) group, a relapse was considered to be the first hospital admission after having been granted a disability pension for schizophrenia.

#### 4.10 Antipsychotics and antidepressants (IV)

Details of purchases of prescribed medication were based on register-based data obtained from the SII. For the purpose of this study, purchased antipsychotics

were categorized as first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs), and antidepressants. In addition, the four most commonly purchased FGAs, SGAs and antidepressants were extracted from the SII register and analysed separately.

The four most commonly purchased FGAs were levomepromazine, perphenazine, thioridazine and chlorprothixene. The four most commonly purchased SGAs were risperidone, clozapine, olanzapine and quetiapine. The four most commonly purchased antidepressants were citalopram, fluoxetine, mirtazapine and venlafaxine. Citalopram and fluoxetine are second-generation antidepressants (SSRIs), while mirtazapine and venlafaxine are new antidepressants.

#### 4.11 Statistical methods

Statistical analyses were performed using the SAS software package version 9.1 and 15.0, SPSS 15 for Windows, and PASW version 18.0.

*Original publication I.* The standardized mortality ratios (SMR = observed deaths/expected deaths) were calculated using the age-, gender-, place-of-residence- (i.e. hospital district) and year-of-death-matched general Finnish population as the reference population. The expected deaths are derived from national figures, while the observed deaths are the deaths in the study data. An SMR of 1 indicates that the age-standardized mortality rate in the group being studied is the same as that of the overall or standard population. A ratio less than 1 indicates a lower than average and a ratio over 1 a higher than average death rate. Hospital districts' overall SMRs and SMRs for circulatory system diseases were correlated (Pearson correlation coefficient) with a general morbidity index and morbidity index for coronary artery disease, respectively. These indexes were obtained from the index databank of ISS (http://raportit.kela.fi).

*Original publication II.* The Cox proportional hazard model was used to examine the gender difference in time from first admission for schizophrenia to granting of disability pension for schizophrenia as well as the difference in mortality between patients with and without disability pension. The hazard ratios (HRs) and 95% confidence intervals (95%CI) from the model were adjusted for age and history of physical diseases of the patients. The relationship between disability pension rates and social variables by hospital districts was assessed with Pearson's or Spearman's correlation.

Original publication III. The Cox proportional hazard model was used to estimate the effect of initial treatment setting (hospital-treated versus outpatienttreated care) on difference in mortality and relapses during the five-year followup after adjusting for age, physical diseases (yes/no) and sex.

Original publication IV. Logistic regression analysis was used to examine the association between use of antipsychotics or antidepressants and mortality (allcause, suicide, and cardiovascular death) after controlling for age, gender, patient group (hospital- vs. outpatient-treated patients) and physical diseases (yes/no). Patient groups were created as follows: patients included in the study population from the FHDR are "hospital-treated patients" and patients included from the registers for disability pension are "outpatient-treated patients". Physical diseases before the onset of schizophrenia included the following groups: hypertensive diseases, ischemic heart disease, atrial fibrillation and flutter, heart failure, atherosclerosis, diabetes mellitus, disorders of lipoprotein metabolism and other lipidemias, neoplasms, chronic obstructive pulmonary disease, asthma, epilepsy, multiple sclerosis and Parkinson's disease. For statistical analyses, these physical diseases were aggregated to form the group "Physical illness" indicating that at least one special medication reimbursement for the physical diseases listed above was prescribed to a patient or information of the diagnoses of physical diseases in the FHDR. After controlling for age, gender, physical disease (yes/no) and patient group (hospital-treated vs. outpatient), separate logistic regression analyses were conducted to examine whether FGAs and SGAs had a different effect on mortality (all-cause death, suicide, cardiovascular death) by categorizing the antipsychotics as follows: 0 = no antipsychotics, 1 = FGAs only, 2 = SGAs only, 3 = bothFGAs and SGAs.

In logistic regression, the medication was the last purchased medication prior to death or during the final six months before the end of the follow-up. Of all purchased antipsychotics, 86.6% were purchased at most 90 days before death or the end of the follow-up period. For antidepressants, 81.5% were purchased a most 90 days before death or the end of the follow up period.

#### 5 Ethical considerations and personal involvement

This study forms part of the PERFormance, Effectiveness, and Cost of Treatment episodes (PERFECT) project, which is a collaboration between the National Institute for Health and Welfare (THL), the hospital districts, and the Social Insurance Institution (SII) of Finland. The PERFECT project includes seven subprojects (stroke, preterm infants, hip fracture, bypass surgery and angioplasty, schizophrenia, acute myocardial infarction, replacement surgery). The schizophrenia subproject is headed by the North Ostrobothnia Hospital district under Principal Investigator Professor Matti Isohanni, assisted by the author of this dissertation psychiatric nurse Marjo Kiviniemi (formerly Karvonen), Master of Health Science, as a doctoral student. The author has participated in the PERFECT-schizophrenia project as a researcher since 2007. At the beginning of the project a short report in Finnish was published defining the study population and variables and introducing some preliminary data and results (Karvonen et al. 2008). The author is authorized to handle data that has been gathered and encrypted by the National Institute for Health and Welfare. Only data relevant for the purposes of this study was released to the author.

The author has signed an agreement with the National Institute for Health and Welfare regarding the transfer of research material and the use of this study. The processing of personal data for research purposes is subject to the Finnish Personal Data Act (523/1999). Personal data may be processed for scientific research if the research cannot be carried out without the data identifying the person and if personal consent is not possible to acquire by reason of large amount of data subjects. Use of personal data files requires an appropriate research plan and a designated responsible person for the research. As the identification of persons and study subjects is not possible, and large register linkage study does not require the permission of an ethics committee (Räisänen *et al.* 2013).

The author of this dissertation, Marjo Kiviniemi, has participated in the design of all of the original studies. The systematic literature searches and statistical analyses of all original publications have been design and conducted by the author together with statistical expert Helinä Hakko, PhD. In addition to the preliminary report (Karvonen *et al.* 2008), the author has written the first and final versions of all of the original publications. The author has also been the corresponding author in the original studies and coordinated the correction and resubmission process of all of the original studies.

#### 6 Results

#### 6.1 Mortality (I)

#### 6.1.1 Causes of death in schizophrenia (I)

During the five-year follow-up of 7,591 schizophrenia patients, 403 (5%) firstonset schizophrenia patients died: 286 (6%) men and 117 (4%) women. Of all deaths, 191 (47%) were natural deaths: 131 (46%) in men and 60 (51%) in women.

Schizophrenia individuals were shown to have significantly increased allcause mortality (SMR 4.4) and mortality from natural (SMR 2.9) and unnatural causes (SMR 8.6) compared to the general population (Publication I: Table 1). The most common natural causes of death were circulatory diseases (44%) and neoplasms (13.6%). The highest SMR (24.8) was found in ill-defined and unknown causes of death.

Suicide accounted for the majority (74%) of unnatural deaths and exhibited the highest SMR (14.0). Mortality from suicide was followed by mortality due to accidents and violence (20.7%), the SMR of which was 6.7-fold compared to the general population.

The results of gender-specific analyses showed the most common natural cause of death in both men and women to be circulatory diseases (men: 44%; women: 47%). The highest SMR, however, was found in ill-defined and unknown causes of death, with SMRs of 22.8 in men and 28.9 in women. In both genders, suicide was the most common category of all unnatural death, accounting for 72% of unnatural deaths in men and 81% in women. Mortality due to suicide also showed the highest mortality ratio in both men (SMR 12.0) and women (SMR 23.4).

#### 6.1.2 Mortality by age group and gender (I)

Figure 1 of Publication I, and Table 4, presents the age-specific SMRs for all causes, circulatory diseases and suicides. Regarding the total mortality, all-cause SMRs were statistically significantly increased in all age groups in both men and women, with the exception of age groups 15–19 and 65–69. The highest total SMRs were found in age group 25–29 in male patients, and in 20- to 24-year-olds

in women. In the total data for both men and women, SMRs decreased with increasing age.

Age	All-caus	e SMRs		Suicide S	MRs		Circulatory s	ystem disea	ases
groups	Men	Women	Total	Men	Women	Total	Men	Women	Total
15–19	5.5	5.5	5.5	18.2	26.4	19.7	-	-	-
20–24	7.2	13.0	8.1	11.0	32.1	13.2	14.8	21.0	16.4
25–29	10.2	10.8	10.3	17.9	26.8	18.7	17.0	20.0	14.2
30–34	7.3	10.6	7.9	13.4	30.6	15.6	2.8	18.9	6.5
35–39	6.1	5.3	5.9	12.7	15.8	13.2	1.4	11.1	1.1
40–44	3.8	6.7	4.6	5.0	22.9	8.2	3.7	3.3	3.6
45–49	3.4	4.0	3.6	8.7	30.1	14.1	4.0	4.4	4.1
50–54	3.5	4.2	3.7	10.7	12.2	11.1	5.0	8.1	5.7
55–59	2.7	2.5	2.6	5.7	11.0	7.5	3.5	7.5	4.5
60–64	3.4	3.5	3.4	12.9	28.3	17.7	2.8	5.4	3.4
65–69	2.0	2.2	2.1	10.5	41.2	20.8	1.5	2.1	1.8

Table 4. Age-specific five-year standardized mortality ratios (SMRs) of 7,591 patients with schizophrenia, by gender.

The SMRs for suicide were significantly increased in all age groups in the total data set and in both genders, except in men aged 55–59 and 65–69 and in women aged 15–19. The highest SMRs were found in age groups 15–19 and 65–69 in the total data set. In men, the SMR was highest at age 15–19 and in women at age 65–69.

The SMRs for circulatory diseases were significantly increased in all age groups, with the exception of ages 35–39 and 65–69, and the highest SMR was seen among 20- to 24-year-olds. In men, the SMRs were increased between the ages of 20–29 and 45–64 years, being the highest among 25- to 29-year-olds. In women, the SMRs were increased between the ages of 20–34 and 50–64 years, being the highest at age 20–24 years.

#### 6.1.3 Disability pension and mortality (II)

Schizophrenia individuals who retired during the five-year follow-up (n= 1944) (compared to those without disability pension, n=1931) were shown to have statistically significantly lower overall mortality (n=55, 2.8% vs. n=153, 7.9%, p<0.000) and suicide rates (n=20, 1.0% vs. n=67, 3.5%, p<0.000) (Publication II: Figure 2).



## Fig. 3. All-cause mortality and suicide rates among schizophrenic patients with and without disability pension five years after first-onset of schizophrenia (Publication II: Figure 2).

The most common causes of death in first-onset schizophrenia patients with disability pension due to schizophrenia were suicide (n=20, 37%), accidents and violence (n=20, 35%) and death due to circulatory system diseases (n=16, 16%). Correspondingly, the most common causes of death in patients without disability pension were suicide (n=67, 44%), circulatory system diseases (n=31, 20%), accidents and violence (n=27, 18%) and neoplasms (n=9, 6%).

The Cox proportional hazard model was used to examine the differences in all-cause and suicide mortality between patients with and without disability pension with adjustment for age, sex and physical diseases before the onset of schiz-ophrenia. Decreased likelihood of all-cause (HR 0.5, 95% CI 0.3–0.6, p=0.000) and suicide mortality (HR 0.3, 95% CI 0.2–0.5, p≤0.000) was found among patients with disability pension when compared to schizophrenia patients without disability pension.

## 6.1.4 Mortality among outpatient-treated vs. hospitalized patients (III)

The mortality of schizophrenia patients was also compared between the hospitalized (HP, n=5980) and outpatient-treated (OTP, n=1220) patient groups. Among the HP group, there were 312 (5%) deaths compared with 46 (4%) deaths among the OTP group (p=0.026). After controlling for age, sex and physical diseases, the likelihood of death (all causes) was statistically significantly increased among the HP patients compared to OTP patients (HR=2.0, 95%CI 1.4–2.7, p<0 001).

Regarding suicide, a total of 116 (2.0%) patients in the HP group died by suicide compared to six patients (0.5%) in the OTP group (p<0.001). The likelihood of death due to suicide was shown to be over four-fold (HR 4.5, 95%CI 2.0–10.3, p<0.00) in the HP compared to the OTP group.

#### 6.1.4 Mortality SMRs by hospital districts (I)

All-cause mortality of first-onset schizophrenia patients was significantly increased in 18 (90%) out of 20 hospital districts in Finland (Figure 5; Publication I: map in online supplement). In Lapland (SMR 1.7) and Central Ostrobothnia (SMR 1.8) the mortality of schizophrenia patients was at the same level as the general population. In all other hospital districts schizophrenia patient mortality was higher compared to the general population, and the SMR of these regions varied from 2.9 to 7.2 (whole country 4.4). The highest SMR was observed in the Southwest Finland hospital district (SMR 7.2).



Fig. 4. Five-year overall mortality of first-onset patients with schizophrenia in 20 hospital districts in Finland (Publication I: map in online supplement).

In death by suicide, the mortality of patients with schizophrenia was significantly increased in 16 (80%) out of 20 hospital districts (Figure 6; Publication I: map b) in online supplement). Two hospital districts (Central Ostrobothnia and Etelä-Savo) had no suicides. In the Lapland (SMR 6.1) and Kymenlaakso hospital districts (SMR 2.4) the suicide mortality of schizophrenia patients did not differ significantly from the general population. In all other hospital districts suicide SMRs varied from 7.8 to 22.9 (whole country 14.0).



Fig. 5. Five-year suicide mortality of first-onset patients with schizophrenia in 20 hospital districts in Finland (Publication I: map b in online supplement).

The highest SMRs were observed in the Vaasa (SMR 22.9), Southwest Finland (SMR 20.5) and Itä-Savo (SMR 20.3) hospital districts.

Regarding death due to circulatory system diseases, increased SMRs for circulatory diseases were observed in 10 (50%) of the 20 hospital districts (Figure 7; Publication I: map c in online supplement). SMRs varied across hospital districts from 1.3 to 8.8, averaging at 3.9 nationwide. The highest SMRs were observed in the Itä-Savo (SMR 8.8), Southwest Finland (SMR 8.2), Satakunta (SMR 7.8) and South-Karelia (SMR 7.5) hospital districts. The SMRs for circulatory system

diseases at the regional level did not, however, correlate with the morbidity index for coronary artery diseases in the general population in the same regions (r=0.198, n=20, p-value=0.417).



Fig. 6. Five-year circulatory system disease mortality of first-onset patients with schizophrenia in 20 hospital districts in Finland (Publication I: map in online supplement).

#### 6.2 Disability pension (II)

The data of the original study III included 3,875 schizophrenia patients who were followed up for 5 years after first-onset of schizophrenia. Onset of schizophrenia was defined as the date of the beginning of first hospitalization for schizophrenia or, alternatively, as the date of the beginning of first hospitalization due to other psychotic disorder with later received diagnosis of schizophrenia.

A total of 1,944 (50.2%) first-onset schizophrenia patients were pensioned off during the five-year follow-up between the years 1998 and 2001. The pension rates were statistically significantly higher in men (n=1217, 54%) than in women (n=727, 45%) (p<0.001). The mean age of the patients at the time of retirement was 31±10 years, and the retirement age of men was significantly younger (30±9 years) than that of women (33±11 years) (p<0.001). The mean age of patients who were not pensioned (n=1931) by the end of the five-year follow-up was 40±13 years, and men were significantly younger (n=1057, 38±13 years) compared to women (n=872, 43±14 years) (p<0.001).

The gender-specific survival curves for the time from first admission to disability pension for schizophrenia during the five-year follow-up period are visualized in Figure 1 of original Publication II. The results of the Cox proportional hazard model show a significant gender difference in the time of disability retirement (HR, 1.3; 95% CI, 1.2–1.4; P<.001). During the first year after onset of schizophrenia no difference was seen in the time of retirement. After one year from onset of schizophrenia, men had received disability pension more commonly than women.

## 6.2.1 6.2.1 Retirement in relation to medication, comorbidity and psychiatric hospital admissions (II)

Patients with disability pension had statistically significantly higher rates of psychotropic medication use in all medication groups, excluding first-generation antipsychotics and anxiolytics (Publication II, Table 1). For example, the use of antipsychotics was more common (p<0.001) in schizophrenia patients with disability pension (n=1889, 97%) compared to those without pension (1745, 90%).

Regarding psychiatric hospital treatment (Publication II: Table 1), patients with disability pension spent more days in psychiatric hospital treatment (338 days vs. 198 days, p<0.001) and a greater proportion of them had had involuntary treatment periods (n=1381, 71% vs. n=1190, 62%, p<0.001) compared to those

without disability pension. Patients with disability pension had also more commonly experienced relapses (n=1527, 79% vs. n=1405, 73%, p<0.001) and their mean time to first relapse was shorter (378 days vs. 423 days, p=0.005) than schizophrenia patients without disability pension.

The prevalence of comorbid physical illness, particularly hypertensive diseases and diabetes mellitus, as well as depression rate was significantly lower in patients with disability pension.

## 6.2.2 Disability pension index and time of retirement by hospital district (II)

As presented in Figure 3 of Publication II, and in Table 5 (Publication II: supplement table), the disability pension index ranged from 75–118 (index of whole country=100) across hospital districts. The lowest index values were found in the Kanta-Häme (index=75) and Länsi-Pohja (index=76) hospital districts. In both of these regions about 35% of first-onset schizophrenia patients had retired by the end of the five-year follow-up period. The highest disability pension index was found in Kymenlaakso (index=118), Päijät-Häme (index=115) and Satakunta (index 115) hospital districts, where about 60% of schizophrenia patients had received a disability pension.

The median time from onset of first hospitalization to retirement was 370 days nationwide and varied by hospital district from 347 to 850 days. The highest median values were found in Central Ostrobothnia (index=850 days) and Länsi-Pohja (index=718 days), and the lowest in South Karelia (index=347) and Kanta-Häme (index=348).

The mean age at the time of retirement was 30.7 years nationwide and ranged from 28.3 to 36.1 years between hospital districts. The youngest first-onset schiz-ophrenia patients with disability pension were found in the Central Ostrobothnia (28.3 years) and Päijät-Häme (29.6 years) hospital districts and the oldest in the hospital districts of Kanta-Häme (35.4 years) and Lapland (36.1 years).

A large majority of first-onset schizophrenia patients with disability pension were men (62.6%). The highest proportion of men were found in the Kainuu (87.1%) and Lapland (75.8%) hospital districts and the lowest in the Kanta-Häme (41.4%) and Southwest Finland (55.8%) hospital districts.

lis suppl. Table 1).						
Hospital district	All cases	Disability pension n(%)	Disability pension index <sup>1</sup>	Median in days from onset of illness to retirement (IQR 25%-75%)	Mean age at time of retirement (S.D)	Men (%)
1. Helsinki and Uusimaa	1352	680 (50.3)	98	370 (332–791)	30.2 (9.32)	62.9
2. Åland <sup>2</sup>						
3. Southwest Finland	302	156 (51.7)	104	380 (345–802)	30.7 (10.11)	55.8
4. Satakunta	128	72 (56.3)	115	366 (325–644)	29.9 (10.27)	63.9
5. Kanta-Häme	81	29 (35.8)	75	348 (143–1167)	35.4 (11.02)	41.4
6. Pirkanmaa	257	144 (56.0)	110	405 (325–912)	31.0 (9.15)	59.0
7. Päijät-Häme	190	110 (57.9)	115	357 (327–704)	29.6 (10.46)	6.09
8. Kymenlaakso	107	64 (59.8)	118	551 (352–978)	29.7 (8.46)	70.3
9. South Karelia	115	56 (48.7)	103	347 (188–587)	31.9 (9.59)	66.1
10. Etelä-Savo	75	37 (49.3)	105	452 (295–977)	31.8 (10.76)	56.8
11. Itä-Savo	46	24 (52.2)	107	355 (297–450)	30.5 (9.06)	75.0
12. North Karelia	113	48 (42.5)	92	434 (345–955)	31.5 (10.06)	60.4
13. Pohjois-Savo	222	104 (46.8)	93	359 (283–570)	30.0 (9.80)	60.6
14. Central Finland	146	78 (53.4)	104	372 (315–837)	31.2 (9.87)	64.1
15. South Ostrobothnia	102	57 (55.9)	114	362 (311–568)	33.6 (11.13)	71.9
16. Vaasa	102	43 (42.2)	83	453 (306–845)	32.8 (10.57)	60.5
17. Central Ostrobothnia	38	18 (47.4)	93	850 (358–1228)	28.3 (6.26)	72.2
18. North Ostrobothnia	327	148 (45.3)	91	368 (312–929)	30.3 (9.40)	60.1
19. Kainuu	68	31 (45.6)	96	383 (321–931)	30.6 (11.12)	87.1
20. Länsi-Pohja	34	12 (35.3)	76	718 (305–1223)	32.0 (9.67)	66.7
21. Lapland	70	33 (47.1)	66	558 (367–1160)	36.1 (11.19)	75.8
Total	3875	1944 (50.2)	100	370 (329–800)	30.7 (9.74)	62.6
<sup>1</sup> Age- and gender-adjuste	ed index for o	disability pension (index=10	0 for whole country)	). <sup>2</sup> The province of Åland was exclude	ed from the study data.	

Table 5. Regional differences in disability pension due to schizophrenia in Finland during the 5-year follow-up period (Publication

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The time from the onset of schizophrenia to retirement (in days) varies between regions (Figure 7). The longest times between onset of schizophrenia and granting of disability pension were found in the Central Ostrobothnia (2.3 years) and Länsi-Pohja hospital districts (2 years). In the Satakunta, Päijät-Häme, South Karelia, Itä-Savo, Pohjois-Savo and South Ostrobothnia hospital districts the majority of schizophrenia patients were granted disability pension within two years from the onset of illness.



(in days) from the onset of schizophrenia to retireme due to schizophrenia

# Fig. 7. Time in days from onset of illness to retirement of first-onset patients with schizophrenia by hospital district. The bottom and top of each box represent the 25th and 75th percentiles, and the band in the box is the 50th percentile. (Publication II, Figure 4).

The association between disability pension rates and the various social indicators (unemployment rate, net price of social welfare and health care per inhabitant, net price of primary health care per inhabitant, net price of special health care per inhabitant, mean number of psychiatric hospital beds, number of physicians per 10,000 inhabitants, number of health care staff per 10,000 inhabitants, overall

SMR, suicide SMR) were also analysed at hospital district level (Publication II: Table 2). Correlations varied from -0.35 to 0.21, but none were statistically significant. However, the median time between first-onset and retirement due to schizophrenia correlated negatively with overall mortality (r=-0.586, p=0.007) and mortality by suicide (r=-0.483, p=0.031) indicating that the shorter the time from onset to retirement the higher the risk of all-cause mortality and mortality by suicide.

#### 6.3 Psychiatric treatment (III)

Gender differences in the outcomes of hospitalized (HP) and outpatient-treated (OTP) patients, as well as differences between HP and OTP patient groups were examined for various characteristics relating to hospitalization, involuntary treatment and purchases of medicine during the follow-up period between 1998 and 2003.

The results of the assessment of gender differences in psychiatric treatment (hospitalization, involuntary treatment) during the follow-up period (Publication III: Table 1) showed that in the HP group of first-onset schizophrenia patients, men had spent more days in psychiatric inpatient treatment (median 159 vs. 136 days, p<0.001) and had a greater proportion of total hospital days exceeding one vear during the five-year follow-up (24% vs. 18%, p<0.001) than women, whereas, conversely, men had a lower proportion of single hospital admissions due to schizophrenia (30% vs. 33%, p=0.009) and less men were living at home at fiveyear follow-up (76% vs. 83%, p<0.001) compared to women. In the OTP group of first-onset schizophrenia patients, men had a shorter length of first involuntary treatment (29 vs. 43 days, p=0.027) and lower overall proportion of involuntary treatment during the five-year follow-up period (19% vs. 25%, p=0.017) and a lower proportion of them lived at home at five-year follow-up (87% vs. 93%, p=0.003) compared to women in the OTP group. In relation to differences between the HP and OTP patient groups during the five-year follow-up (III: Table 1), patients from the HP groups were shown to have more psychiatric hospitalizations, treatment days in psychiatric hospital, and involuntary treatment, whereas patients from the OTP group were characterized by a greater proportion of living at home at five-year follow-up.

In terms of gender differences in purchases of medicines, a greater proportion of users of antipsychotics were women both in the HP (women vs. men, 91% vs. 87%, p<0.001) and OTP (88% vs. 79%, p<0.001) patient groups. Statistically
significant female preponderance in both patient groups was also seen in the use of typical and atypical antipsychotic and antidepressants (Publication III: Table 1). As for differences in the purchase of medicines between the HP and OP groups, the users of antipsychotics, particularly the users of typical antipsychotics and clozapine, were more commonly patients from the HP group than from the OTP group (Publication III: Table 1). During the year preceding first-onset of schizophrenia, however, the patients in the OTP group had more commonly used antipsychotics and antidepressants compared to the HP patients (Publication III: Table 1). Substance abuse was more prevalent in the HP group than the OTP group (19% vs. 11%, p<0.001).

# 6.3.1 Relapses (III)

In the HP group of schizophrenia patients, relapse was defined as the next psychiatric hospital admission after the index hospitalization due to schizophrenia. In the OTP group, a relapse was considered to be the first hospital admission after having been granted a disability pension for schizophrenia. In the HP group, the majority of patients (74.2%) had experienced a relapse requiring hospitalization during the five-year follow-up, compared to 39.6% in the OTP group (p<0.001). In the HP group no gender difference in relapses was found, being 74.2% in both genders (p=1.000), while in the OTP group, the relapse rate for women was significantly higher (44.0%) compared to men (36.2%) (p=0.006).

In the HP group, the median (IQR) time to first relapse was 283 days (IQR 115–613) in men and 295 days (IQR 119–644) in women (p=0.091), while the corresponding values in the OTP group were 287 days (IQR 86–684) in men and 300 days (IQR 60–790) in women (p=0.649). When the Cox proportional hazard model was used to estimate the group differences in occurrence of first relapse, the likelihood of relapse was statistically significantly increased among the HP group compared to the OTP group (HR=2.3, 95CI%=2.1-2.5, p<0.001)(Publication III: Figure 4).

# 6.3.2 Non-hospitalized outpatient-treated patients (III)

An additional analysis was performed for the outpatient-treated (OTP) patients who had not needed any psychiatric inpatient hospitalization for schizophrenia during the whole five-year follow-up period. The total number of these patients was 737, accounting for approximately 60% of the outpatient-treated patient

group. This subgroup of non-hospitalized OTP patients included statistically significantly more men 439 (64%) than women 298 (56%) (p=0.006) and the men were shown to be younger (40.8±11.2 years) at the onset of schizophrenia than women (43.3±10.2 years) (p<0.001). Furthermore, a total of 34 (4.6%) patients had died during the follow-up period and statistically significant differences were observed in total mortality between men and women (6.4% vs. 2.0%, p=0.006). Of all deceased non-hospitalized OTP patients, three (0.7%) had died by suicide and all were male patients.

As for purchases of medication, most of the non-hospitalized OTP patients (75%) had purchased some antipsychotic medication. These purchases consisted of 43% first-generation and 59% second-generation antipsychotics. Clozapine was used by only 2.3% of patients, while about 57% had used antidepressant medication. No statistically significant difference was observed in mortality between non-hospitalized OT patients with or without antipsychotic medication (4.4% vs. 5.4%, p=0.566).

# 6.4 Antipsychotic and antidepressant medication (IV)

#### 6.4.1 Use of medication and all-cause mortality (IV)

The mortality of first-onset schizophrenia patients was analysed in relation to the use of antipsychotics, separately for second- (SGA) and first-generation (FGA) antipsychotics, and antidepressants. A statistically significantly decreased risk of premature death (all-cause mortality) among schizophrenia patients was found in SGA users (OR 0.7; P=0.005), particularly among those taking clozapine (OR 0.35; P<0.001) and quetiapine (OR 0.5; P=0.001) compared to non-users of any antipsychotics (Publication IV: Table 2). Conversely, an increased mortality risk was observed among FGA users (OR 1.3; P=0.001), specifically among those who used levomepromazine (OR 1.8; P=0.001), thioridazine (OR 3.1; P=0.001) or chlorprothixene (OR 1.8; P=0.001). Of the antidepressants, an increased mortality risk was found among users of venlafaxine (OR 1.5; P=0.044). In addition, patients with physical illnesses before the onset of schizophrenia and having later used antipsychotics had notably higher mortality (n= 60, 9.9% of all users of antipsychotic medication) compared to users of antipsychotics who were physically healthy (n= 189, 4.1%).

# 6.4.2 Use of medication and suicides (IV)

The association between medication and death by suicide was also examined (Publication IV: Table 3). Use of clozapine was shown to reduce the likelihood of suicide (OR 0.29;, P=0.002) in patients with schizophrenia, while the use of FGAs was associated with an increased suicide risk compared to non-users of any antipsychotics (OR 1.6, P=0.041), particularly the use of chlorprothixene (OR 2.8, P=0.003). Antidepressant use was also associated with increased risk of suicide (OR 1.5, P=0.022) compared to non-users, particularly the use of mirtazapine (OR 3.2, P<0.001). A slightly higher proportion of users of antipsychotics who were known to have physical illnesses before the onset of schizophrenia died from suicide (16, 2.9%) compared to users of antipsychotics who had no history of somatic illnesses (74, 1.6%).

# 6.4.3 Use of medication and circulatory system deaths (IV)

Regarding death due to diseases of the circulatory system during the five-year follow-up (Publication IV: Table 4), users of SGAs and users of antidepressants were not found to have any elevated risk of cardiovascular death compared to non-users of antipsychotics. Of the most commonly used FGAs, only levome-promazine (OR 2.7, P=0.004) was related to increased risk of death due to cardiovascular diseases. Among users of antipsychotics, patients with physical illnesses es diagnosed before the onset of schizophrenia were shown to exhibit higher cardiovascular mortality (18, 3.2%) compared to those who had no somatic illness (38, 0.8%).

# 6.5 Summary of results on mortality, psychiatric treatment and medication in different patient groups

Table 6 presents a summary of first-onset age, mortality, medication, involuntary hospital treatment and relapses among different first-onset schizophrenia patient groups.

Hospitalized patients with first-onset schizophrenia had a younger first- onset age than patients whose illness began in outpatient settings. Overall, suicide mortality was highest in the hospitalized non-retired patient group, and lowest in the outpatient-treated first-onset patients group. Antipsychotic medication use, involuntary hospital treatment and relapses were more common among hospitalized first-onset patients.

Table 6. First-onset	age, mortality	, medication and	l hospital treatme	nt in different pati∉	ent groups with a	schizophrenia.	
	Publication I: Sample 1995– 1998	Publication II: Sample 1998–2001		Publication III: Sample 1998–2003			Publication IV: Sample 1998– 2003
Onset age and outcome indicators	Total data (n=7591)	Hospitalized and later retired patients (n=1944)	Hospitalized non- retired patients (n=1931)	Hospitalized patients (n=5867)	Outpatient- treated patients (n=1220)	Non-hospitalized outpatient- treated patients (n=737)	Total data (n=6987)
First-onset age (mean)	33.5	29.5	35.4	32	38	42	33.8
Died during follow-up time	5%	2.8%	7.9%	5.3%	3.8%	4.6%	5.1%
Suicide during follow-up time	2.1%	1.0%	3.5%	2%	0.5%	0.7%	1.7%
Antipsychotic treatment		97.2%	90.4%	88.9%	82.6%	74.8%	Deceased: 69.7% Alive: 75.4%
Antidepressant treatment		62%	57.9%	61.2%	64.2%	57.1%	Deceased: 38.9% Alive: 34.8%
Involuntary hospital treatment		71%	61.6%	66.4%	21.4%	%0	
Relapse		78.5%	72.8%	74.2%	39.6%	%0	

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# 7 Discussion

# 7.1 Main findings

The main findings of the study are summarized below:

- First-onset schizophrenia individuals had a 4.5-fold higher mortality than the general population in Finland and their mortality was significantly elevated in all age groups. The most prominent single unnatural cause of death was suicide (SMR 14). The most common natural cause of death was circulatory diseases (SMR 4). As for age-related gender differences in mortality, the SMRs for all-cause mortality, circulatory system diseases and suicides were higher for female than male patients in almost all age groups. Regional differences in the mortality of these schizophrenia patients were evident among hospital districts in Finland. (I)
- 2. About half of all first-onset schizophrenia patients had retired on disability pension by the end of the five-year follow-up period. Men retired on pension at an earlier age and more commonly than women. Regional disability pension rates and retirement times for schizophrenia varied between hospital districts. Patients with disability pension had lower overall mortality and suicide mortality compared to non-retired patients. (II)
- 3. When comparing the course and outcome of first-onset schizophrenia between hospitalized (HP) patients and outpatient-treated (OTP) patients, patients diagnosed for schizophrenia in outpatient services had better outcomes than patients whose schizophrenia diagnosis was based on psychiatric inpatient treatment. The mortality rates, number of psychiatric hospital treatment days and relapse rate during the five-year follow-up were significantly lower in the OTP group. Interestingly, 36% of patients from the HP group and 60% of those from the OTP group survived the five-year follow-up period outside hospital. (III)
- 4. Differences in mortality of first-onset schizophrenia patients existed between users of first- (FGA) and second-generation (SGA) antipsychotics. In general, use of SGAs was associated with reduced risk of all-cause mortality in patients with schizophrenia compared to non-users of any antipsychotics. In particular, clozapine was associated with decreased suicide risk. Use of FGAs was associated with increased risk of all-cause mortality. FGAs, particularly chlorprothixene, were associated with increased suicide mortality. An in-

creased likelihood of cardiovascular death was found among users of levomepromazine in the group of FGA users. In antidepressants, the use of mirtazapine associated with increased risk of suicide. In total, 81% of patients used antipsychotics in the first year compared to 79% at the end of the follow-up period. (IV)

# 7.2 Discussion of results

#### 7.2.1 Mortality

In this five-year follow-up study of first-onset schizophrenia patients, excess mortality among schizophrenia patients compared to the general Finnish population was an expected finding. The risk of mortality was four-fold higher than in the general population. The result clearly indicates that schizophrenia patients are still in need of special attention in terms of clinical work, routine health screening and health promotion. In Finland, the focus has shifted towards treating psychiatric patients through outpatient rather than inpatient mental health care services. The ongoing mental health service reform has already increased psychiatric treatment in primary care and the social sector (Wahlbeck *et al.* 2011) where skills are need for suicide assessment, treatment and prevention, and health screening for specific health issues of schizophrenia patients. At the same time, in many Finnish hospital districts there is shortage of specialized workers, especially psychiatrists, and this may worsen the situation of psychiatric patients.

The mortality ratios for natural causes was almost three-fold, being 3.0 in men and 2.6 in women, which is higher than in earlier international studies (Brown 1997, Harris & Barraclough 1998, Saha *et al.* 2007). In one recent study, the SMR for natural causes among Finnish patients with schizophrenia was reported to be 3.2 in men and 3.0 in women (Laursen *et al.* 2013b), which is slightly higher than that observed in the current study. The accumulating evidence on mortality indicates a mortality gap between schizophrenic patients and the general population (Gissler *et al.* 2013, Saha *et al.* 2007). Life expectancy is lower for male individuals of schizophrenia. This life expectancy gap has remained largely unchanged in over 20 years, despite the deinstitutionalization of mental health services in the Nordic countries (Laursen *et al.* 2013b, Wahlbeck *et al.* 2011). Life expectancy at age 15 among people with schizophrenia and other psychoses has increased during the period 1981–2003, but the mortality gap between the general

population and people with schizophrenia remains wide (Westman *et al.* 2012). Patients with schizophrenia may not have benefited from the improvements in health outcomes that have been available to the general population. It is also known that socio-economic differences such as unemployment and lower level of income affect people's ability for self-care and health (Kainu *et al.* 2013, Manderbacka *et al.* 2013, Prättälä *et al.* 2012, Talala *et al.* 2009, Tarkiainen *et al.* 2013) and may affect people with mental disorders more than the general population. It is also reported that poor continuity of mental health care may increase the mortality of patients with schizophrenia (Hoertel *et al.* 2014).

The single most common natural cause of death was circulatory diseases, the SMR being four-fold, which was higher than in previous studies (Brown 1997, Joukamaa *et al.* 2001, Laursen *et al.* 2007, Saha *et al.* 2007). Patients with schiz-ophrenia are reported to have many lifestyle risk factors for cardiovascular diseases (Brown *et al.* 1999). In addition, medication side-effects are known to cause metabolic disorders (Green *et al.* 2000, Lund *et al.* 2001, Reist *et al.* 2007) and thus increased risk of cardiac death (Koponen *et al.* 2008, Ray *et al.* 2001). In addition to metabolic disorders being often left untreated in patients with schizophrenia (Nasrallah *et al.* 2006), also the quality of treatment of cardiovascular diseases may be poorer than in the general population (Druss *et al.* 2000, Laursen *et al.* 2013, Lawrence *et al.* 2003). About 33–50% of schizophrenia patients have been shown to suffer from depressive symptoms, in addition to which many have cognitive deficits (Husa *et al.* 2014, Rannikko *et al.* 2012) or comorbid substance abuse (Buckley *et al.* 2009, Conley *et al.* 2007, Murray *et al.* 2006), which may decrease their level of function, motivation and capacity for self-care.

Among the first-onset schizophrenia patients of this study, the SMR for illdefined and unknown causes was almost 25-fold compared to the general population. In an earlier study this SMR was 14-fold (Allebeck & Wistedt 1986). In Finland, the official practice for determining cause of death is comprehensive and reliable, with only 1–2% remaining unknown (Jääskeläinen 2003). This rate of unknown causes of death is not, however, separately evaluated for persons with mental illnesses. A Swedish (Nilsson & Logdberg 2008) population-based study reported an increased proportion of patients with schizophrenia who were not discovered until many days after death and, thus the exact cause of death was impossible to determine. It is also reasonable to suggest that some deaths classified as due to ill-defined and unknown causes were actually deaths by suicide. A high SMR for ill-defined and unknown causes of death category may indicate a strong increase in social isolation and unavailability of adequate mental and somatic diagnostics and care among schizophrenia patients.

In this study, the SMR for suicides among patients with schizophrenia was as high as 14-fold. This result is in line with previous studies that show that suicide risk is highest after onset of the illness (Alaräisänen et al. 2009, Andriopoulos et al. 2011, Hirokawa et al. 2012, Melle & Barrett 2012, Mork et al. 2013, Nordentoft *et al.* 2013). In Finland, suicide rates in the general population, especially among men, have shown a decreasing trend since the 1990s (Hiltunen et al. 2009). The Suicide Prevention Project implemented in Finland between 1986 to 1996 increased awareness of suicide and decreased the country's proportionally high suicide rate by 20% (Lehtinen & Taipale 2001). Depressive symptoms are associated with a greater risk of suicide, sufficient attention should be paid to the diagnosis and treatment of depressive symptoms occurring during schizophrenic psychoses (Möller 2005). The results of this study of first-onset schizophrenia patients further support the notion that identification and treatment of depression reduces suicide. Namely, the patient groups showing lower suicide rates were those treated with antidepressants: the outpatient-treated group of patients and hospitalized patients who retired on disability pension during the five-year follow-up. It is also known that alcohol problems are associated with poor mental health and low life satisfaction (Mäkelä et al. 2014). Reducing excess alcohol use and treatment of substance use diseases may decrease suicide mortality and depressive symptoms.

The results regarding age-specific SMRs clearly demonstrated that a higher risk of premature death was not directly associated with age. In particular, the suicide mortality of patients was higher in all age groups compared to the general population. Furthermore, female patients of schizophrenia had a higher mortality rate compared to the general population than male schizophrenia patients. In a Swedish study, SMRs for natural causes for women in all age groups were also higher compared to men (Ösby *et al.* 2000). Furthermore, a women excess SMRs by age group was found in a study by Mortensen and Juel (Mortensen & Juel 1993). In that study, however, there were no cardiovascular deaths among women under the age of 50, whereas in our study SMRs for circulatory diseases were especially high among 20- to 44-year-old women.

In this study, the large variation in mortality between hospital districts was an unexpected finding. The lack of association between SMRs and morbidity indexes, however, indicate that the general health status of the population in a hospital district does not solely explain mortality. For example, the Vaasa hospital district has a healthier general population and lower suicide rate compared to the country as a whole (http://uusi.sotkanet.fi/portal/page/portal/etusivu), yet among schizophrenia patients overall mortality and suicide rates were high. Respectively, the general population of Central Ostrobothnia has low suicide mortality, and no suicides were recorded in the study population, which suggests that people of schizophrenia are also benefitting from the social and health policies of that area. Also, the various indexes describing the use of psychiatric services, socioeconomic status or degree of urbanization were shown to be unrelated to SMRs at the hospital district level. Instead, the patient's long distance to the nearest health centre, although not investigated in the present study, may be one explanation for the observed regional differences in mortality. In the Finnish follow-up study, residential area determined the use of psychiatric care. Those living in urban areas used significantly more psychiatric outpatient services than those living in rural areas. The regional variation in the use of inpatient care was modest. (Paananen *et al.* 2013).

A recent Finnish study reported that the availability of health services is hampered by distance (Vaarama *et al.* 2010). In Finland, hospital districts have to organize medical care for those living within the district and all citizens have the same legal right to receive necessary medical care. Patients should, thus, receive equally good service and treatment in every hospital district in Finland. In reality, however, municipalities' and hospital districts' outpatient services, resources and contents of treatment vary between regions, which may at least partly explain the regional variations in mortality of the first-onset schizophrenia patients in the present study.

# 7.2.2 Disability pension

About half of first-onset schizophrenia patients had been granted a disability pension by the end of the five-year follow-up period after onset of schizophrenia. This proportion is lower than reported in one Swedish outcome study, in which 63% of first-episode schizophrenia patients received disability allowance at fiveyear follow-up (Svedberg *et al.* 2001). In another study of early-onset schizophrenia, more than a quarter of the study sample was unable to work at all at 13year follow-up (Reichert *et al.* 2008), and in a Finnish cohort 56% of schizophrenia patients aged 34 were pensioned within 10.6 years of the follow-up period (Miettunen *et al.* 2007). The predisposing factors for early retirement of patients with schizophrenia are the severity of symptoms, low functional level and need for assistance or care in the patient's everyday life, older age at first diagnosis of schizophrenia, and antipsychotic treatment with typical antipsychotics (Schnabel *et al.* 2008). In the present study, of the hospital-treated schizophrenia patients, those with disability pension had more commonly used psychotropic medication, especially clozapine, a greater number of psychiatric hospital days and involuntary treatment, and a younger onset age compared to patients without disability pension. These findings likely indicate, however, that patients having a disability pension had a more severe illness than patients who were not retired.

People with schizophrenia face significant challenges in daily functioning. Disease often leads to a progressive decline in cognitive and psychosocial functioning (Rossler *et al.* 2005). However, antipsychotic medication treatment for schizophrenia also seems to be associated with structural brain changes (Torres *et al.* 2013, Veijola *et al.* 2014) and poorer cognitive functioning (Husa *et al.* 2014). For example, heavy use of antipsychotic medication seems to be associated with poorer memory (Rannikko *et al.* 2012). These changes in cognitive functioning can be crucial to the success of rehabilitation and employment in today's cognitively and socially demanding workplace.

The high mortality in regions where hospital-treated patients with first-onset schizophrenia received disability pension status within a rather short period from onset might be an indicator of a demoralizing or disappointing effect of a relatively fast, perhaps non-rehabilitation-oriented pensioning process. A high mortality rate may be associated with weaker regional resources for rehabilitating schizophrenia patients, leaving rapid retirement as a common solution for this group of severely ill patients. Receiving a diagnosis of schizophrenia may be challenging for schizophrenia individuals and may influence mortality risk, particularly with regard to suicide.

The results of the present study also showed that the median number of days from the onset of first hospitalization due to schizophrenia to disability pension for schizophrenia among patients aged between 16–65 was about one year (370 days), while in a French study of schizophrenia patients (aged 20 years or more) it was four years (Cougnard *et al.* 2007). In a Northern Finland 1966 Birth Cohort Study the average time from first psychiatric admission to pension for schizophrenia was 3.3 years (Miettunen *et al.* 2007). An interesting finding of the present study was that 28% of all hospital-treated schizophrenia patients had been prescribed antipsychotics for one year before first hospital admission due to

schizophrenia. Clearly, these patients had already received some kind of outpatient diagnosis and treatment before their first psychiatric hospitalization. Therefore, the time between onset of illness and granting of disability pension for schizophrenia was actually longer than that determined based on the time of first hospitalization due to schizophrenia.

It is also assumable that the disability pension rate of all first-onset schizophrenia patients in Finland is greater than 50%. In original Publication II, the study population consisted of hospitalized first-onset patients with diagnoses of schizophrenia and of patients with hospital admission with psychoses who received a later diagnosis of schizophrenia. This procedure enabled the analysis of time of retirement from first-onset schizophrenia to disability pension to be performed. Patients treated only in outpatient services were excluded from the data of Publication II, because their schizophrenia status was based on information on the granting of disability pension for schizophrenia. The true disability pension rate of first-onset schizophrenia patients might be somewhere between the rate observed in the current study and the result of the Northern Finland 1966 Birth Cohort psychoses project, where it was 56% at 10-year follow-up (Miettunen *et al.* 2007).

It seems that disability pension rates due to schizophrenia have increased among first-onset patients with schizophrenia in recent decades in Finland. In a Finnish study carried out in 1977, 33% of all hospitalized first-onset patients were disabled within a 7.5-year follow-up period (Salokangas 1977), while in a later study 44.8% of first-admission schizophrenia patients were disabled at five-year follow-up (Pakaslahti 1992). This time trend is worrying, as although knowledge and treatment of schizophrenia has developed in recent decades, schizophrenia outcomes seem not to have improved. The reasons for this adverse development, whether due to lack of effective rehabilitation, therapies and medication for schizophrenia, can only be speculated. In addition, the work may have become more stressful and demanding, placing higher demands for working people, including those with mental illness.

An unexpected result was the regional differences in disability pension rates and retirement times of first-onset schizophrenia patients. Regional differences in disability retirement in Finland were also shown in another Finnish study by Laaksonen and Gould. In that study, in the region with the highest incidence of disability pension the all-causes disability pension rate was nearly twice that of the region with the lowest incidence. Disability retirement due to mental disorder was highest in the North Ostrobothnia, Pohjois-Savo, Kymenlaakso, South Karelia, Kainuu and Lappi hospital-districts, and lowest in the Åland and Vaasa hospital districts (Laaksonen & Gould 2013). These results differ from the disability retirement rates due to schizophrenia. In the present study, the highest disability retirement rates were in the Kymenlaakso, Päijät-Häme and Satakunta hospital districts and the lowest in the Kanta-Häme and Länsi-Pohja hospital districts.

The observed differences suggest that the practices of granting disability pension and rehabilitation services to patients with mental disorders vary between hospital districts in Finland, which may increase patient inequality between regions. This conclusion is supported by the finding showing an association between a short median time from onset to retirement and higher regional overall mortality and suicide mortality, as well as between higher involuntary treatment rates and higher regional disability pension rates. The findings also show that use of rehabilitation services varied between municipalities in Finland. The probability of different types of rehabilitation services being used was highest in larger municipalities (Pulkki *et al.* 2011).

Regional disability pension rates did not correlate with regional unemployment rate, number of psychiatric beds, and number of health care staff. Opposite results have been obtained in other Nordic countries in studies of disability retirement due to all mental health diagnoses. In a Swedish study, unemployment was a predictor of disability pension due to mental health diagnosis (Samuelsson *et al.* 2012). In Norway, greater provision of beds and staff was associated with increased incidence of disability pension due to psychiatric diagnoses. These studies suggest that greater provision of psychiatric health care increases accessibility and the number of individuals obtaining disability pension (Andersson *et al.* 2007).

First-onset schizophrenia patients with disability pension were shown to have lower rates of suicide mortality than schizophrenia patients without disability pension. This is in contrast to that reported for the general population, where subjects with disability pension had increased mortality rates compared with nonretired subjects (Quaade *et al.* 2002, Wallman *et al.* 2006). It is possible that in the general population ability to work is a protective factor against suicide, but among schizophrenia patients work is an additional burden in addition to sickness symptoms. The results of the present study also showed that patients with disability pension had higher antidepressant and antipsychotic use, indicating that their symptoms have been identified and treated with appropriate medication, which thus might prevent the likelihood of premature death.

#### 7.2.3 Psychiatric treatment

The utilization and need for psychiatric treatment during the five-year follow-up period of first-onset schizophrenia patients was evaluated by comparing the outcomes between a group of hospitalized patients (HP) and a group of outpatienttreated patients (OTP). When the outcome of treatment was evaluated using mortality rate, amount of treatment and relapses as indicators, the schizophrenia patients in the OTP group managed better with their illnesses than patients in the HP group. Mortality rates, number of psychiatric treatment days and relapses during the five-year follow-up were notably lower among the OTP group compared to the HP group.

The mean age at onset of schizophrenia was lower in the HP group (32 years) compared to the OTP group (38 years). This is in line with the results of a Danish register study, which reported that institutionalized patients had earlier onset of schizophrenia than non-institutionalized patients (Uggerby et al. 2011). Furthermore, in both first-onset schizophrenia patient groups of the present study, men had an earlier age at onset than women with a difference of about 3-5 years, which accords well with several previous studies (Häfner et al. 1993, Häfner et al. 1998a, Leung & Chue 2000, Maurer & Häfner 1995). Being directly comparable with the findings of the previous first-admission studies, the average age of the first-onset schizophrenia patients in the HP group was 31 years in men and 35 in women, while in earlier studies it has varied from 26 to 33 years in men, and from 27 to 38 years in women (Häfner et al. 1993, Häfner et al. 1998a, Salokangas et al. 2003). The time lag between occurrence of first sign of schizophrenia and first hospital admission with schizophrenia has been reported to be on average 6.3 years (Maurer & Häfner 1995). This is assumedly true also in our study sample, although this could not be verified in the current study because the Finnish national registers lack comprehensive information on outpatient treatments, which may have revealed the occurrence of first psychotic symptoms.

When mortality rate during the five-year follow-up period was used as an outcome measure for first-onset schizophrenia patients, all-cause mortality was two-fold and suicide mortality 4.5-fold in the HP group compared to the OTP group. One explanation for this result may relate to the data sampling method used. Namely, the patients in the OTP group were identified through the registers for pension and disability and, thus, the patients were already on disability pension. Before being granted disability pension, these patients supposedly received a

diagnostic evaluation and treatment for schizophrenia in outpatient services, which may have had a stabilizing effect on their course of illness.

Secondly, suicide risk is highest after onset of illness (Alaräisänen *et al.* 2009, Andriopoulos *et al.* 2011, Hirokawa *et al.* 2012, Melle & Barrett 2012, Mork *et al.* 2013, Nordentoft *et al.* 2013), which might have occurred in outpatient settings among the OTP group. Thirdly, the use of antipsychotics and/or antidepressants for one year before inclusion in the study was about two-times more common in the OTP group compared to the HP group. This result agrees with previous studies that report that adequate medication may protect against premature death (Heilä *et al.* 1999, Palmer *et al.* 1999, Szanto *et al.* 2007, Tiihonen *et al.* 2009).

Fourthly, it is justifiable to assume that the initial symptoms of schizophrenia and illness in general were more severe in the HP group. In a non-experimental design patients are not treated randomly, instead very sick patients often receive higher doses and a longer duration of antipsychotic medication. This presumption is supported by the finding that the HP patients experienced more psychiatric hospitalization during the follow-up compared to the OTP patients. Furthermore, the onset age for schizophrenia in the HP group was about six years lower than in the OTP group. Early age at onset is reported to indicate more severe psychopathology and poorer long-term course and outcome of illness than later onset of schizophrenia (Harrison et al. 2001, Jääskeläinen et al. 2013, Rabinowitz et al. 2006, Vahia et al. 2010). Earlier age at onset is also associated with higher suicide risk among patients with schizophrenia (Gupta et al. 1998). On the other hand, the severity of schizophrenia symptoms might also prevent adequate treatment of physical diseases (Druss et al. 2001) leading to increased risk of death due to somatic reasons. The patients in the HP group also had more substance use, which is known to increase the risk of poor outcomes, e.g. depression and suicide (Berglund & Ojehagen 1998).

The outcome of the first-onset schizophrenia patients was also evaluated based on the number of hospital days in psychiatric treatment during the five-year follow-up period. The results clearly show that male patients were hospitalized more often and for longer periods than women. These results may indicate that men's severe negative symptoms, poorer premorbid functioning and poorer social networks (Thorup *et al.* 2007) may have delayed their discharge from hospital. Men with schizophrenia are also more likely to live alone and to have higher use of substances (Abel *et al.* 2010, Thorup *et al.* 2014), both of which may lengthen the duration of hospital treatment. On the other hand, women have been reported

to have better treatment response in first-onset schizophrenia than men (Räsänen *et al.* 2000, Szymanski *et al.* 1995). In general, male gender has been found to predict a continuous illness course at five-year follow-up (Bertelsen *et al.* 2009).

The results of the Danish OPUS trial showed that first-episode patients with hospital-based rehabilitation had more days in inpatient hospital care than patients with assertive community treatment. The authors of that study concluded that hospital-based rehabilitation causes patients to be more dependent on institutional care and to continue to rely on institutional care in the future (Nordentoft *et al.* 2010). In the present study, the OTP group had less hospital admissions during the five-year follow-up period. It is possible that the OTP patients' treatment and rehabilitation in outpatient services had already promoted their ability to live independently. Alternatively, the same factors that helped the patients in the OTP group to manage in outpatient care in their early phases of illness – possibly less severe illness or better social support causing residual confounding – continued to support their managing in outpatient care during the whole five-year follow-up.

In terms of the relapses of the first-onset schizophrenia patients during the follow-up period, the majority (74%) of patients in the HP group experienced at least one relapse requiring hospitalization during the five-year follow-up compared to about 40% of patients in the OTP group. In earlier studies of psychiatric patients, the relapse rate has varied between 61-82% (Robinson et al. 1999, Wheeler et al. 2011). In the Northern Finland 1966 Birth Cohort study of patients with schizophrenic psychoses, 73.8% of patients with first hospitalization were re-hospitalized within five years (Miettunen et al. 2006), which is a similar result to that for the HP group in the present study. Several characteristics of hospitalized patients with schizophrenia have been associated with a high risk of relapse. such as greater use of substances, more severe symptoms and worse performance in everyday life (Ascher-Svanum et al. 2010, Swofford et al. 1996, Swofford et al. 2000). In this study, non-adherence to medication could not be investigated, but in earlier studies it has been shown to be one of the most notable predictive factors of relapse among patients with schizophrenia (Ascher-Svanum et al. 2010, Caseiro et al. 2012, Moilanen et al. 2013, Novick et al. 2010, Robinson et al. 1999).

An interesting finding of the present study was that in the OTP group of firstonset schizophrenia patients there was a subgroup of patients (N=737) who had not needed any inpatient psychiatric treatment for schizophrenia during the fiveyear follow-up period and, notably, also had survived without any hospitalization for schizophrenia before entry into the study. The prominent characteristic of this subgroup of patients is that they were more commonly men and their onset age was older compared to those OTP patients needing hospitalization during the follow-up period. In addition, although the majority of the subgroup used some antipsychotic medication, about 25% had coped without any use of antipsychotic medication.

Several explanations are possible for this special non-hospitalized group of patients with schizophrenia. Firstly, the symptom severity of schizophrenia is shown to decrease with increasing age of onset in men, while being stable in women with schizophrenia, except for an increase in negative symptoms with later onset of schizophrenia (Häfner *et al.* 1998b). Secondly, in older first-onset age, patients with schizophrenia have been shown to have a better social network and functioning and a milder course of disorder (Cowling *et al.* 2012, Häfner *et al.* 1998a), and patients with early onset have higher levels of cognitive impairment and impulsivity traits (Kao & Liu 2010). In a British three-year follow-up cohort study, never-admitted patients with first episode of psychosis had fewer negative symptoms and better GAF-scores (Global Assessment of Functioning), indicating a better functional outcome in the future (Sipos *et al.* 2001).

# 7.2.4 Effect of medication

The impact of antipsychotics and antidepressants on the mortality of first-onset schizophrenia was also assessed for the period from onset of schizophrenia to the end of the five-year follow-up. The results revealed that second-generation antipsychotics (SGAs) were associated with reduced risk of premature death. Clozapine, in particular, seemed to decrease the risk of premature death from all causes and suicide in first-onset schizophrenia patients. In contrast, the use of first-generation antipsychotics (FGAs) was shown to increase all-cause mortality and mortality by suicide. The mortality of first-onset schizophrenia patients was even higher if the users of antipsychotics had somatic illnesses diagnosed before the onset of schizophrenia.

Regarding the all-cause mortality of patients with schizophrenia, the risk was notably decreased among users of any SGAs, and, particularly, in users of clozapine and quetiapine. Several studies have demonstrated that use of any antipsychotic, compared no antipsychotic, is associated with lower mortality in schizophrenia (Haukka *et al.* 2008, Tiihonen *et al.* 2006, Tiihonen *et al.* 2009, Tiihonen *et al.* 2011), although contradictory findings are also reported (Enger *et al.* 2004, Joukamaa *et al.* 2006). Some evidence exists that clozapine, olanzapine and risperidone may be more efficacious than quetiapine or FGAs in treating key symptoms of schizophrenia (Davis *et al.* 2003, Leucht *et al.* 2009).

Of all SGAs analysed in the present study, clozapine was the only one that was associated with lower likelihood of suicide. This result is in agreement with several studies (Jagodic *et al.* 2013, Meltzer & Okayli 1995, Meltzer *et al.* 2003, Modestin *et al.* 2005, Reid *et al.* 1998, Ringbäck Weitoft *et al.* 2014, Sernyak *et al.* 2001, Walker *et al.* 1997). Notably, clozapine is usually not the first-line treatment for persons with their first acute symptom episode (Buchanan *et al.* 2010). However, suicidal behaviour among patients with schizophrenia is common in the early phase of illness and at young age (Alaräisänen *et al.* 2009, Andriopoulos *et al.* 2011, Hirokawa *et al.* 2012, Melle & Barrett 2012, Mork *et al.* 2013). If clozapine could be used as first-line antipsychotics probably some suicides occurring at early phase of schizophrenia would be avoidable. This, in turn, would require increased effort and costs in monitoring the risk of serious side-effects of clozapine use, such as agranulocytosis, myocarditis and cardiomyopa-thy. (Raja 2011).

Regarding FGAs, the first-onset patients with schizophrenia who had used FGAs, especially chlorprothixene, were shown to be at increased risk of suicide compared to non-users of FGAs. One explanation for this might be that FGAs are not as efficacious for positive and negative symptoms and have a higher number of side-effects than SGAs (Leucht *et al.* 2009). These features may worsen patient quality of life and contribute to suicide, although at the same time the role of other factors (biological, psychosocial, genetic, environmental) cannot be ruled out. The impression gained from previous studies, however, is that SGAs have a positive impact on quality of life compared to FGAs (Awad & Voruganti 2004, Leucht *et al.* 2009). Ritsner & Gibel 2006).

Excess morbidity and mortality due to cardiovascular diseases of patients with schizophrenia are commonly explained at least partly by the use of antipsychotic medication (Joshi *et al.* 2013, Khasawneh & Shankar 2014, Murray-Thomas *et al.* 2013). In the present study of first-onset schizophrenia patients, the users of SGAs did not have elevated risk of cardiovascular death. This finding may, however, be affected by the short follow-up time. Earlier studies report SGA users as having an increased risk of cardiovascular events (Citrome *et al.* 2013, Darba *et al.* 2013). Furthermore, SGA users have been found to suffer from several cardiovascular diseases risk factors, such as increased levels of BMI, serum triglycerides and cholesterol, and hyperglycemia (Dieset *et al.* 2012, O'Donoghue *et al.* 2013). An interesting finding of the present study was that patients who had a somatic illness diagnosed before the onset of schizophrenia had a notably increased risk of cardiovascular mortality. This suggests that the presence of somatic illness should be taken into account when prescribing antipsychotic medication for the first time.

While the use of SGAs in our data on first-onset schizophrenia patients was not associated with mortality due to cardiovascular diseases, among the users of FGAs levomepromazine was related to increased risk of cardiovascular death. In an earlier study of schizophrenia patients, users of FGAs showed a five-fold higher risk of myocardial infarction than subjects without schizophrenia. Cardiovascular risk was inversely associated with the intensity of antipsychotic drug use (Enger *et al.* 2004). However, higher prescribed doses of antipsychotics have also been shown to predict greater risk of mortality from coronary heart disease and stroke (Osborn *et al.* 2007). The use of antipsychotics is a significant risk factor for adverse cardiac events, including sudden cardiac death (Honkola *et al.* 2012). Some antipsychotics may cause prolongation of QT-time, serious ventricular arrhythmias and predisposition to sudden death (Koponen *et al.* 2008).

The results of previous studies have suggested that in the FGAs high doses of thioridazine may carry a risk of increased rates of cardiac arrest, ventricular arrhythmia and of death and sudden death due to drug-induced arrhythmias (Hennessy *et al.* 2002, Reilly *et al.* 2000, Reilly *et al.* 2002, Stöllberger *et al.* 2005). In our study, thioridazine was only marginally related to an increased risk of cardio-vascular death. The difference with previous findings may be related to the study populations used. Our study consisted of first-onset patients only, whereas participants in the studies by Hennessy *et al.* (2002) and Reilly *et al.* (2000, 2002) were not solely first-onset patients.

One naturalistic study with 10-year follow-up reported that clozapine-treated patients appear to be at a 9% increased risk of death from cardiovascular diseases (Henderson *et al.* 2005). In the present study of first-onset schizophrenia patients with a shorter follow-up (5 years), mortality due to cardiovascular disease was decreased among clozapine users. One explanation may relate to the different samples and patient selection as, in Finland, clozapine is not usually being initiated for patients with cardiovascular diseases, although clozapine has been used with severely ill patients who are resistant to other drugs. In addition, our study population of first-onset schizophrenia was racially homogenous.

In addition to antipsychotics, also the use of antidepressant medication was common (about 40%) after first-onset of schizophrenia and was related to in-

creased all-cause and suicide mortality. Of all antidepressants examined in the present study, mortality was increased in users of venlafaxine. Venlafaxine is associated with cardiovascular changes (Johnson *et al.* 2006, Thase 1998) and gastrointestinal bleeding has also been reported (Ghio *et al.* 2012). In the current study of first-onset schizophrenia patients, suicide mortality was notably increased with the use of mirtazapine. In an earlier study, antidepressant medication use was associated with lower mortality from suicide and all-cause deaths when used in combination with antipsychotics (Haukka *et al.* 2008). Overall, about 28–50% of schizophrenia patients have comorbid depression (Buckley *et al.* 2009, Tsai & Rosenheck 2013), which poses challenges for proper care and medication selection. It is also known that schizophrenia itself increases premature mortality (Brown *et al.* 2000), Enger *et al.* 2004, Saha *et al.* 2007, Wahlbeck *et al.* 2011, Ösby *et al.* 2000), and symptoms of depression increase mortality even further (Laursen *et al.* 2007).

In this study, antidepressant use in general was associated with increased risk of suicide compared to non-users. In other Finnish study, antidepressant use was associated with decreased suicide deaths (Tiihonen *et al.* 2012). The differences in results may be due to different sampling methods and different antidepressants. In the study by Tiihonen *et al.*, the sampling only included hospitalized patients with schizophrenia, and thus their mean age was higher. As suicide risk is highest after first-onset of the illness, the highest risk phase had passed and the number of suicides recorded was consequently less than in the present study. The sampling time was also more recent, and therefore it is possible that group of antidepressants include more newer antidepressants.

In terms of polypharmacy of antipsychotics among first-onset schizophrenia patients, no effect on mortality was observed. This is in contrast to a recent Dutch study in which polypharmacy was found to be associated with lower likelihood of mortality (Katona *et al.* 2014). This difference in results may be explained by the data sampling, since in the present study the patients were first-onset schizophrenia patients while in the Dutch study they were antipsychotic users with schizophrenia or schizoaffective disorders. It is known that many patients with schizophrenia have an incomplete symptom response to antipsychotic monotherapy (Buchanan *et al.* 2010) and so antipsychotic polytherapy can help relieve symptoms of schizophrenia and improve quality of life.

# 7.3 Strengths and limitations of the study

## 7.3.1 Strengths of the study

The major strength of study is the large, high-quality data, which is based on Finnish national health and social welfare registers. The national registers cover the whole country, and a unique identification number assigned to every Finnish citizen ensures the full coverage and quality of data linkages. Finnish national registers have been shown to be valid tools for scientific research (Gissler & Haukka 2004, Isohanni *et al.* 1997, Miettunen *et al.* 2011, Moilanen *et al.* 2003, Pihlajamaa *et al.* 2008, Sund 2012). This study showed that linkage of social and health registers provides extensive opportunities for diverse research. The large and nationwide sample covers all first-onset schizophrenia patients with an accurate diagnosis of schizophrenia, as specified in the registers. In Finland, variations in racial, socio-economic and educational status are very small, and it is thus very unlikely that the findings are biased due those factors.

Data collection and linkage between Finnish national registers was conducted by the National Institute for Health and Welfare. The success of the data collection was evaluated and the data was sent back for correction until it was considered sufficiently accurate for research purposes. All statistical analyses have been verified by professional statisticians.

Another strength of the register linkage study was that the sample of firstonset patients was further expanded when the national registers of pensions were also scanned in addition to the information from hospital discharge registers. By combining search results from these two registers it was possible to identify patients with schizophrenia before their first hospital admission and also patients needing no hospitalization for schizophrenia. Using this sampling method it can be assumed that the true onset age of schizophrenia is more accurately defined than if based only on hospital treatment episodes (Miettunen *et al.* 2011).

The definition of first-onset age of schizophrenia used in the present study justifies the assumption that the schizophrenia patients were at the same stage of disease when the follow-up period began. In addition, the information on schizophrenia diagnosis can be considered reliable since it was based on the primary diagnoses recorded in the FHDR.

First-onset studies provide the most accurate estimate of the excess mortality of schizophrenia, because other cohorts include participants who have already survived the period of greatest excess mortality (Brown 1997). In the original Publication I, SMRs were calculated using the age-, genderand region-matched general Finnish population as a reference. Our study provided regionally adjusted SMRs, which may have produced more accurate estimates for SMRs than those reported in previous studies. Analyses at the hospital district level showed variations in mortality and highlighted differences in content and quality of psychiatric treatment.

Age-specific SMRs are a new approach in Finnish schizophrenia research. The approach showed that first-onset patients with schizophrenia have higher allcause, suicide and cardiovascular mortality risk in all age groups and that attention should be paid to mortality and especially suicide prevention not only among younger patients, but across all age groups. This study also confirmed the results of previous studies regarding excess mortality and the mortality gap between schizophrenia patients and the general population.

In original Publication II, we presented new information on disability pension rates and retirement times due to schizophrenia in different hospital districts, and showed that the retirement process varied between regions. The results confirm that schizophrenia is a severe disorder that reduces ability to function and continues to lead to disability retirement. The disability pension rate has remained unchanged at the same level as the previous Finnish cohort study.

In original Publication III we compared the outcome of schizophrenia between hospitalized and outpatient-treated groups of schizophrenia patients. This comparison between outpatient-treated and hospitalized patients represented a new approach in register-based research. Using this approach, we also identified a group of patients with schizophrenia who had no psychiatric hospitalization within the five-year follow-up period.

In original Publication IV, comprehensive nationwide data on schizophrenia patients provided opportunities to study the association between specific drugs and causes of death. The results confirmed the differences between FGAs and SGAs with respect to mortality.

# 7.3.2 Limitations of the study

One limitation of the study is that the Finnish health and social welfare registers used were originally prepared for administrative purposes (Gissler & Haukka 2004, Miettunen *et al.* 2011). Although the registers provide a lot of information, the extent and quality of information is limited. Register-based data is less likely to include detailed information on treatments, life events before death, patient

lifestyle, severity of illness, or how patient outpatient treatment was arranged. In addition, no information on outpatient primary visits was available before the year 2011 or on special outpatients visits before 1998 (Sund 2012). Consequently, some first-episode patients may have had outpatient contacts prior to inpatient treatment. Unfortunately, there are no compressive and reliable national registers for treatment in outpatient settings in Finland. Consequently, since some schizophrenia patients are treated exclusively in outpatient settings, these patients are missing from the data of the present study. However, this same methodological bias is likely to exist in the great majority of previous register-based first-episode studies, and therefore, the findings of these studies and the present study are comparable with each other.

There are many potential confounding and intervening factors during followup period that may affect the results, such as severity of illness, length of illness, comorbid diseases, commitment to drug treatment and treatment of outpatient settings. Some of the confounding factors have been taken into account in the statistical analyses, such physical diseases, but not all confounding effects can be controlled.

Comparison between hospital districts in Finland is difficult, as districts contain several psychiatric hospitals and municipalities with different types and amounts of health care resources. Each hospital district contains different hospitals with different clinical practices and resources. Thus, interpretation of the findings relating to the comparison between hospital districts must be done with caution.

As numerous statistical tests have been performed, risk of Type I error and change in findings are possible. On the other hand, some subgroup analyses may be underpowered (Type II error) due to the small number of cases in some subgroups and the likelihood of Type II error may also exist.

Methodological differences complicate the comparison of our findings concerning the definition of age at first-onset schizophrenia with previous definitions. In earlier studies, onset of schizophrenia has been defined as starting from first hospitalization for schizophrenia (Heilä *et al.* 2005, Laursen *et al.* 2007, Mortensen & Juel 1993, Ösby *et al.* 2000). Previous studies have also used a mixed population of first-onset and chronic patients (Black 1988, Brown *et al.* 2000, Ringbäck Weitoft *et al.* 1998) or included only chronic schizophrenia patients (Räsänen *et al.* 2004, Salokangas *et al.* 2002). The age at first-onset of the studied schizophrenia patients was younger than previous study samples, which would explain at least in part the increased SMRs observed in the present study. As excess mortality in schizophrenia is worse in the beginning stages of the disease, mixed population studies may give lower SMR values than first-onset studies.

Original Publication IV examined the association between purchased antipsychotics and antidepressants and mortality. Notably, a purchased medication does not necessary mean actual use of the medication. Poor compliance with medication use is common (Rabinowitz *et al.* 2009).

The correctness of the FHDR data depends on the quality and correctness of the data submitted by the data suppliers. All data requested for the Finnish Health Care Register is retrieved from the health care units' own data systems. Once submitted to THL, the data is routinely checked and, where necessary, data suppliers are requested to correct or re-submit the data. The rules regarding data checks and corrections are also described in the HILMO manual (http://www.thl.fi/en\_US/web/en/statistics/information/quality\_descriptions/specialised\_health\_care).

Register-based study research presents challenges regarding the examination of outcomes or effectiveness of treatment of patients. In general, the amount of information recorded in the registers is limited and usually intended for administrative purposes. Thus, the selection of outcome and effectiveness indicators for the research purposes is based on available information.

Mortality and disability of psychiatric patients were an important mental health indicator of the outcome and quality of psychiatric and medical health care as well as preventive programmes (Burns 2007, Korkeila *et al.* 2003, Ringbäck Weitoft *et al.* 1998, Ösby *et al.* 2000). Both indicators can be used to evaluate negative and adverse health outcomes of patients, reflecting the ineffectiveness of care and rehabilitation (Klazinga *et al.* 2001). In addition, by evaluating relapse rates and use of hospitalization, some indication of the outcome and effectiveness of mental health services and treatment can be revealed.

# 8 Conclusion

#### 8.1 Main conclusions

The purpose of this study was to investigate the outcome of first-onset schizophrenia patients using Finnish health care register data. The analysis was conducted using mortality, disability pension, psychiatric treatment and medication as outcome indicators. Excess mortality in first-onset schizophrenia was clearly observed. These findings were established after taking into account the general health status of the regional population. The risk of premature death among firstonset schizophrenia patients was higher in all age groups compared to the general population. Regional differences in mortality were not, however, associated with the population characteristics or psychiatric health resources of the hospital districts. Although regional differences in mortality were clearly seen in the current register-based study, future studies on causal factors are needed.

Half of the first-onset schizophrenia patients were retired during the fiveyear follow-up period, which is not a desired outcome. Disability pension rates and retirement time varied regionally between hospital districts. Regions with a short median time from onset of schizophrenia to disability retirement had higher overall mortality and suicide mortality. Disability pension rates were also higher in regions with high rates of involuntary treatment. These findings may indicate different treatment practices and possibilities for rehabilitation between hospital districts, but also differences in attitude towards people with schizophrenia.

Disabled patients with first-onset of schizophrenia had lower suicide mortality, which may indicate that their depressive symptoms had been identified and treated, but it may also indicate that permanent disability pension helps them cope with their illness.

Outpatient-treated patients with first-onset schizophrenia had better outcomes than hospitalized patients, including lower rates of mortality and fewer hospital days and relapses. An interesting finding was that within the outpatienttreated group of patients with schizophrenia there was a subgroup of patients who had no hospital admissions during the entire five-year follow-up, despite having severe illness and being granted disability pension for schizophrenia. The higher mortality rate of the hospitalized patients suggests that hospital treatment does not protect against suicide. The study also demonstrates that a notable number of first-onset schizophrenia patients can be identified through various types of registers other than hospital discharge registers.

Differences were found between users of first- and second-generation antipsychotics in relation to mortality. Users of second-generation antipsychotics had a reduced risk of premature death, while the use of first-generation antipsychotics increased the risk of all-cause premature death and death by suicide. In particular, first-onset schizophrenia patients with physical illnesses before the onset of schizophrenia who had later use of antipsychotics showed increased mortality risk. This should be taken into account when prescribing antipsychotic medication to this group.

To summarize, one of the main results of the study is that the outcome of schizophrenia remains poor. First-onset patients with schizophrenia had higher mortality risk than the general population across all age groups. The severity of disorder is also reflected in the disability pension rate. Half of the first-onset patients with schizophrenia were granted disability pension for schizophrenia during the five-year follow-up period. The need for continuous support and treatment was evident, with 74% of hospital-treated patients and 40% of outpatient-treated patients needing hospital treatment for schizophrenia after first-onset of the disorder. From the hospital-treated group of first-onset schizophrenia patients, 66% had received involuntary treatment and 20% did not live at home. The outpatient-treated group of patients managed better, with only 21% needing involuntary treatment and 10% not living at home. A total of 79% of patients used antipsychotic medication at the end of the follow-up, indicating a constant need of care. Regional differences between hospital districts were evident in the mortality and treatment of patients with first-onset schizophrenia.

# 8.2 Clinical implications of the study

The results presented here are of importance not only when planning and improving the treatment of patients with first-onset schizophrenia but also when planning and developing health care systems for these patients with severe mental illness. In clinical work more attention should be paid to health promotion and somatic screening, especially for diseases of the circulatory system, among patients with schizophrenia. It should be noted that first-onset patients with schizophrenia have considerably increased risk of all-cause mortality, suicide and death due to circulatory diseases across all patient age groups. Schizophrenia patients' depressive symptoms should be examined and treated, and attention should also be paid to other means of suicide prevention. Identification and treatment of substance use disorders may also reduce depressive symptoms and suicides. Appropriate treatment of depression and substance use problems will help people with schizophrenia take better care of their own health and well-being.

Suicide prevention should be given special attention, especially near to firstonset of schizophrenia and across all ages. The shorter life expectancy and high suicide rates during the first phase of illness should send a clear message to the health services to improve treatment and support for people with schizophrenia. When prescribing antipsychotic medication to patients with schizophrenia it is important to take into the account the patient's somatic condition and other risk factors in order to avoid adversities caused by prescribed antipsychotics.

Hospitalization of patients with schizophrenia seems to be associated with higher suicide risk. Therefore, it should be primarily considered whether it is possible to treat schizophrenia patients more intensively in outpatient services. Hospital-treated first-onset patients with schizophrenia also had more hospital days compared to outpatient-treated first-onset patients with schizophrenia during the follow-up, indicating that hospitalized patients are at greater risk of institutionalization. In municipalities and local health care systems thorough consideration must be given to what mental health services should be provided for patients with schizophrenia. Should we invest in outpatient treatment, which seem decrease suicide mortality and improve quality of life of this patient group? Or invest in hospital-centred services, which cost money and seem to cause higher mortality and increased hospital days, and risk for institutionalization? A balance is needed between outpatient and inpatient services that supports outpatienttreatment but also allows hospital admission when it is needed.

Disability pension rates and regional differences in the rates and retiring time of first-onset schizophrenia patients are a point of concern that raises several key questions. What are the real possibilities of municipalities and local authorities to rehabilitate patients with schizophrenia or to provide them opportunities to work at least part time? How do outpatient services support the rehabilitation of schizophrenia patients and their ability to manage in society? How do the mental health system, rehabilitation, social services and employment services collaborate for the best of the patient, to improve their well-being and functional ability? In today's are limited health and social resources, these services should work more effectively together. Collaboration between health and social care authorities is clearly in the patient's best interest and would save costs to society and promote patients' ability to cope in and contribute to society. Another cause of concern is the apparent inequality of patient outcomes between hospital districts. In some hospital districts the retirement process for schizophrenia is fast, and in some the retirement rates are generally high. It seems that a relatively short rehabilitation process is associated with increased risk of premature mortality among patients with schizophrenia, while regions with a greater amount of involuntary treatment have higher disability pension rates due to schizophrenia. Regional indicators such as unemployment rate, cost of social and mental health or number of health care staff and physicians did not explain these differences in retirement rate. Is it possible that attitudes, treatment methods and possibilities to rehabilitate patients with schizophrenia are different in these regions? It can never be overemphasized that decisions regarding disability pension and treatment in general should always be taken on an individual level. Furthermore, alternative treatment methods and rehabilitative options should be tried with each patient before making final decisions regarding disability retirement.

Second-generation antipsychotics were associated with reduced risk of mortality. These should therefore be used as the first-line treatment of first-onset schizophrenia. Clozapine, in particular, was associated with lower mortality. Inversely, first-generation antipsychotics were associated with increased risk of allcause mortality. When prescribing medication for patients with schizophrenia, the well-known side-effect profile of antipsychotics should be taken into account. Furthermore, serious attention should be focussed on comorbidities, as previous physical illness and later use of antipsychotics increases the risk of premature death of schizophrenia patients.

# 8.3 Future research

Schizophrenia as a severe mental illness continues to present great challenges for health care providers. Even though schizophrenia has been widely studied and the major risk factors have been identified, many aspects of the disease need further research.

New opportunities for register-based scientific research have incrementally opened up in recent years. However, while the use of information from hospital discharge registers for research purposes is common practice in Finland, the data is limited to inpatient treatments of patients in Finnish hospitals. As regards treatment in outpatient settings, the National Institute of Health and Welfare has collected data on specialized outpatient care since 1998 and on outpatient visits to primary health care since 2011. This outpatient data is becoming increasingly available to researchers. The use of health care system information on outpatient visits enables deeper research into the functioning of mental health services and, for example, the study of patients with schizophrenia at an earlier stage of their illness compared to information based only on inpatient hospitalization. Notably, the current growing trend in Finland is to treat patients with schizophrenia primarily in the outpatient setting of the local health care system. It is therefore necessary to use information on outpatient visits in register-based research to achieve a comprehensive understanding of the current state of patients with schizophrenia. This also enables real comparison between the outcomes of outpatient-treated and hospital-treated schizophrenia patients, as well as the study of course of illness and treatment of patients of schizophrenia who have no psychiatric hospital admissions.

Although the excess mortality of schizophrenia is well known, it would be of great interest for future research to repeat the analyses of the present study using information from outpatient visits to primary health care. Have mortality rates decreased in regions were the number of outpatient visits has increased? Moreover, what other effects have changes to the mental health services brought about regarding the mortality of schizophrenia patients?

Regional differences in mortality, retirement time and rates of retirement of patients with schizophrenia raise several questions and emphasize the need for more research. How do treatment practices and attitudes to the disease of schizophrenia differ between regions with a high and low rate of disability pensions and mortality? It would be interesting to compare regions and identify good practices that support coping and rehabilitation and help avoid premature mortality and early retirement.

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# List of original publications

- I Kiviniemi M, Suvisaari J, Pirkola S, Häkkinen U, Isohanni M & Hakko H (2010) Regional differences in five-year mortality after a first episode of schizophrenia in Finland. Psychiatric Services 61(3):272–279.
- II Kiviniemi M, Suvisaari J, Pirkola S, Läksy K, Häkkinen U, Isohanni M & Hakko H (2011) Five-year follow-up study of disability pension rates in first-onset schizophrenia with special focus on regional differences and mortality. General Hospital Psychiatry 33:509–517.
- III Kiviniemi M, Suvisaari J, Isohanni M, Saarento O, Häkkinen U, Pirkola S & Hakko H (2013) The characteristics and outcomes of hospitalized and outpatient-treated firstonset schizophrenia patients: a five-year register linkage study. The International Journal of Clinical Practice 67 (11): 1105–1112.
- IV Kiviniemi M, Suvisaari J, Koivumaa-Honkanen H, Häkkinen U, Isohanni M & Hakko H. (2013). Antipsychotics and mortality in first-onset schizophrenia: prospective Finnish register study with 5-year follow-up. Schizophrenia Research 150(1):274–80.

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