Acta Universitatis Tamperensis 2104

TIINA TALASLAHTI

Finnish Older Patients with Schizophrenia

Antipsychotic Use, Psychiatric Admissions, Long-Term Care and Mortality

TIINA TALASLAHTI

Finnish Older Patients with Schizophrenia

Antipsychotic Use, Psychiatric Admissions, Long-Term Care and Mortality

■

ACADEMIC DISSERTATION
To be presented, with the permission of
the Board of the School of Medicine of the University of Tampere,
for public discussion in the small auditorium of building B,
School of Medicine, Medisiinarinkatu 3, Tampere,
on 6 November 2015, at 12 o'clock.

UNIVERSITY OF TAMPERE

TIINA TALASLAHTI

Finnish Older Patients with Schizophrenia

Antipsychotic Use, Psychiatric Admissions, Long-Term Care and Mortality

Acta Universitatis Tamperensis 2104
Tampere University Press
Tampere 2015

UNIVERSITY OF TAMPERE

ACADEMIC DISSERTATION
University of Tampere, School of Medicine
Oulu University Hospital, Department of Psychiatry
University of Oulu, Institute of Clinical Medicine, Psychiatry
National Institute for Health and Welfare, Centre for Health and Social Economics
Finland

Supervised by
Professor Esa Leinonen
University of Tampere
Finland
MD, PhD Hanna-Mari Alanen
University of Tampere
Finland

Reviewed by
Professor Sirpa Hartikainen
University of Eastern Finland
Finland
Professor emeritus Raimo K.R. Salokangas
University of Turku
Finland

The originality of this thesis has been checked using the Turnitin OriginalityCheck service in accordance with the quality management system of the University of Tampere.

Cover design by
Mikko Reinikka

Distributor:
verkkokauppa@juvenesprint.fi
https://verkkokauppa.juvenes.fi

Acta Universitatis Tamperensis 2104
ISBN 978-951-44-9934-0 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 1598
ISBN 978-951-44-9935-7 (pdf)
ISSN 1456-954X
http://tampub.uta.fi

Suomen Yliopistopaino Oy – Juvenes Print
Tampere 2015

To Pekka, Hilla,
Väinö and Eino

Abstract

Objective: Despite a growing population of older patients with schizophrenia in future decades, research on this patients group is still limited. This nationwide register-based study of almost 10,000 Finnish older patients with schizophrenia provides new information on their mortality, psychiatric hospitalizations, drug treatments and long-term care.

Materials and methods: The data for the four independent studies (I-IV) were obtained from the Finnish national registers (the Finnish Hospital Discharge Register, the Finnish Causes-of-Death Register, pension registers and reimbursed medicines register). The study sample consisted of patients whose main diagnosis was ICD schizophrenia or schizoaffective disorder and who were alive and at least 65 years on 1 January, 1999. The sample was further divided into two groups according to age at onset of schizophrenia. The patients in the very-late-onset schizophrenia-like psychosis (VLOSLP) group had been diagnosed at age 60 years or later and the patients in the earlier onset group before the age of 60 years. The follow-up time from the registers varied between one and ten years depending on the study during the period 1998-2008.

Results: The overall mortality rate compared with the general age- and gender matched population (Standardized Mortality Ratio, SMR) was 2.7 over ten years in all older patients with schizophrenia. The most common causes of death, such as cardiovascular diseases and neoplasms, were the same as those in general older population. Mortality, however, was especially high for unnatural causes of death (accidents, suicides) being up to 11-fold, otherwise SMR was elevated in every cause-of-death category (I). When dividing the sample into two subcategories, overall mortality in patients with VLOSLP was higher (SMR 5.0) than that of the patients with earlier onset (SMR 2.9). In direct comparison, after adjusting for several variables, there was only a minimal difference in hazard of death between these onset groups (HR 1.16) (III). The use of first generation antipsychotics (FGAs) decreased and the use of second generation antipsychotics (SGAs) as well as combined use of FGAs and SGAs increased during the period 1998-2003. Two out of every five outpatient had not purchased any antipsychotics. The one-year risk of relapse (hospitalization) was 9% and was associated with combined use of

FGAs and SGAs as well as with the use of antidepressants. Cardiovascular diseases suggested a negative association with risk of psychiatric hospitalization (II). A greater proportion of patients in the VLOSLP group than in the earlier onset group needed psychiatric hospitalizations (27% vs. 23%, p=0.020) during the five-year follow-up. The shorter the time was since the onset of illness the longer was the length of stay in psychiatric hospital in the VLOSLP group in the first year of follow-up. Patients from both onset groups ended up in institutional care in equal proportions, and those with any cardiovascular disease or respiratory disease at the beginning of follow-up were less likely to end up in institutions (IV).

Conclusion: The risk of premature death in schizophrenia seems to remain high until old age. The mortality rate was even more elevated in patients with VLOSLP, especially in men, and these findings were mostly explained by physical diseases and accidents. The risk of psychiatric hospitalization, i.e. a schizophrenic relapse, was associated with antipsychotic polypharmacy and the use of antidepressants. The likelihood of ending up in long-term care was diminished in patients with cardiovascular disease or respiratory disease, which may mean that patients suffering from major physical illnesses had received better monitoring of both their mental and physical health. Patients with schizophrenia would probably benefit from careful screening of symptoms and medications and treatment of both psychiatric and physical health in the prevention when fighting against premature death and long-term care.

Tiivistelmä

Tavoitteet: Ikääntyviä skitsofreniapotilaita käsitteleviä tutkimuksia on edelleen niukalti, vaikka heidän määränsä on arvioitu kasvavan seuraavien vuosikymmenien aikana. Tässä rekisteritutkimuksessa oli lähes 10 000 suomalaista iäkästä skitsofreniaa sairastavaa henkilöä ja sen tavoitteena oli selvittää näiden henkilöiden kuolleisuutta, psykiatrista sairaalahoitoa ja lääkehoitoa sekä pitkäaikaishoitoon joutumista.

Aineisto ja menetelmät: Neljän osatutkimuksen aineisto koostuu suomalaisten kansallisten rekistereiden tiedoista (hoitoilmoitusrekisteri, kuolinsyyrekisteri, eläkerekisterit, lääkekorvattavuustiedot). Tutkimusjoukkona olivat skitsofreniaan tai skitsoaffektiiviseen häiriöön sairastuneet henkilöt, jotka olivat elossa ja vähintään 65-vuotiaita 1. tammikuuta vuonna 1999. Potilasjoukko jaettiin edelleen kahteen eri alaryhmään skitsofrenian toteamishetken perusteella. Hyvin myöhäisellä iällä skitsofreniaan sairastuneet henkilöt (very-late-onset schizophrenia-like psychosis, VLOSLP) olivat diagnoosin saadessaan vähintään 60-vuotiaita, kun taas varhemmin sairastuneet henkilöt (earlier onset) olivat saaneet skitsofreniadiagnoosin tätä nuorempana. Seuranta-aika vaihteli eri osatöissä vuosien 1998 ja 2008 välillä.

Tulokset: Koko tutkimusjoukon kokonaiskuolleisuus oli 2,7-kertainen verrattuna saman ikäiseen ja samaa sukupuolta olevaan väestöön (Standardized Mortality Ratio, SMR) vuosina 1999 - 2008. Yleisimmät kuolinsyyt, kuten sydän- ja verisuonisairaudet ja kasvaimet, olivat samoja kuin muulla iäkkäällä väestöllä. Kuolleisuus oli erityisen korkea epäluonnollisten kuolemien (onnettomuudet, itsemurhat) osalta eli noin 11-kertainen verrattuna väestöön. Kuolleisuus oli koholla kaikissa kuolinsyyluokissa (I). Kun tutkimusjoukko jaettiin kahteen ryhmään sairastumisiän perusteella, kokonaiskuolleisuus oli korkeampi hyvin myöhäisellä iällä sairastuneiden ryhmässä (SMR 5,0) kuin varhemmin sairastuneiden ryhmässä suhteutettuna väestöön (SMR 2,9). Kun kokonaiskuolleisuutta verrattiin näiden kahden ryhmän välillä, todettiin, että ero kuolemanriskissä oli pieni (HR 1.16). Ylikuolleisuutta hyvin myöhään sairastuneiden ryhmässä selittivät sairaudet ja onnettomuudet (III). Kuuden vuoden seuranta-aikana ensimmäisen polven psykoosilääkkeiden käyttö väheni ja toisen polven psykoosilääkkeiden käyttö lisääntyi, samoin ensimmäisen ja toisen polven

psykoosilääkkeiden samanaikainen käyttö. Kaksi viidestä aineiston henkilöstä ei ostanut psykoosilääkkeitä. 9 % joutui psykiatriseen sairaalahoitoon vuoden 1999 aikana. Psykoosilääkkeiden yhdistelmäkäyttö ja masennuslääkkeiden käyttö lisäsivät todennäköisyyttä joutua psykiatriseen sairaalahoitoon, mutta sydän- ja verisuonisairaudet vähensivät sitä (II). Useampi potilas hyvin myöhään sairastuneiden ryhmässä verrattuna varhemmin sairastuneisiin tarvitsi psykiatrista sairaalahoitoa viiden vuoden seurannassa (27 % vs. 23 %, p=0.020). Mitä lyhyempi aika oli kulunut skitsofreniadiagnoosista, sitä kauemmin psykiatrinen sairaalahoito kesti ensimmäisenä seurantavuonna hyvin myöhään sairastuneiden ryhmässä. Pitkäaikaishoitoon joutumisessa ei ollut eroja ryhmien välillä, mutta ne, joilla oli sydän- ja verisuonisairauden tai hengityselinsairauden diagnoosi, päätyivät harvemmin mihin tahansa pitkäaikaiseen laitoshoitoon (IV).

Johtopäätökset: Skitsofreniapotilaan ennenaikaisen kuoleman vaara näyttää säilyvän vanhuuteen asti. Kuolleisuus oli enemmän koholla hyvin iäkkäinä skitsofreniaan sairastuvilla verrattuna iäkkäisiin varhemmin sairastuneisiin, erityisesti miehillä. Tutkimuslöydöstä selittävät sekä sairaudet että onnettomuudet. Psykiatriseen sairaalahoitoon joutumisen (relapsin) vaara liittyi masennuslääkkeen tai usean psykoosilääkkeen käyttöön. Todennäköisyys joutua pitkäaikaishoitoon puolestaan väheni, jos potilaalla oli sydän- ja verisuonisairaus tai hengityselinsairaus. Tämä voisi johtua siitä, että potilaita, joilla on skitsofrenian lisäksi fyysinen perussairaus, seurataan huolellisemmin ja samalla skitsofreniaan liittyvät oireet havaitaan ajoissa. Iäkkäiden skitsofreniapotilaiden ennenaikaisen kuoleman ja laitoshoidon vaaraa voidaan luultavasti vähentää fyysisen ja psyykkisen terveydentilan hyvällä hoidolla.

Content

List of original studies

The present thesis is based on the following original studies, referred to in the text by the Roman numerals I-V. Some additional data is also presented.

I Talaslahti T, Alanen H-M, Hakko H, Isohanni M, Häkkinen U, Leinonen E (2012): Mortality and causes of death in elderly patients with schizophrenia. International Journal of Geriatric Psychiatry, 27(11), 1131-1137.

II Talaslahti T, Alanen H-M, Hakko H, Isohanni M, Häkkinen U, Leinonen E (2013): Change in antipsychotic usage pattern and risk of relapse in older patients with schizophrenia. International Journal of Geriatric Psychiatry 28(12): 1305-1311.

III Talaslahti T, Alanen H-M, Hakko H, Isohanni M, Häkkinen U, Leinonen E (2015): Patients with very-late-onset schizophrenia-like psychosis have higher mortality rates than elderly patients with earlier onset schizophrenia. International Journal of Geriatric Psychiatry 30(5), 453-459.

IV Talaslahti T, Alanen H-M, Hakko H, Isohanni M, Kampman O, Häkkinen U, Leinonen E (2015): Psychiatric hospital admission and long-term care in patients with very-late-onset schizophrenia-like psychosis. International Journal of Geriatric Psychiatry (early view), 30. doi: 10.1002/gps.4333.

Abbreviations

APA	American Psychiatric Association
ATC	Anatomical Therapeutic Chemical classification of drugs
CI	confidence interval
CNS	central nervous system
CNV	copy number variant
COPD	chronic obstructive pulmonary disease
D2	central dopamine D2
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSP	Discharged Schizophrenic Patients (Project)
ECT	electro convulsive therapy
EOS	early-onset schizophrenia
EPS	extrapyramidal symptoms
EXP	expected
FCDR	Finnish Causes-of-Death register
FCP	Finnish Center for Pensions
FGA	first generation antipsychotic drug
FHDR	Finnish Hospital Discharge Register
GAF	Global Assessment of Functioning
GWAS	genome-wide association studies
HR	hazard ratio
ICD	International Classification of Diseases
KELA	Kansaneläkelaitos
LLP	long-lasting psychiatric care
LOS	late-onset schizophrenia
LTC	long-term care
LUNSERS	Liverpool University Negative Symptom Side-Effect Rating Scale
MD	Medical doctor

MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
OBS	observed
OR	odds ratio
PANSS	Positive and Negative Syndrome Scale
PERFECT	Performance, Effectiveness and Cost of Treatment Episodes project, THL
RR	rate ratio
SD	standard deviation
SGA	second generation antipsychotic drug
SII	Social Insurance Institution
SMR	Standardized Mortality Ratio
SNP	singly nucleotide polymorphism
SSRI	selective serotonin re-uptake inhibitor
STG	superior temporal gyrus
THL	Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos)
VLOSLP	very-late-onset schizophrenia-like psychosis
WHO	World Health Organization

1 Introduction

Older people with schizophrenia are a growing population group the number of which is expected to double in the next few decades (Cohen et al. 2008). The current prevalence of schizophrenia in patients over 65 years is around 1%, and three out of a hundred of these people have received this diagnosis at 60 years or later (very-late-onset schizophrenia-like psychosis, VLOSLP) (Howard et al. 2000; Perälä et al. 2007). Little is so far known about the onset of schizophrenia in very old age even among those professionals working with older people. In order to make the disorder better understood this thesis focuses on those older people suffering from the disorder since early adulthood and also on those who received the diagnosis in old age.

The course of schizophrenia is associated with accelerated physical ageing, but the aetiology is not yet fully understood (Jeste and Maglione 2013). There are some genetic overtones, but also unhealthy life habits and exposure to antipsychotic medication, all of which may predispose patients to general health problems (De Hert et al. 2006; Koponen et al. 2002; Suvisaari et al. 2007). In addition, the increasing cognitive impairment and negative symptoms may hamper communication and help-seeking resulting in a delayed treatment. There is lot of evidence of excess mortality in the schizophrenia of middle-aged and younger patients (Brown et al. 2000; Bushe et al. 2010; Kiviniemi et al., 2010; McGrath et al. 2008; Nordentoft et al. 2013). However, less information is available on mortality among the oldest old. It is unknown if schizophrenia in old age also leads to premature death or if the causes of death differ from those in younger people with this disorder.

Despite premature physical aging, some people with schizophrenia who have received the diagnosis in young adulthood may achieve better psychosocial balance when they get old, especially those living in the community (Gareri et al. 2014; Harding 2003; Jeste and Maglione 2013). This is explained by the level of previous social functioning, rehabilitation and close relationships as well as by survival bias, i.e. the more seriously ill have already died, but at least partly by diminishing of

psychotic symptoms in the majority of aging patients with schizophrenia. However, some patients still suffer from troublesome hallucinations and delusions throughout their illness history and depression is a common comorbidity also among elderly patients with schizophrenia. Treating these situations may easily result in polypharmacy and unforeseeable side effects. There is a lack of studies on usage of psychotropics in this patient group and the influence of these on prognosis.

The vast majority of patients with schizophrenia have a history of psychiatric hospitalizations. Several factors, such as living alone, resilience of relatives, lack of adherence due to poor illness insight, and deficient psychic condition at the latest discharge have been associated with admissions (Lesage et al. 1994). Functional disability and issues not dependent on the individual, such as the social and health care services, have an impact on the need for premature long-term care, especially in older patient groups. People with this disorder generally live in institutions for longer time than people suffering from dementia. Additional information is needed to elucidate what reasons may influence psychiatric admissions and early institutionalization.

Despite the special needs of older patients with schizophrenia in treatment and every-day life, research concerning this illness in old age is still scanty. In this thesis mortality rates and associated risk factors as well as risk of institutionalization and usage of psychiatric drug treatments were studied in elderly patients with schizophrenia paying attention to the separate onset age groups.

2 Review of the Literature

2.1 Schizophrenia

Schizophrenia is a serious psychiatric disorder that usually causes permanent changes over person's lifespan. Causing multiple symptoms such as hallucinations, delusions, affect flattening and cognitive decline, it disturbs a person's ability to concentrate on work, personal relationships and every-day tasks, and causes a great deal of human suffering.

Around 1% of the world's people get schizophrenia during their lifetimes, and the onset of the illness usually occurs in early adulthood (Perälä et al. 2007). However, one fifth receive the diagnosis between 40 and 59 years (late-onset schizophrenia, LOS) and 3% of patients at 60 years or later (very-late-onset schizophrenia-like psychosis, VLOSLP) (Howard et al. 2000). The prevalence of community-dwelling VLOSLP is estimated to be 0.05% (Meesters et al. 2012) while the annual incidence of non-affective and non-organic psychoses increases by 11% for every five years after the age of 60 (van Os et al. 1995). Most of those persons diagnosed at young age are men. However, women are overrepresented in older onset age groups. The symptoms of schizophrenia vary across the lifespan. The vast majority of patients with early-onset schizophrenia suffer from active symptoms throughout their lives, but research suggests that 13.5-27% of people achieve recovery depending on the definition used (Jääskeläinen et al. 2013). In any case, greater number of family members, fewer lifetime traumatic events, and better cognitive functioning may help to achieve remission and recovery, whereas lack of insight may lead to failure to comply with treatment and delay in achieving remission (Bankole et al. 2008).

2.1.1 Risks and aetiological factors

Both genetic and environmental factors influence the appearance of schizophrenia. Recent evidence suggests that the role of heredity is approximately 64-83% (Suvisaari and Pietiläinen 2015). It is, however, impossible to determine the genetic risk for a single person. There are some genes, such as DISC1, DTNBP1 and RGS4, which have been widely studied and reported to slightly increase the risk of schizophrenia. Genome-wide association studies (GWAS) have resulted in, several single nucleotide polymorphisms (SNPs) being reported also to be associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, Consortium 2014). The genetic vulnerability is probably based on thousands of polymorphisms of which only few are known, for example BCL9 and C9orf5, which have been associated with negative symptoms in schizophrenia (Xu C et al. 2013). The GWAS studies have also found rare copy number variants (CNV), which increases the risk of schizophrenia (Malhotra and Sebat 2012). One of the most well-known, a deletion of 22q11.2, associated with velocardiofacial syndrome, is overpresented (2-5%) in schizophrenia patients. In addition to genetic load, there are some environmental factors such as pregnancy and delivery complications, central nervous system infections or traumas, childhood maladjustment, parental psychosis in childhood, or cognitive disability, which are predictive to schizophrenia (Huttunen et al. 1994; Isohanni et al. 2006; Mäki et al. 2005; Salokangas and McGlashan 2008).

2.1.2 Diagnostics of schizophrenia

Emil Kraepelin (1893) was the first to publish a description of "dementia praecox". He described an endogenous psychotic disorder with progressive long-term decline mostly starting from early adulthood. Schizophrenia was first named by Eugen Bleuler in 1911 and there were four main criteria for the disorder, i.e. four "A's": Affect inappropriateness, Autism, Association defect, and Ambivalence. The main symptoms named by Kraepelin were secondary to Bleuler's way of thinking. Finally, Kurt Schneider's first-rank symptoms have probably had the greatest influence on the current diagnostics of schizophrenia: three special forms of auditory hallucinations (hearing one's thoughts spoken aloud, hearing voices in the third person, running commentary auditory hallucinations), thought disorder (withdrawal,

insertion, and interruption), thought broadcasting, somatic hallucinations, delusional perception and ideas of passivity (Lewis 2009).

The diagnoses of schizophrenia in the present studies are based on the World Health Organization (WHO) International Classification of Diseases (ICD). The ICD-10 has been the official diagnostic classification system in Finland since 1996. The other, widely used classification of psychiatric disorders, especially in science, comes from the American Psychiatric Association (APA) Diagnosis and Statistical Manual for Mental Disorders (DSM) of which the 5th version (DSM-5) was published in 2013. The content of the DSM resembles that of the ICD, but in places the DSM contains more precise criteria for psychiatric disorders and is therefore suitable for teaching and research purposes. The 11th version of the ICD will probably be published in 2017 and the differences between the DSM-5 and the ICD-11 are expected to diminish in general, but the minimum duration of symptoms of schizophrenia (6 months in the DSM versus 1 month in the ICD) and the inclusion of social and/or occupational dysfunction criteria of illness (present in the DSM but absent in the ICD) are likely to remain (Tandon et al. 2013) (Table 1).

Symptoms of basic schizophrenia and their severity vary enormously depending on the patient, stage of the illness and the response to treatment. Hallucinations, delusions and disorganized behavior and speech, so-called positive symptoms, occur especially in the acute stage of the illness. Delusions may be persistent and their content may range from perceptions of persecutions and thoughts of being followed to pathological jealousy and sensations of control or influence. Hearing voices is the most typical hallucination, usually commenting on the person's behavior or doings, but other kinds of hallucinations are also possible such as visual illusions or experiences of smell or taste that other people cannot feel. Negative symptoms include affect flattening, anhedonia, attentional impairment, lack of motivation and decreased emotional expression. Patients with schizophrenia may also suffer from anxiety or mood symptoms, suicidal thoughts and motor symptoms (e.g. catatonia) (Heckers et al. 2013). A Finnish nationwide research project dealing with discharged schizophrenic patients (the DSP Project) between 1982 and 1997 found that almost one third of the patients had serious psychotic symptoms and three out of five depressive symptoms three years after discharge (Salokangas et al. 2000). Cognitive deficits vary from severe deterioration to milder cognitive symptoms with which a person can still continue working. In the DSP Project, only less than 10% of the

patients had not been granted a pension (Salokangas et al. 1996). The diagnostic criteria for schizophrenia according to the ICD-10 are described in Table 1.

Table 1. Diagnostic criteria and subtypes of schizophrenia (ICD-10).

	Core symptoms (minimum one symptom)	Other symptoms (or at least two of the following symptoms)	Diagnoses of schizophrenia F20	Minimum Duration
ICD-10	- thought echo, thought insertion or withdrawal, and thought broadcasting - delusions (control, influence, passivity, clearly referring to body or limb movements or specific thoughts, actions, or sensations, delusional perception) - hallucinatory voices - persistent delusions	- persistent hallucinations - breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms - catatonic behaviour - negative symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses - a significant and consistent change in the overall quality of some aspects of personal behaviour (manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal)	F20.0 Paranoid F20.1 Hebephrenic F20.2 Catatonic F20.3 Undifferentiated F20.4 Post schizophrenic depression F20.5 Residual F20.6 Simple F20.8 Other F20.9 Unspecified and course of schizophrenic disorders: F20.x0 Continuous F20.x1 Episodic with progressive deficit F20.x2 Episodic with stable deficit F20.x3 Episodic remittent F20.x4 Incomplete remission F20.x5 Complete remission F20.x8 Other F20.x9 Course uncertain	One month

2.1.3 Schizoaffective disorder

Schizoaffective disorder was firstly named by Jacob Kasanin in 1933. He discovered young patients with good premorbid level of functioning who suddenly experienced simultaneous schizophrenic and mood symptoms (Fochtmann et al. 2009). According to the ICD-10, diagnosis of schizoaffective disorder can be set when moderate or severe mood symptoms occur concurrently within at least two weeks of schizophrenic symptoms for most of the time (ICD-10). In ICD-10, it also has its own separate code F25, but in the ICD-8 and ICD-9 it has been classified in the same category with schizophrenia (295). In the DSM-III-R and in DSM-IV, schizoaffective disorder was classified as a subtype of schizophrenia, but in the latest version of the DSM it is coded separately having longer duration of mood symptoms, i.e. diagnosis entails the majority of symptoms for the total duration of the illness throughout life. There must be also delusions or hallucinations without major mood symptoms for at least two weeks. Bipolar or depressive types of the disorder should be also specified as well as the type with catatonia (Malaspina et al. 2013).

2.2 Older persons with schizophrenia

2.2.1 Older persons with early-onset schizophrenia

There is a lack of literature on patients with schizophrenia getting older and living in late life (Cowling et al. 2012; Harvey et al. 2005). The majority of them have received a diagnosis of schizophrenia in adolescence or early adulthood. Schizophrenia shortens life (Joukamaa et al. 2001; Laursen et al. 2007; Ösby et al. 2000; Ran et al. 2008; Saha et al. 2007; Tsan et al. 2012). In Finland men with schizophrenia-type psychosis die approximately 16 years and women 11 years earlier than people in general population of the same age and gender (Nordentoft et al. 2013).

2.2.1.1 Symptoms

Positive symptoms tend to become less prominent in one third of aging early onset patients with schizophrenia. However, numerous individuals still suffer severely from positive symptoms until the end of their lives (Cohen et al. 2008; Huber et al. 1975; Riecher-Rössler et al. 1999). In a 37-year follow-up of almost 300 patients with schizophrenia, there was a tendency for symptoms to abate and improve with increasing age. Only on average 20% of initial schizophrenic symptoms had remained unchanged or intensified (Ciompi 1980). Another longitudinal-study from 1930 to 1970 reported poorer prognosis in late onset patients more than 40 years old. As many as 40% still suffered from severe psychotic symptoms 30-40 years after onset of schizophrenia (Hinterhuber 1973; Riecher-Rössler et al. 1999).

Instead, the results from earlier studies concerning negative symptoms are contradictory. The symptoms may either stay stable, diminish or became more serious causing enormous difficulties in social life and ability to function (Cohen et al. 2008). Negative symptoms may be aggravated by depression, or medication adverse effects can be confused with affect flattening or decreased emotional expression. Long hospitalization or staying in residential care without adequate stimuli may also cause apathy and lack of motivation in every-day tasks. Depression among middle-aged and older individuals with schizophrenia living in the community is estimated to vary between 44% and 75% (Diwan et al. 2007). Multiple comorbidities, functional limitation or lack of social support are strong predictors of depressive mood in patients with schizophrenia (Meesters et al. 2014). In a longitudinal study of early-onset patients aged 55 or more, two-fifths had persistent symptoms and one-fourth had fluctuating depressive symptoms (Cohen et al. 2014). Increased auditory hallucinations have also been associated with depression in older patients with schizophrenia (Cohen et al. 2014)

2.2.1.2 Cognition

Older patients with schizophrenia have greater difficulties in both global and domain-specific neuropsychological functioning compared with age peers (Irani et al. 2011). Deficits in executive functions, visuo-spatial constructional abilities, verbal fluency and psychomotor tasks are the most frequent problems in old age

(Loewenstein et al. 2012; Rajji and Mulsant 2008). In a longitudinal study with a follow-up time of eight years, the performance in cognitive tasks changed towards more prominent delayed recall and recognition and learning impairments in elderly patients with schizophrenia (Bowie et al. 2004). High doses of antipsychotics may be associated with increasing difficulties with memory and verbal learning (Husa et al. 2014).

Estimates of course of cognitive decline across the lifespan vary distinctively according to the earlier history of illness and symptom severity. Patients with a less adverse lifetime course of illness possibly have better cognitive performance in old age (Harvey et al. 2006). Also, several moderating factors such as gender, age, living circumstances, level of education or support available from nearest may also influence the level of impairment in that age. Studies on cognition usually include only individuals in hospital or institutional care, which may skew the results of studies on cognition.

An article by Rajji and Mulsant (2008) concludes that cognitive dysfunction is at its most rapid weakening soon after the onset of schizophrenia in young adulthood, but then remains stable until the age of 65. After that scores on the Mini Mental State Examination (MMSE) decrease one point per year i.e. slower than in Alzheimer's disease. Other studies suggest that cognition in old age schizophrenia weakens as in elderly general population, but results in a more serious level of disability because of deterioration from the premorbid level in the early years of the illness (Jeste et al. 2011). Cognitive decline seems to correlate strongly with functional disability (McGurk et al. 2000). Individuals over 70 years of age with schizophrenia are especially vulnerable to functional disability together with cognitive decline because of accelerated ageing (Loewenstein et al. 2012). Living in institutional care or suffering from negative symptoms has been associated with more serious cognitive problems than living in the community, also in patients with later onset of schizophrenia (Friedman et al. 2001; Harvey et al. 1999; Holden 1987; Mazeh et al. 2005).

2.2.1.3 Brain morphology

Grey matter reduction has been associated with schizophrenia in different stages of the illness. It is already present in a group at high risk of getting schizophrenia and becomes even more extensive with longer duration of the illness (Chan et al. 2011; Haijma et al. 2013; Shepherd et al. 2012). In an earlier meta-analysis, a progressive volume loss of grey matter in the left hemisphere and the superior temporal structures (total cortical grey matter, left superior temporal gyrus, left anterior, left Heschl gyrus, left planum temporale and posterior STG bilaterally) was detected and was partly moderated by the type of antipsychotics taken (Vita et al. 2012). In a recent study on the differential effects of first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) on the brains of patients with early first-onset schizophrenia, FGA-treated patients tended to show dose-related decreased cortical thickness than did healthy controls and this led to higher negative symptom scores. Conversely, the SGA-treated group showed increases in thickness in frontal brain areas resulting into lower scores on positive symptoms (Ansell et al. 2015). In post-mortem studies, frontal grey matter volume has been reported to be 12% smaller in patients with schizophrenia than in non-schizophrenic subjects (Selemon et al. 2002). Schizophrenia is also characterized by smaller overall brain volume, white matter decreases and lateral ventricular volume increases, and some of these changes may be connected to cumulative exposure to antipsychotics (Fusar-Poli et al. 2013; Tanskanen et al. 2009; Veijola et al. 2014).

When assessing the results of different studies on age-related changes in MRI studies in schizophrenia, three interconnected issues should be considered, namely phase of the illness, age of the patients and history of medication. Most studies concern patients under 55 years of age. In a systematic review of functional MRI studies no clear differences in brain morphology between the results on studies of mid-life and elderly patients with schizophrenia were found (Chiapponi et al. 2013). In a study with diffusion tensor and structural MRI, patients with schizophrenia showed faster decrease in anisotropy in white matter areas of the frontal and temporal lobes (Brodmann area 10 bilaterally, 11 in the left hemisphere and 34 in the right hemisphere) with age than did non-schizophrenic subjects (Schneiderman et al. 2011).

2.2.2 Patients with late-onset schizophrenia and very-late-onset schizophrenia-like psychosis

2.2.2.1 Diagnosis of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis

"I am not of this world", a phrase from an experimental study of patients living with late-onset schizophrenia, reflects the thoughts of those who have received the confusing diagnosis of schizophrenia in old age (Quin et al. 2009). The onset of the illness in mid-life, between 40 and 59 years, is called late-onset schizophrenia (LOS) and onset of the illness at the 60 or later very-late-onset schizophrenia-like psychosis (VLOSLP) (Howard et al. 2000).

Emil Kraepelin introduced the term "paraphrenia", a subtype of "dementia praecox", to refer to a disorder with better prognosis starting with paranoid delusions and diverse hallucinations but not including late onset in the term. In 1943, Manfred Bleuler described "late-onset schizophrenia" with an onset age after 40 years. The concept of "late paraphrenia", meaning onset age after 55, was first presented by Roth and Morrisey in 1952 (Roth and Morrissey 1952). Since then, there has been a debate on whether late paraphrenia is a relevant independent diagnosis, or if it has some affinity with an affective disorder, or if it could be related to brain diseases, or if it is combination of several conditions (Almeida et al. 1995; Castle and Murray 1991; Holden 1987). In their review in 1998, Roth and Kay concluded that late paraphrenia is a variant of schizophrenia but requires a broader definition (Roth and Kay 1998). In 2000, several decades after the coining the concept, the international expert consensus panel directed by Howard stated that diagnoses of VLOSLP and LOS, i.e. subtypes of schizophrenia, are valid and useful when assessing medical treatment plans for older psychotic patients (Howard et al. 2000). The additional purpose of the consensus was to stimulate research. The age of 60 years offered the strongest evidence for a cutoff to define VLOSLP. Previously the ICD-9 included late paraphrenia (both later delusional disorder and schizophrenia) and the DSM-III-R had a category for patients with onset age at 45 years or later. However, in the ICD-10 or DSM-5 there is no specific classification for patients with later onset of this illness. The literature on patients with latest onset

of the schizophrenia is still scarce which may hamper progress in the diagnostic classification in this patient group

2.2.2.2 Theoretical background of very-late-onset schizophrenia-like psychosis

At least two different theories underlying VLOSLP have been proposed. The first is that the neuronal loss or vascular changes related to ageing, e.g. postmenopausal estrogen loss in women, lead to modification in the balance of central dopamine Type 2 (D2) receptors in the basal ganglia. Another hypothesis is that there is no genetic burden but a single random event in old age, such as a vascular event or an early phase of dementia, which may precipitate schizophrenia. Hence, aetiopathology on the basis of late-onset psychosis is perhaps a mixture of delayed early-onset and age-related organic causes (Karim and Burns 2003).

2.2.2.3 Symptoms and characteristics

Despite similarities in the symptoms of patients with early-onset schizophrenia (EOS) and LOS, according to the International Late-Onset Schizophrenia Group some of the symptoms are more prominent in those with later onset (Howard et al. 2000). Patients with LOS report more multimodal hallucinations, persecutory and partition delusions, and third-person, running commentary, accusatory or abusive auditory hallucinations than do the patients with EOS (Uchida et al. 2008). Patients with LOS are also more likely to complain of olfactory, visual, or tactile hallucinations, but they are less likely to have formal thought disorder and negative symptoms, especially those with onset after 60 years. Indeed, in some later studies, negative symptoms have not been prominent in these individuals (Vahia et al. 2010). Compared to recent diagnosed patients with EOS or LOS, VLOSLP patients have more positive symptoms (Hanssen et al. 2014). In some studies, typical psychomotor abnormalities, prominent hallucinations and poor insight but an absence of grandiosity and mystic delusions in VLOSLP patients have also been found (Alici-Evcimen et al. 2003; Girard and Simard 2008; Mason et al. 2013; Tan and Seng 2012).

There is no unambiguous evidence of familial burden in VLOSLP. Women have a 2-6 times greater risk for LOS than men, which has been explained by the

possibility that estrogen may protect women against the illness in earlier years (Castle and Murray 1993; Riecher-Rössler et al. 1997; Schurhoff et al. 2004). Premorbid personality may have contained strains of schizoid introversion or paranoid sensitivity predisposing to later onset of schizophrenia (Jeste et al. 1995; Kojo 2010). Despite that, premorbid educational, occupational and psychosocial functions are less impaired in VLOSLP than in EOS but more than in age-matched people without schizophrenia (Barak et al. 2002). In a study of first-onset psychoses, the relationship between depression or neuroticism and the risk of psychosis diminished as the illness onset shifted towards older ages (Köhler et al. 2007). The decreased effect of neuroticism may partly explain why older late onset patients cope better with the illness. Several possible risk factors for VLOSLP have also been identified, such as social isolation, immigrant status, hearing loss or visual impairment (Reeves et al. 2002; Reeves et al. 2003; Rodriguez-Ferrera et al. 2004).

A qualitative study found patients with VLOSLP to have long-term experiences of being different and lonely with solitary coping style and trying to find a meaning for their psychosis (Shepherd et al. 2012). On the other hand, Theory in Mind abilities, i.e. the ability to attribute mental states to others in order to explain, predict and manipulate behavior, have been reported to be better in LOS patients than in EOS patients, and it has been suggested that this may be a protective factor postponing the onset of schizophrenia (Smeets-Janssen et al. 2013). However, VLOSLP patients' insight into their own illness is apparently poor (Rodriguez-Ferrera et al. 2004).

2.2.2.4 Cognition and brain morphology

According to the consensus statement of the International Late-Onset Schizophrenia Group, no major difference in type of cognitive deficits has been found between early- and late-onset cases, although the latter are associated with milder cognitive deficits especially in the areas of cognitive flexibility, abstraction and learning (Howard et al. 2000). Patients with later onset schizophrenia also tend to have better speed processing and verbal memory as well as certain aspects of better executive function than do earlier onset elderly patients with schizophrenia (Vahia et al. 2010). In a recent cross-sectional study by Hanssen et al. (2014), VLOSLP patients performed parallel on neuropsychological tests with EOS and LOS patients

with a duration of schizophrenia less than ten years. The study consisted of both in- and outpatients with schizophrenia-spectrum disorders (57% had diagnoses of schizophrenia) (Hanssen et al. 2014). However, patients with VLOSLP have shown more remarkable decline in many domains of neurocognitive performance than normal subjects (Vahia et al. 2010). Studies on cognition of patients with later onset schizophrenia show conflicting results, mainly because of patients' heterogeneity in the domains of age, non-controlled organic background or affective symptoms. Sample sizes in these studies are often small.

The issue of VLOSLP being organic in origin, i.e. neurodegenerative process, has been debated. In earlier longitudinal studies, 23-35% of very late onset patients with paranoid or schizophrenic symptoms have shown more marked global cognitive deterioration than non-schizophrenic controls, but notably fewer have become demented (Hymas et al. 1989; Reeves et al. 2002). Compared to general population, patients with LOS and VLOSLP have also been reported to have a three times higher risk of developing dementia (Kørner et al. 2009). Thus the risk is comparable to that of late-onset major depression disorder or delusional disorder (Leinonen et al. 2004). Accordingly, imaging studies in VLOSLP patients have reported non-specific findings such as enlarged third ventricle volume, lower volume in the left temporal lobe or superior temporal gyrus and higher ventricle-to-brain ratio compared to age peers and increased focal white-matter and cortical abnormality (Chen et al. 2013; Howard et al. 2000; Jones et al. 2005; Tan and Seng 2012). These findings have sometimes been considered to be within the normal range for age, comparable to EOS and not related to present cognitive profile.

2.2.2.5 Genetics

Recent studies on genetic risk of have suggested that later onset of illness may be influenced by some specific genes such as a 32 base-pair deletion allele in chemokine receptor CCR5 and a polymorphism rs2734829 located in D2 receptor (Rasmussen et al. 2006; Voisey et al. 2012). Elevated c-reactive plasma protein has also been associated with a 6- to 11-fold increased risk of late- and very-late-onset schizophrenia, but more research is needed to establish the causality of this finding (Sharma et al. 2014; Wium-Andersen et al. 2014).

2.2.3 Mortality in older persons with schizophrenia

The lives of patients with schizophrenia are expected to be 15-20 years shorter than those general population (Laursen et al. 2013). The gap between people with schizophrenia and rest of the population has widened despite efforts to develop more effective treatment options (Saha et al. 2007). In earlier studies, mortality risk in schizophrenia has varied from 1.8-fold to 4.5-fold compared with general population or comparison subjects (Brown et al. 2000; Bushe et al. 2010; Heilä et al. 2005; Kiviniemi et al. 2010; McGrath et al. 2008; Nordentoft et al. 2013; Saha et al. 2007). The risk of death has been reported to be highest some years after diagnosis (Heilä et al. 2005; Mortensen and Juel 1990; Nordentoft et al. 2013; Palmer et al. 2005; Salokangas et al. 2002). In Finnish five-year follow-up of new patients with schizophrenia aged 15 to 44 years (n=227), mortality was 6%. Three out of four of the deceased, mostly men, died in two years after the onset of the disorder (Salokangas et al. 1991).

The number of studies on mortality of older patients with schizophrenia is limited. Mortality rates have reported to be around 1.4 and 3.7 depending on the research frame (Almeida et al. 2014; Fors et al. 2007; Kredentser et al. 2014; Mortensen and Juel 1990; Ösby et al. 2000; Räsänen et al. 2003). In studies in which age groups begin from early adulthood, mortality rates have often decreased with age (Fors et al. 2007; Kredentser et al. 2014; Laursen et al. 2007; Ösby et al. 2000). Studies on mortality of older patients with schizophrenia are given in Table 2.

Table 2. Studies on mortality of older patients with schizophrenia.

Author, year	Main topic of the article	Number of older subjects with schizophrenia	Follow-up time, maximum	Main findings
Almeida et al. 2014	Mortality among people with severe mental disorders	444 men (schizophrenia spectrum disorder)	14 years	Age-adjusted Mortality HRs in schizophrenia spectrum disorders in men: 65-85 years 2.3 (95%CI 1.8-2.9). Age adjusted life expectancy was reduced by 2.0 years (1.6-2.3) in schizophrenia spectrum disorders.
Erlangsen et al. 2006	Suicide among older psychiatric inpatients	NR (total 37,172)	11 years	ORs for suicide in schizophrenia: 60+ years 0.6 (0.4-1.0) in all, and 0.5 (0.3-1.0) in men and 0.8 (0.4-1.4) in women.
Erlangsen et al. 2012	Suicide risk of older adults with schizophrenia	8893 men and 9165 women	17 years	SMRs for suicides: 50-69 years 7.0 (5.8-8.4) in men and 13.7 (11.3 – 16.6) in women, 70+ years 2.1 (1.1-9.3) in men and 3.4 (2.0 – 5.8) in women, and in patients with VLOSLP: 2.6 (1.3 – 5.3) in men and 6.4 (4.0 – 10.4) in women.
Fors et al. 2007	Mortality among persons with schizophrenia in Sweden: An epidemiological study	47	10 years	Relative risk of dying: 65+ years, from all causes 1.6 (p= 0.003), from circulatory diseases 1.8 (p= 0.028).
Kredentser et al. 2014	Cause and rate of death in people with schizophrenia across lifespan	2,373 (schizophrenia spectrum disorder)	12 years	Relative risk of dying: 60+ years, from all causes 1.4 (p<0.0001), from circulatory diseases 1.4 (p<0.0001), from respiratory diseases 1.7 (p<0.0001).

Laursen et al. 2007	Mortality among patients admitted with major psychiatric disorders	NR (total 17,660)	28 years	SMRs in schizophrenia: 55-79 years 2.4 (2.2-2.6) in men and 2.4 (2.1-2.5) in women, 80+ years 1.7 (1.4-2.1) in men and 1.5 (1.3-1.7) in women. SMRs in schizoaffective disorder: 55-79 years 1.9 (1.7-2.2) in men and 2.2 (2.0-2.4) in women, 80+ years 1.5 (1.1-2.0) in men and 1.3 (1.2-1.5) in women.
Mortensen and Juel 1990	Mortality and causes of death in schizophrenic patients	NR (total 9,156, first admitted)	18 years	SMRs: 65-84 years 1.8-2.0 in men and 1.2-2.2 in women, 85+ years 0.8 in men and 1.1 in women. Suicide rates were highest among men aged 70 years or more (RR 25-48).
Osborn et al. 2007	Relative risk of cardiovascular and cancer mortality in people with severe mental illness	NR (18,555 with schizophrenia)	16 years, median follow-up 4.7 years	HRs of coronary heart disease mortality in people with severe mental illness: 50-74 years 1.96 and 75+ years 1.0 (not significant), and of stroke mortality 50-74 years 2.0 and 75+ years 1.3.
Ösby et al. 2000	Mortality and causes of death in Stockholm County, Sweden	770 first-onset patients with schizophrenia	23 years	SMRs in schizophrenia, aged 65+ years: for natural causes of death 1.7 (1.3-2.1) in men and 1.5 (1.3-1.8) in women, and for suicides/unspecified violence 2.6 (0.9–7.2) in men and 2.8 (1.2–6.4) in women, for more than 5 years after the onset of schizophrenia.
Räsänen et al. 2003	Mortality among long-stay psychiatric patients	33 long-stay patients with schizophrenia	9 years	SMRs in schizophrenia: 65-74 years 3.7 (2.4-5.8) in all and 4.0 (2.3-6.9) in men and 3.3 (1.6-6.9) in women; 75-84 years 3.0 (1.7-5.2) in all and 2.9 (1.2-6.9) in men and 3.1 (1.5-6.4) in women.

NR: not reported; HR: Hazard Ratio; OR: Odds Ratio; SMR: Standardized Mortality Ratio; VLOSLP: very-late-onset schizophrenia-like psychosis

2.2.3.1 Causes of death

There is a lack of studies on the causes of death of older patients with schizophrenia, but it is known that similar reasons as in the general population kill individuals with schizophrenia in both younger and later age (Almeida et al. 2014). In a study on mortality in mentally ill Scandinavian patients with recent onset schizophrenia, mortality for natural reasons, i.e. physical diseases, after second year or later from the first discharge was 2.8-fold and 2.2-fold in Finnish men and women with schizophrenia respectively (Nordentoft et al. 2013). On the other hand, in five-year follow-up one in twelve died of natural causes (Salokangas et al. 1991).

Most of the deaths were due to natural causes. In studies of younger patients with schizophrenia, cardiovascular and respiratory diseases are the most common single causes of death, the former being 1.4-2.8 –fold and the latter 2.0-3.5 -fold compared with general population (Brown et al. 2010; Joukamaa et al. 2001; Kiviniemi et al. 2010). Patients with schizophrenia often have a one-sided diet, neglect physical exercise and are heavy smokers all of which increase the risk of these diseases (Dipasquale et al. 2013; Roick et al. 2007). Furthermore, antipsychotics may cause metabolic problems and weight gain (De Hert et al. 2006; Koponen et al. 2002; Suvisaari et al. 2007). On the other hand, the use of antipsychotics has been reported to reduce mortality and the risk can be described by a U-shape; that is to say that those patients using the smallest effective doses of antipsychotics probably have the smallest risk of death (Tiihonen et al. 2009). For sudden cardiac-, cerebrovascular-, and infection-related diseases, the link between antipsychotic use and death is unclear, but possible mechanisms accounting for this include e.g. heart failure, sudden death associated with QT prolongation leading to arrhythmia and pneumonia (Koponen et al. 2008; Leon et al. 2010).

The level of cancer mortality has mostly been lower than in general population. However, the tendency may be increasing (Hodgson et al. 2010). In a study of Kisely et al. (2013), people with schizophrenia had more metastases at the time of cancer diagnosis. Some autoimmune diseases, osteoporosis and caries as well as some eye diseases such as pigmentation of lenses or glaucoma have also been reported to be

common among patients with schizophrenia (Salokangas 2009). Genetic factors possibly common to both schizophrenia and some major somatic diseases may also play a role in excess mortality in schizophrenia.

The category of unnatural causes of death includes accidents, suicides and homicides. Among patients with schizophrenia the lifetime risk of suicide is about 4-6% (Hor and Taylor 2010; Palmer et al. 2005). In a Scandinavian study by Nordentoft et al. (2013), observed/expected mortality ratio due to unnatural causes of death after the second year or longer after the first discharge from hospital was seven to eight fold for both Finnish men and women with mental disorders. Risk of death is usually highest in the first years after onset of the disease and some weeks after discharge from psychiatric hospital care (Alaräisänen et al. 2009; Nordentoft et al. 2004; Nordentoft et al. 2013; Ösby et al. 2000). In a recent systematic review, several risk factors for suicide were reported in both in- and outpatients (Popovic et al. 2014). A history of a suicide attempt is the most alarming sign for both genders, then depression and greater number of admissions, in addition male gender, awareness of the deteriorating course of the condition, and a sense of hopelessness with loss of faith in treatment even without marked comorbid depression (Jablensky 2009). For outpatients, quick readmission after discharge, male gender, substance abuse, younger age, period close to illness onset and hopelessness may increase suicidal ideations and attempts. Older age at illness onset, i.e. after 30 years of age, has also been reported to increase the risk for suicide (Popovic et al. 2014; Reutfors et al. 2009). Even if there are substantial differences in mortality rates among patients with schizophrenia between different health care districts, the risk of death by suicide seems to be similar in different parts of Finland (Salokangas et al. 2008).

In middle-aged and older patients with schizophrenia, suicide risk decreases with age (Erlangsen et al. 2006). In a British study by Osborn et al. (2008), the risk of suicide persisted up to the age of 70. Male gender has been associated with risk of completed suicide in older people in general as well as in those with schizophrenia (Barak et al. 2004; Kiosses et al. 2014). Those with dual diagnoses, e.g. some alcohol-related disorder, are at the greatest risk. Cohen et al. (2008) reported that up to 75% of older patients with schizophrenia have depressive symptoms which may lead to suicidal ideation. Positive symptoms of schizophrenia, e.g. somatic delusions and commanding hallucinations, or painful physical diseases may lead to suicidal thoughts. Suicide attempts at older age in general are often violent, but research on older schizophrenia patients on this issue is scarce (Karvonen et al. 2008).

Most of the accidents in older people are caused by falls and the reasons for these are many and varied. There is plentiful data that both benzodiazepines and antipsychotics may cause fatal falls in the mentally ill elderly (Hartikainen et al. 2007; Huang et al. 2012; Lavsa et al. 2010). The pharmacokinetics and pharmacodynamics of psychotropic drugs may change with ageing which is one reason why older individuals are more vulnerable to adverse effects (Jeste 2004; Leon et al. 2010). These may include extrapyramidal symptoms such as parkinsonism and tardive dyskinesia, or dizziness, tiredness and cognition decline, and they are related to the general health and age of an individual as well as length of exposure and daily doses of medication. There is also some evidence that benzodiazepines may increase the risk of suicide, especially if prescribed at discharge (Salokangas et al. 2002; Tiihonen et al. 2012).

People with schizophrenia have been reported to be at approximately twofold increased risk of homicidal death in general, but this risk decreases with age (Crump et al. 2013). The risk is higher in men and with comorbid substance abuse disorder (Hiroeh et al. 2001).

2.2.4 Psychotropic medication

Antipsychotics are also the first treatment option in older patients with schizophrenia. They are classified into two main groups: first-generation antipsychotics (FGAs) i.e. typical antipsychotics, and second-generation antipsychotics (SGAs) i.e. atypical antipsychotics according to their action profile. In a recent meta-analysis of studies including younger patients, the classification of antipsychotics was challenged, but was concluded to be the prevailing system (Leucht et al. 2013). Antidepressants, mood stabilizers and benzodiazepines are frequently combined, but multi-medication should be avoided if possible. Treating patients with psychotropics should also be combined with psychosocial interventions along with medical controls.

Pharmacokinetic and pharmacodynamic age-related changes are patient and medication specific and have to be taken into account when prescribing psychotropics, e.g. antipsychotics, for older people. These changes include an increase in the volume distribution and prolongation in the elimination half-life of some medications and a decrease in hepatic protein synthesis, which may lead to an

increase in the free drug fraction. This biologically active part of drug in the blood enhances drug effects in CNS. Pharmacodynamic changes include an increase in the permeability of the blood-brain barrier resulting in greater CNS vs. blood concentration ratio. In addition, the absolute number of dopaminergic neurons and the density of D2 receptors in the brain diminish along with increasing age (Jeste et al. 2011).

2.2.4.1 First generation and second generation antipsychotics

Antipsychotic medication alleviates the patient's psychotic symptoms, reduce the risk of relapse, and improves quality of life. There are no major differences in efficacy between FGAs and SGAs, however no direct head-to-head comparisons have been reported in older schizophrenia patients (Kishimoto et al. 2013; Lieberman 2007). Unfortunately the effect of antipsychotics on negative symptoms is weak, and FGAs may even accelerate cognitive decline. In general, the smallest recommended antipsychotic dose in acute psychosis of schizophrenia is 300-600 mg chlorpromazine equivalents for physically health younger patients and 150 mg chlorpromazine equivalents in maintenance treatment of schizophrenia (Current Care Guideline 2015), which doses can be too high for many older patients.

The most frequent adverse effects caused by antipsychotics are extrapyramidal symptoms (EPSs) such as parkinsonism (tremor, bradykinesia, and rigidity), akathisia i.e. motor restlessness, and dystonias (spasms, muscle contractions). In general EPSs are more common in the elderly and with degenerative brain diseases. Tardive dyskinesia (irregular, jerky movements) is an adverse effect that results from years of exposure to antipsychotics, but in older patients it may occur even in months of treatment. The risk of tardive dyskinesia is at least five times greater in older patients than in younger adults (Jeste 2004). Antipsychotics are also associated with falls, pneumonia and decline in cognition especially in older patients (Lavsa et al. 2010; Leon et al. 2010; Pratt et al. 2012). In addition, weight gain, insulin resistaence, tachycardia, QT prolongation, hyperprolactinaemia, agranulocytosis, and malignant neuroleptic syndrome are well known adverse effects of antipsychotics many of them with increased risk. Orthostatic hypotension associated with falls and fractures is common in older patients taking medication which block alpha-1 adrenoreceptors, for example quetiapine, risperidone and olanzapine, as well as conventional low-

potency antipsychotic drugs. Long exposure with high doses of FGAs, such as chlorpromazine, may predispose to a cataract or a hyperpigmentation of the lenses (Leucht et al. 2007). The risk of death when antipsychotics are used to treat the behavioural symptoms of dementia has been reported in several reviews, but such results have not been confirmed in treating older patients with schizophrenia (Gareri et al. 2014; Pratt et al. 2012).

Antipsychotic drug treatment in schizophrenia started in the 1950's, when the first FGA, chlorpromazine, came on the market and was rapidly followed by several other FGAs, such as haloperidol, perphenazine or thioridazine. These all block postsynaptic dopamine D2-receptors in the limbic and frontal cortical regions of the brain. So-called high potency drugs (such as haloperidol, and perphenazine) have stronger affinity in these receptors than the low potency drugs (such as chlorpromazine or thioridazine). The risk of EPS and tardive dyskinesia has generally been reported to be higher in FGAs than in SGAs especially in older patients (Jeste 2004; Kinon et al. 2015). EPS are even more common when taking high potency drugs than low potency drugs, but the latter usually have higher risk of sedation and anticholinergic adverse effects (Stroup et al. 2006).

SGAs (risperidone, olanzapine, quetiapine, aripiprazole etc.) in general are associated with lower prevalence of extrapyramidal side effects than FGAs because of lower D2 receptor affinity and higher serotonin 5-HT2A receptor affinity (Kane et al. 2013). However, in some later studies, SGAs have not been clearly beneficial compared to FGAs for self-care outcome, cognition, long-term manifestation of symptoms, and physical care (Kisely et al. 2009; White et al. 2006). According to some earlier reports, changing from FGAs to SGAs achieved a significant improvement in psychopathology in older patients with schizophrenia (Jeste et al. 2003). However, clozapine is still the most effective drug for alleviating psychotic symptoms, but the treatment should be monitored meticulously in older patients because of serious adverse effects such as agranulosytosis, the risk of which is highest in older women. Contrary to promising expectations of the benefits of SGAs, many of these drugs seem to cause various metabolic problems.

The doses of antipsychotics recommended for older adults are smaller than those prescribed to younger patients, and in very-late-onset schizophrenia they may be only a half or even only a quarter of the standard doses (Alexopoulos et al. 2004; Uchida et al. 2008). Dose recommendations are mostly based on data extrapolated from studies not including individuals over 60 years. The research available on

dosage is often naturalistic and cross-sectional. In a systematic review from 2006, only three limited, but reliable studies were found on antipsychotic medication for older schizophrenia patients, but no recommendations could be made on this basis (Marriott et al. 2006). In 2004 the Expert Consensus Panel published a guideline for administering antipsychotic drugs to patients aged 65 years or more (Alexopoulos et al. 2004). Their first-line recommendation for late-life schizophrenia was risperidone with a daily dose of 1.25-3.5 mg followed by quetiapine (100-300 mg/day), olanzapine (7.5-15 mg/day), and aripiprazole (15-30 mg/day). Experts also suggest that antipsychotic treatment should be permanent at the lowest effective dose. In a recent case report and review antipsychotic medication was successfully withdrawn from four older early-onset patients with schizophrenia, but no other earlier studies on withdrawal of antipsychotics concerning patients at 65 years or more were found (Suzuki and Uchida 2014).

There is no trial-based evidence for guidelines on medication for very-late-onset schizophrenia (Essali and Ali 2012). However, there are some case series and open-label studies reporting the effects of antipsychotic medication with small numbers of patients. In a naturalistic retrospective study by Scott et al. (2010) the available SGAs (quetiapine, olanzapine, risperidone, aripiprazole) achieved had responses at low doses in patients with VLOSLP. The older the patients were, the stronger was the response. Nearly 62% of the patients responded and those patients with more severe symptoms at an even higher rate (Scott et al. 2010). Amisulpiride has also shown some promising results in alleviating psychotic symptoms in VLOSLP, but more research is needed to verify the findings (Psarros et al. 2009).

2.2.4.2 Antidepressants

Antipsychotic medication alone can sometimes alleviate depressive symptoms in patients with schizophrenia by reducing anxiety and improving mood. The Expert Consensus Guideline recommends treating major depression and schizophrenia firstly with SGAs, secondly with SSRI and then with venlafaxine or bupropion if extra treatment in addition to these antipsychotics is still needed (Alexopoulos et al. 2004). Likewise in cases of subsyndromal depression augmentation with an SSRI is advised (Kasckow and Zisook 2008). Citalopram together with antipsychotic medication seems to improve depressive and also negative symptomatology, as well

as social and mental health functioning and quality of life, but not cognition (Dawes et al. 2012; Felmet et al. 2011; Kasckow and Zisook 2008). Antidepressants for patients with schizoaffective disorder must be used with caution because of the risk of phase acceleration and manic symptoms. Antidepressants are prescribed for up to 30% of inpatients and 43% of outpatients of all ages with schizophrenia and depressive symptoms (Felmet et al. 2011; Kasckow and Zisook 2008).

Despite the advantages of antidepressants, they have some noteworthy adverse effects such as nausea, diarrhoea, increased sweating and sexual dysfunction. They have also been associated with worsening of psychotic symptoms and agitation especially in the elderly. When augmenting SSRIs with adjuvant psychiatric medications, older patients must be monitored carefully because of the increased risk of interactions and multiple adverse effects.

2.2.5 Psychiatric hospitalizations

The vast majority of Finnish patients with schizophrenia are hospitalized in psychiatric units at some stage of the illness. The mean length of stay in psychiatric hospital has become much shorter in recent decades, also in patients with schizophrenia or schizoaffective disorder aged 65 years or more: the mean length of stay was 89 days in 2004 while in 2013 it was 51 days in (THL, 2015). The latest systematic review of the Cochrane database (updated in 2014) concludes that there is only a limited amount of low quality data on this issue, but it seems that a planned short-stay policy does not encourage a 'revolving door' pattern of admission (Alwan et al. 2008). No studies specifically on older people with schizophrenia were found. Between the 1980's and the 2000's in Finland the number of beds in psychiatric hospitals was drastically cut and an attempt was made to transform psychiatric health care in direction of more community-based open care services. Despite deinstitutionalization, the satisfaction with life situation and life-expectancy of patients with schizophrenia improved during those years (Honkonen et al. 1999, Rantanen et al. 2009; Westman et al. 2012).

Longer length of stay in psychiatric hospitals has been associated with several factors such as diagnosis of schizophrenia, male gender, psychiatric symptom severity, and sometimes with comorbid physical illnesses (Blank et al. 2005; Douzenis et al. 2012; Suokas et al. 2013). It has been suggested that patients with

schizophrenia may not receive appropriate treatment for either medical or psychiatric problems which may result in increased number of hospital days (Douzenis et al. 2012). Length of stay in psychiatric hospital among older patients with schizophrenia have been reported to be longer than that of younger patients with schizophrenia, although older patients had fewer admissions (Barry et al. 2002; Hendrie et al. 2013; Low and Draper 2009; Mitford et al. 2010). Electro convulsive therapy (ECT) may be an effective treatment to reduce the durations of psychiatric hospitalization, also in some older patients with schizophrenia (Shelef et al. 2014). In addition, there are several other reasons for longer hospitalizations not dependent on psychiatric patients such as hospital or regional practices or level of aftercare facilities (Masters et al. 2014).

Some additional risk factors for psychiatric rehospitalization, such as medication noncompliance, drug selection, and symptom severity, have been identified in earlier studies on patients with schizophrenia (Goff et al. 2010; Kishimoto et al. 2013; Leucht et al. 2003). Fairly new-onset patients seem to have the highest rates of rehospitalization, which often results from poor treatment adherence due to poor illness insight (Addington et al. 2007). Those late-life psychiatric patients who are unmarried, whose family relations are strained, and whose clinical functioning at discharge is insufficient are more likely to end up in psychiatric hospital care than are subjects in the respective comparison groups (Lesage et al. 1990; Mercer et al. 1999). Comorbid anxiety symptoms or alcohol/drug dependence also increased the risk of readmission in older patients with non-affective psychosis. On the other hand, and surprisingly, physical comorbidity has been reported to decrease the likelihood of rehospitalization (Prince et al. 2008). Some other factors decreasing the risk of rehospitalization, in addition to successful drug treatment, have been sometimes ECT as well as good experienced quality of life (Boyer et al. 2013; Olivares et al. 2013). Finally, in addition to the individual characteristics of patients, level of outpatient care may be one of the most critical predictors of rehospitalization.

2.2.6 Long-term care

Entry into long-term care, i.e. institutional care, in old age has been associated with more advanced age, living alone, not owning a home and having a low income, factors all of which are common among people with schizophrenia and which may partly explain the risk of earlier institutionalization compared with general population (Martikainen et al. 2008). People with schizophrenia age faster with increased premature comorbidities compared with general population (Jeste et al. 2011). Together with cognitive problems and other symptoms related to schizophrenia, accelerated physical decline may lead to earlier long-term care.

Individuals with schizophrenia may end up in long-term care even 15 years younger than individuals with no psychiatric illness (Andrews et al. 2009). They may sometimes even lack a clear indication for admittance (Aschbrenner et al. 2011). Women are at even higher risk than men, which may be due to several factors such as women being widowed for longer periods in old age. In a Finnish six-year register-based (1998-2003) study on long-term care among population over 65 years old, the prevalence of patients in long-term care with any chronic psychosis was 2.9% in women and 1.8% in men. Of these women, 28.6% entered institutions and 17.3% died without institutionalization. In men, the corresponding figures were 19.4% and 28.8%, respectively. These results mean that female patients with psychosis stay for longer time in institution than men before death. Having chronic psychoses was one of the strongest predictors among all diseases of ending up in an institution, especially when compared with any physical illnesses (HR 1.95, 1.84-2.07 in women, HR 1.40, 1.26-1.56 in men) (Nihtilä et al. 2008).

2.3 Summary of literature

Positive symptoms of schizophrenia, such as auditory hallucinations and delusions, often become less prominent as people with early-onset schizophrenia grow older, but at least one fifth of patients may suffer from troublesome symptoms throughout their lives. A few per cent of people with schizophrenia get this diagnosis after 60 years. They usually suffer from more severe positive symptoms such as persecutory delusions or multimodal hallucinations, have less thought disorder, but perhaps even poorer insight than older patients with early-onset schizophrenia in spite of more normal family situation and better occupational history.

Older patients with schizophrenia face difficulties in visuo-spatial and psychomotor tasks, verbal fluency and executive functions. High doses of antipsychotics, multimedication and living in an institution may exacerbate cognitive deficits. People with VLOSLP have similar but usually milder cognitive impairment which however seldom leads to dementia.

A limited number of studies on mortality in older patients with schizophrenia, especially those with VLOSLP has been presented, but these also suggest excess mortality compared with age peers. The reasons for premature death are multiple. Risk of circulatory diseases is increased by adverse effects of psychotropics and unhealthy living habits. Physical comorbidities may not be found because of communication problems. Ageing has previously been suggested to be associated with decreasing risk of death from suicide in schizophrenia.

Antipsychotics are effective in treating positive symptoms of schizophrenia, but should carefully be monitored. Older patients are more likely to suffer from adverse effects such as extrapyramidal symptoms, circulatory problems, sedation, and decline in cognition. SGAs are commonly recommended because of smaller risk of extrapyramidal side effects, especially tardive dyskinesia. The recommended doses of antipsychotics in this age group, especially in VLOSLP, are only around one third of those recommended for younger patients.

Severity of schizophrenic symptoms, poor illness insight, type of antipsychotic medication, insufficient level of functioning at discharge and lack of support from significant others have been associated with a high risk of rehospitalization in older patients with schizophrenia. Longer length of hospital stay is common for elderly patients with schizophrenia and may be associated with the complexity of their problems, both psychiatric and physical, and also with inadequate aftercare facilities.

According to earlier studies, people with schizophrenia end up in long-term care earlier than general population.

3 Aims of the study

The general aim of this thesis was to explore how schizophrenia affects mortality and prognosis in old age. More specifically, the purpose was to study mortality from the Finnish registers in patients with schizophrenia aged 65 or older and for what reasons they die. The use of psychiatric medications and hospitalizations were also studied as well as end-of-life residential care.

The specific aims of the study were:

1. To ascertain the mortality and causes of death in the whole study sample (n=9,461) compared with the age and gender matched Finnish population between 1999 and 2008. (I)

2. To explore the use of antipsychotic medication in the outpatient study sample between 1998 and 2003 and possible factors associated with psychiatric hospitalization in 1999. (II)

3. To ascertain the mortality and causes of death in patients with onset of schizophrenia at 60 years or later (very-late-onset schizophrenia-like psychosis, VLOSLP) in relation to general age and gender matched population between 1999 and 2008, and to compare the results with the mortality of the patients with onset of schizophrenia before 60 years (III).

4. To explore the rates and durations of psychiatric hospitalizations in schizophrenia patients with different ages at onset (VLOSLP vs. others) between 1999 and 2003 as well as their risk of ending up in long-term care and long-lasting psychiatric care between 1999 and 2002. The second aim was to identify the contributing factors to the risk of long-term care or long-lasting psychiatric care. (IV)

4 Material and methods

4.1 Study design

The register-linkage data of older patients with schizophrenia was obtained from the PERFormance, Effectiveness and Cost of Treatment episodes (PERFECT) project, which is a collaboration between five Finnish university hospital districts, the Social Insurance Institution of Finland (SII) and the National Institute for Health and Welfare (THL) (http://www.thl.fi/fi/tutkimus-ja-asiantuntijatyo/hankkeet-jaohjelmat/perfect). The basic data on adult patients with schizophrenia was collected from different national registers and collated by THL. Then those aged 65 or older were separated into their own group. The personal data on each patient was encrypted before delivery from THL to this study. The responsibility for this part was assigned to psychiatrist Tiina Talaslahti MD. The study protocol was approved by the Ethics Committee of the National Institute for Health and Welfare.

4.1.1 The Finnish Hospital Discharge Register

The history of the Finnish Hospital Discharge Register begins from 1967 when the National Board of Health administrated a new register covering all discharges from public hospitals. Since 1994 the FHDR, nowadays known as the Care Register for Health Care, also includes all social institutions, such as residential care homes for mentally disabled or the elderly. The Parliament of Finland passed the legislation on health registers in 1987. The purpose was to start to collect medical and health information on citizens and to protect individual's privacy. The personal identification numbers used in the FHDR since 1968 make it possible to collate the information between the FHDR and different national registers (Gissler and Haukka 2004).

The FHDR contains data on all patients admitted to mental and general hospitals, municipal health centres, military hospitals, as well as prison and private hospitals

(Miettunen et al. 2010). It includes information on patients' age, gender, place of residence, dates of admission and discharge as well as present status of future treatment or residence (long-term care, home, residential care home for the elderly etc.), information about hospital districts and main diagnosis and subdiagnoses of hospitalization at discharge. The statistics of the FHDR is structured on care notifications submitted by health care units all over Finland and carefully checked and corrected by THL if needed. Since 1998 it has also contained specialized outpatient care and day surgery, and since 2010 outpatient care in health centres.

The disease classification of the FHDR is based on the International Classification of Diseases (ICD) by the World Health Organization (WHO). The ICD was established in the 1960's and it has gone through numerous revisions in recent decades. In the FHDR, diseases have been coded according to the ICD-10 since 1996, and the versions ICD-8 and ICD-9 (with Diagnostic and Statistical Manual, 3rd revised edition, DSM-III-R) were used in 1967-1986 and 1987-1995 respectively.

Those subjects of the present sample who have been collected from the FHDR had received schizophrenia or schizoaffective disorder as the main diagnosis at least once in the FHDR (ICD-8, ICD-9: 295, ICD-10: F20, F25). The diagnoses of physical or other diseases of each subject were also collected from the registers of the FHDR (main diagnosis between 1987 and 1998): high blood pressure (ICD-10: I10-I15), atrial fibrillation (I48), congestive heart disease (I50), coronary artery disease (I20-I25), diabetes mellitus (E10-E14), chronic obstructive pulmonary disease (COPD) and asthma bronchiale (J44-J46), neoplasms (C00-C99), alcohol dependence (F10), dementia (F00-F03, G30), and high level of cholesterol (E78).

4.1.2 Registers of the Social Insurance Institution and the Finnish Center for Pensions

The Finnish pension scheme is based on two separate pensions: disability pensions provided by the SII since 1962 and also earnings-related pensions provided by the FCP since 1962. For the present Studies I and II, patients with a disability pension due to schizophrenia were extracted from these registers in order to identify as many

patients with schizophrenia as possible in the age group of 60 years or more. The registers of the SII also contain information on medication purchases and reimbursements for medical expenses used in these studies, as well as various details about the rates and incidence of benefits and their distribution by region and population group (SII 2015).

The diagnoses of physical or other diseases of each subject were collected from the SII in 1998 (reimbursement for medicine expenses and medicines purchased). The data on medicines purchased consisted of antipsychotics and antidepressants used between 1998 and 2003. Antipsychotics were collected with the help of Anatomical Therapeutic Chemical (ATC) classification codes and further divided into four different groups according to the purpose of use and ATC-codes: 1. no use of antipsychotics, 2. use of First Generation Antipsychotics [FGAs, including N05AA01 (chlorpromazine), N05AA02 (levomepromazine), N05AA03 (promazine), N05AB02 (fluphenazine), N05AB03 (perphenazine), N05AC02 (tioridazine), N05AC01 (periciazine), N05AD03 (melperone), N05AD01 (haloperidol), N05AF01 (flupentixol), N05AF03 (chlorprothixene), N05AF05 (zuclopenthixol), N05AL01 (sulpiride)]), 3. use of Second Generation Antipsychotics [SGAs, including N05AX08 (risperidone), N05AH04 (quetiapine), N05AH03 (olanzapine), N05AE03 (sertindole), N05AH02 (clozapine)] and 4. use of both FGAs and SGAs. In addition, the use of antidepressants (code N06A) during 1998 was extracted from the SII.

4.1.3 The Finnish Causes of Death Register

The classification of causes of death was that used by Statistics Finland. The Finnish Causes of Death Register (FCDR) includes all deaths and causes of death among Finnish citizens and permanent residents since 1969. This register includes dates, places of death and diagnoses. The validity of this register has been scientifically demonstrated (Lahti and Penttilä 2001).

The death certificate is usually based on the diseases known before death and all the certificates issued from the physicians are checked by a forensic pathologist at the National Institute for Health and Welfare. If death is unexpected or if the deceased was not under medical supervision, a forensic autopsy is performed in order to ascertain the cause of death. In the period 1999-2008, an autopsy was done

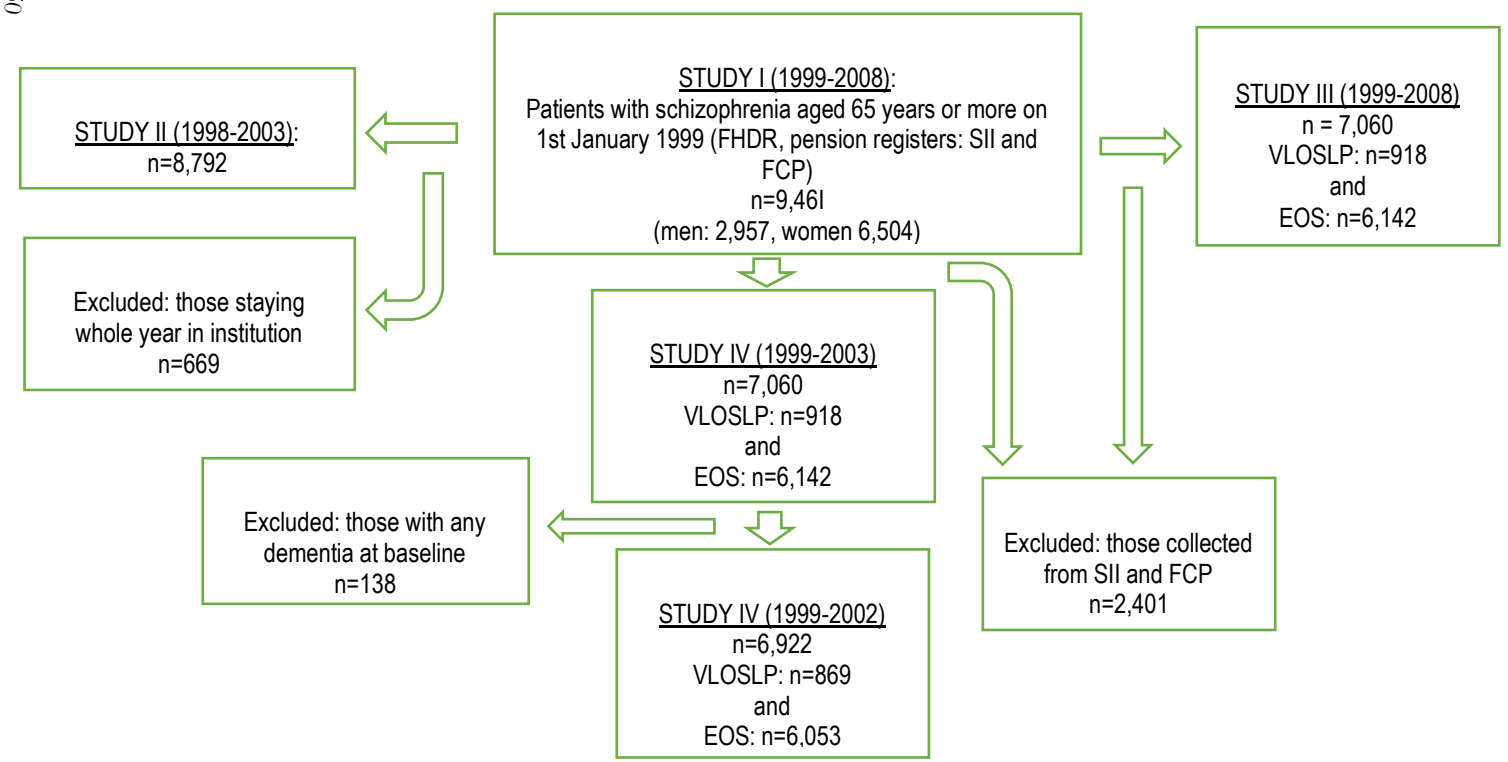
after every fifth death in the age group 65 or older. The causes of death in the present Studies I and III have been categorized into two main groups: unnatural and natural causes of death. The former group includes the codes for suicides (ICD-10: X60-X84), accidents (ICD-10: V01-X59, Y10-Y86, Y972 and Y88-Y89) and homicides (ICD-10: 85-Y871), the latter includes all the other diagnoses such as various diseases.

4.2 Study population

The sample comprised all Finnish people (n=9,461), who were alive and at least 65 years old on 1 January 1999 and had schizophrenia or schizoaffective disorder (ICD-8, ICD-9: 295, ICD-10: F20, F25) as a main diagnosis in the Finnish Hospital Discharge Register. The onset of schizophrenia was defined from the first hospitalization due to any psychosis. In ICD-8 and ICD-9, the diagnoses of schizophrenia and schizoaffective disorder belong to the same category 295, and therefore people with the latter diagnosis were also included in the study sample. In addition, for Studies I and II, people granted retirement because of schizophrenia were collected from the pension registers (register of the SII and the Finnish Center for Pensions) in order to identify the patients with no history of psychiatric hospitalization. Those residents in the Åland Islands or living abroad were removed from the data because of the likelihood of having been hospitalized elsewhere than in Finland.

In Study II patients spending whole year in any unit of the health care system were excluded from the analysis because the drugs were provided by the institution and therefore no record of purchased medication was available. The time trends were calculated especially for antipsychotics, because they are the most important psychotropics for patients with schizophrenia and SGAs came onto the market in the 1990's. The change for newer antidepressants occurred somewhat earlier in the late 1980's. For Studies III and IV the sample was further divided into independent groups based on onset age of schizophrenia (or other non-organic psychosis which later was converted into schizophrenia). The patients collected from the pension registers were excluded from these analyses of Studies III and IV, because the time of probable onset of schizophrenia could not be confirmed. The group of patients with very-late-onset schizophrenia-like psychosis (VLOSLP) included those with

onset at 60 years or later and the group of patients with earlier onset schizophrenia those with onset before 60 years. The mean time from onset of the disease to the beginning of follow-up was 7.1 years (±4.8 SD) in the VLOSLP group and 25.6 years (±6.9 SD) in the earlier onset group. For Study IV, the VLOSLP group was further divided into four subgroups depending on how many years (1-3, 4-5, 6-10, 11 or more) had passed since the first psychosis (onset of schizophrenia) before 1999. When calculating the likelihood of ending up in long-lasting psychiatric hospital care or long-term care, patients having a diagnosis of any dementia at baseline were excluded because the subsequent dementia (F00-F03, G30) after the diagnosis of schizophrenia would strongly influence for need of institutionalization. Long-term care was calculated annually. Detailed descriptions of Studies I-IV (number of patients, follow-up time, excluded) are given in Figure 1.



VLOSLP: very-late-onset schizophrenia-like psychosis; EOS: patients with earlier onset schizophrenia; FHDR: Finnish Hospital Discharge Register; SII: Social Insurance Institution; FCP: Finnish Center for Pensions

Figure 1. Flow chart of studies I-IV.

The sample was followed up from Finnish registers such as the Finnish Hospital Discharge Register, the registers of the Social Insurance Institution (pensions, medicine purchases, reimbursements for costs of medication), the Finnish Center for Pensions and the Finnish National Causes-of-Death Register. The data was collated by the personal identification numbers issued to every Finnish citizen. The characteristics of the whole sample are presented below and in Table 3.

Table 3. Baseline population: number of schizophrenia cases in different age groups and their basic health. (Study I, reproduced with permission of Wiley)

	Total (n=9461) **% (n)**	**Men** (n=2957) **% (n)**	**Women** (n=6504) **% (n)**	**Gender difference, p-value** **χ2**	**df**	**p**
Age at baseline						
65-69	35.0 (3314)	43.7 (1291)	31.1 (2023)	221.76	6	<0.001
70-74	29.0 (2739)	29.6 (875)	28.7 (1864)			
75-79	20.5 (1942)	17.5 (516)	21.9 (1426)			
80-84	9.4 (893)	6.2 (183)	10.9 (710)			
85-89	4.6 (439)	2.3 (69)	5.7 (370)			
90-94	1.2 (111)	0.6 (19)	1.4 (92)			
95 ->	0.2 (23)	0.1 (4)	0.3 (19)			
Psychiatric hospital inpatients, 5 years before baseline*	29.2 (2766)	27.1 (801)	30.2 (1965)	9.59	1	0.002
Patients having any hospital care, one year before baseline	39.5 (3741)	38.0 (1125)	40.2 (2616)	4.03	1	0.045
Patients having antipsychotic drugs, one year before baseline	60.4 (5719)	59.4 (1756)	60.9 (3963)	2.03	1	0.156
Cardiovascular diseases**	39.8 (3765)	39.0 (1153)	40.2 (2612)	1.16	1	0.282
Diabetes**	14.3 (1356)	13.4 (395)	14.8 (961)	3.33	1	0.068
Neoplasm**	6.3 (598)	5.6 (165)	6.7 (433)	3.99	1	0.046
COPD**	7.7 (725)	9.3 (274)	6.9 (451)	15.62	1	<0.001
Dementia**	2.5 (240)	2.1 (63)	2.7 (177)	2.87	1	0.090
Hypercholesterolemia**	1.0 (96)	0.7 (20)	1.2 (76)	4.90	1	0.027
Alcoholism**	1.3 (120)	2.5 (74)	0.7 (45)	52.32	1	<0.001

* At least one psychiatric hospitalization between 1994 and 1998, diagnosis in FHDR during the year 1998.

** Diagnosis in Finnish Hospital Discharge Register during the year 1998.

4.3 Definitions of variables used in the studies

Relapse used in Study II was defined as a psychiatric hospitalization of at least one day in 1999. Those patients who were hospitalized for the whole year 1999 were excluded from the study sample, because all their medication was provided by the institution.

Severity of illness (II) was based on the data on psychiatric hospitalizations between 1994 and 1998, i.e. before entering the study. The patients were dichotomized according to ever admitted to psychiatric hospital or not admitted to psychiatric hospital

Patients with long-term care status had received an official decision from SII been on their need for long-term care in residential care homes, sheltered accommodation or health centres or had stayed in any health care institution for more than 90 days. Patients with long-lasting psychiatric hospital care status had been in psychiatric hospital(s) for at least 180 days.

4.4 Statistical methods

In Studies I, II, III and IV: the significance of group differences in categorical variables was assessed with Pearson's Chi-square test or Fisher's exact test, and in continuous variables with Student's t-test or Mann-Whitney U-test. In all four studies, all statistical tests were two-tailed and the limit for statistical significance was a set at $p<0.05$. Statistical analyses were conducted using PASW for Windows, version 18 (SPSS Inc., Chicago, IL, USA), SPSS for Windows, version 22 (IBM SPSS, Armonk, NY, USA) or SAS for Windows, version 9.2 (SAS Institute Inc., Cary, NC, USA), statistical programs. In addition, the other methods used in different Studies are described below:

Studies I and III: Standardized Mortality Ratios (SMRs) was used to describe the overall and cause-specific mortality of the older patients with schizophrenia (Breslow & Day, 1987). The SMR is an epidemiologic ratio of the observed number of deaths in a study sample to the expected number of deaths calculated on the basis of the number of deaths in the reference population. The reference population used in the present study was Finnish general population matched for gender and age (Statistics Finland 2010). SMRs were compared using rate ratio analysis (RR) and calculating 95% confidence intervals (CIs).

Study II: The use of different groups of antipsychotics (FGAs, SGAs, FGAs plus SGAs) was explored annually and described by time trends. The annual sample size was calculated by taking into account the new deaths registered. For analysing the likelihood of relapse, logistic regression analysis was used with age, gender, source of data (FHDR or pension registers), use of medication (FGAs, SGAs, FGAs plus

SGAs, antidepressants) during the previous year, physical illnesses (cardiovascular diseases, diabetes, dementia, COPD/asthma bronchiale, neoplasms, high cholesterol level), alcohol dependence and severity of illness as independent variables.

Study III: The difference between onset groups (under 60 years, 60 years and over) from 1 January 1999 and to the death of patient or to 31 December 2008 if alive was examined using the Cox proportional hazards model. The Hazard Ratio (HR) for death and its 95%CI was adjusted for gender, age, physical illness (cardiovascular disease, respiratory disease, diabetes mellitus, neoplasm, dementia, high cholesterol level), alcohol related disorder, use of antipsychotics and antidepressants (in unpublished data) at baseline and at least one psychiatric hospitalization in the period 1994-1998.

Study IV: The likelihood of ending up in long-term care/long-lasting psychiatric hospital care was analysed using logistic regression analysis and calculated as ORs with onset of illness (before 60 years/ 60 years or older), age, gender or physical disease (cardiovascular disease, neoplasm, respiratory disease), high cholesterol level or alcohol related disorder as independent variables. Corresponding analyses were made for both genders separately. Deaths were taken into account when calculating annual proportions of hospitalization or long-term care.

5 Results

5.1 Mortality and causes of death in patients with schizophrenia aged 65 or older (I)

5.1.1 Overall mortality (I)

When calculating the overall mortality of the whole sample, SMR was 2.7 (95% 2.6-2.8) between 1999 and 2008. For natural and unnatural causes of death it was 2.6 (2.5-2.7; n=5,301) and 11.0 (9.8-12.5; n=262), respectively.

By gender, the overall SMR was significantly higher in men 3.0 (2.9-3.1) than in women 2.6 (2.5-2.6; n=3,469) (RR 1.18, 95%CI 1.11–1.24, $p<0.05$). Overall SMRs by gender and age groups are given in Figure 2. For natural and unnatural causes of death, overall SMRs were 2.9 (2.7-3.0; n=1,832) and 11.5 (9.4-14.0; n=98) in men, and 2.5 (2.4-2.5; n=3,469) and 10.8 (9.2-12.6; n=164) in women, respectively.

During the ten-year follow-up period, 59% (5,596/9,461) of the patients died, 66% of the men and 56% of the women. The mean age at death in women and men was 79.9+6.0 years and 76.5+6.1 years respectively ($p<0.001$). Of all deaths, 4.7% (274) were unnatural: 5.1% in men and 4.5% in women.

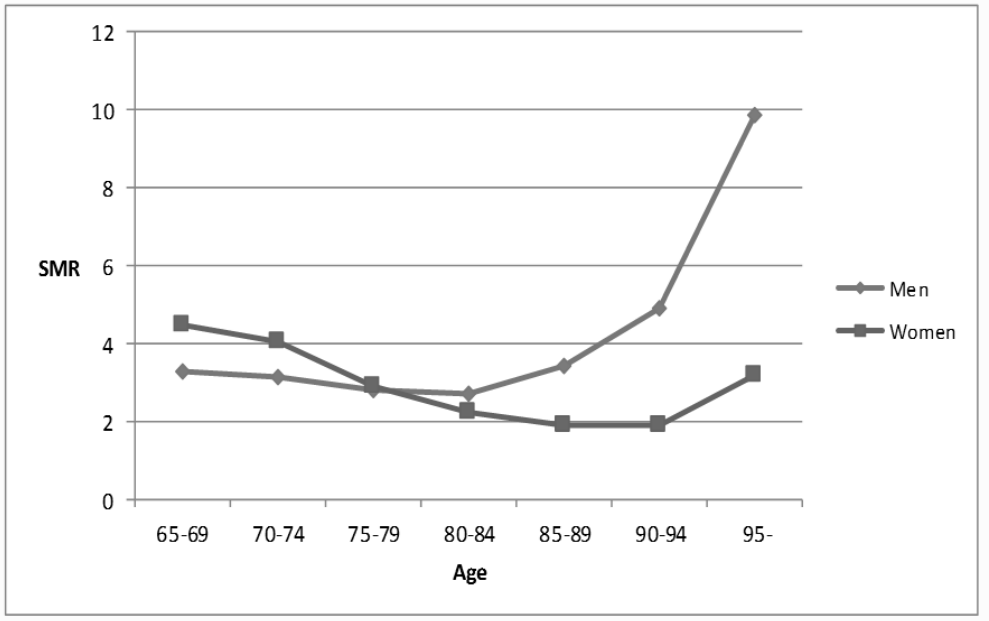


Figure 2. Total Standardized Mortality Ratios (SMR) by age and gender in schizophrenia cases over 65 years old [total SMR for men was 3.0 (95% CI 2.8–3.1); total SMR for women was 2.6 (95%CI 2.5–2.6)]. (Study I, reproduced with permission of Wiley.)

5.1.2 Causes of death (I)

The most common causes of death matched those in the general population (circulatory diseases, neoplasms, dementias). The causes of death having the highest SMRs in older patients with schizophrenia were as expected, infectious diseases and genitourinary diseases had relatively high SMRs likewise suicides (Table 4).

Table 4. Causes of death (ICD-9 and ICD-10) in older patients with schizophrenia. Standardized Mortality Ratios (SMRs) and 95% confidence intervals (CIs). (I)

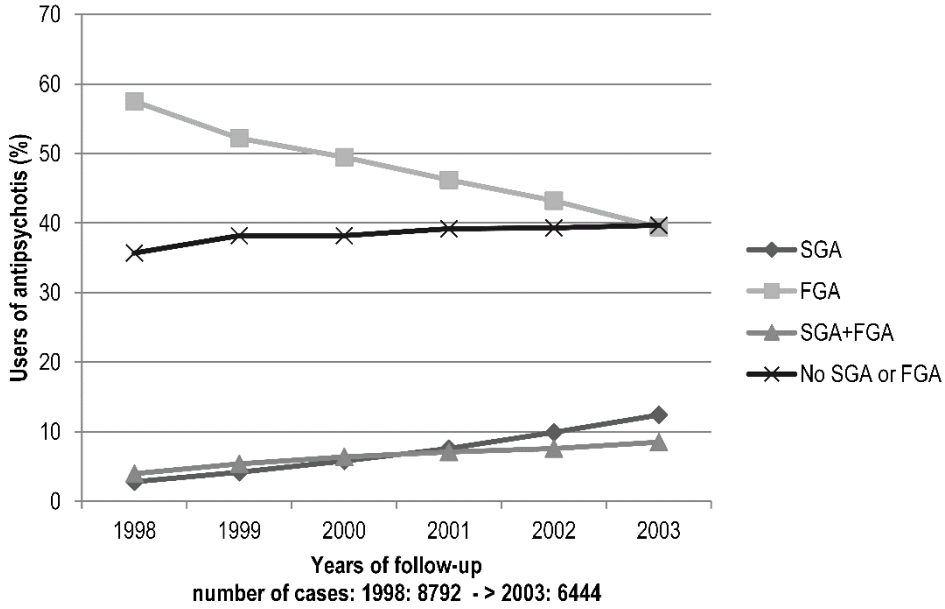
Cause of death	Total			
	SMR	95%CI	OBS	EXP
Suicide	44.1	31.8-59.6	42	1.0
Infectious disease	26.6	20.0-34.6	55	2.1
Genitourinary disease	19.3	15.6-23.4	99	5.2
Endocrine disease	15.3	12.2-18.9	86	5.6
Other nervous disease	10.6	8.4-13.2	81	7.6
Accidents and violence	9.6	8.3-10.9	218	22.8
Digestive disease	9.6	8.3-11.0	207	21.6
Respiratory disease	5.5	5.1-6.0	696	125.6
Dementia	2.8	2.6-3.0	506	181.5
Circulatory disease	1.9	1.8-2.0	2388	1275.6
Neoplasm	1.9	1.8-2.0	827	427.7

SMR: Standardized Mortality Ratio; OBS: observed; EXP: expected.

5.2 Psychiatric medication and predictors of relapse (II)

5.2.1 Time trends of antipsychotic usage (II)

When calculating the time trends of antipsychotic usage during the 1998-2003, the proportion of second generation antipsychotics (SGAs) used by outpatients increased from 2.8% (244/8,792) to 12.4% (800/6,444) ($p<0.001$) and the use of combined FGAs and SGAs increased from 4.0% (350/8,792) to 8.5% (550/6,444) ($p<0.001$). At the same time, the use of first generation antipsychotics (FGAs) decreased from 57.5% (5,054/8,792) to 39.4% (2,538/6,444) ($p<0.001$) (Figure 3). When these analyses were repeated for each age-group (64-79 years, 80 years or over), the results were parallel, and there were no differences between genders in the frequency of type of antipsychotic taken (FGAs vs. SGAs). The proportion of patients not taking antipsychotics increased from 35.8% (3,144/8,792) to 39.7% (2,556/6,444) ($p<0.001$) (Figure 3). The proportions of patients not taking antipsychotics in the age group of 64-79 years varied from 32.8% to 37.1% and in the age group of 80 years or more from 54.2% to 62.8%.



FGAs, first generation antipsychotics; SGAs, second generation antipsychotics; SGAs + FGAs, both antipsychotic categories used simultaneously; No SGA or FGA, no usage of antipsychotics.

Figure 3. Usage and non-usage of antipsychotics in Finnish older schizophrenia patients in 1998-2003. (II)

5.2.2 Predictors of relapse (II)

The share of patients hospitalized on psychiatric wards during 1999 (relapsed) was 8.8%. According to the results of the logistic regression analysis (see the original study II), factors independently associated with increased relapse risk were: use of combined FGAs and SGAs (OR 1.70, 95%CI 1.25-2.31, p=0.001) or use of

antidepressants (14 % of the patients were taking antidepressants at baseline, unpublished data) (OR 1.27, 1.04-1.55, p=0.019). Likewise being in the age group 65-79 years (vs. 80 years or more) (OR 2.18, 1.62-2.95, p<0.001) and those whose data was held in the Finnish Hospital Discharge Register (instead of the register of the Social Insurance Institution or the Finnish Center for Pensions, indicating no prior psychiatric hospitalizations) (OR 1.58, 1.16-2.16, p=0.004) or in those with at least one psychiatric hospitalization during the five years prior to joining the study (severity of illness) (OR 7.39, 6.22-8.79, p<0.001) were at higher risk for psychiatric hospitalization. Conversely, the risk of relapse was modestly decreased in the group of patients with some diagnosis of cardiovascular disease (high blood pressure, atrial fibrillation, congestive heart disease, or coronary artery disease) (OR 0.84, 0.71-0.99, 0.040).

5.3 Patients with very-late-onset schizophrenia-like psychosis – mortality and causes of death (III)

5.3.1 Mortality (III)

Between 1999 and 2008, 543/918 (59%) of patients with onset of disease at 60 years or older (VLOSLP) and 3,371/6,142 (55%) of patients with disease onset before 60 years died. By gender, the corresponding figures were 179/254 (70%) and 1,316/2,050 (64%) in men, and 364/664 (55%) and 2,055/4,092 (50%) in women. The mean age at death was higher in the VLOSLP group (78.2+4.8) than in the group with earlier onset (76.0+4.8) (p<0.001). The other characteristics of VLOSLP group and earlier onset group are given in Table 5.

Table 5. Baseline characteristics of older patients with schizophrenia by illness onset groups (onset at 60 years or later or onset before 60 years). (III)

		Onset age for schizophrenia				
	Total (n=7060)	60+ (n=918)	-59 (n=6142)	P-value		
	% (n)	% (n)	% (n)	t-test or $\chi 2$	df	p*
Socio-demographics						
Age at 1999 (years ±SD)	71	73 (4.3)	71 (4.2)	-14.4	1189	<0.001
Gender, women	67 (4756)	72 (664)	66 (4092)	11.8	1	0.001
Physical or other illnesses at baseline						
Cardiovascular disease	39 (2753)	48 (440)	38 (2313)	35.4	1	<0.001
Diabetes	15 (1024)	15 (137)	14 (887)	0.15	1	0.699
Neoplasm	6 (428)	7 (66)	6 (362)	2.35	1	0.125
Respiratory disease	8 (591)	10 (90)	8 (501)	2.82	1	0.093
Dementia	2 (138)	5 (49)	1 (89)	63.02	1	<0.001
Hypercholesterolemia	1 (81)	1 (13)	1 (68)	0.67	1	0.412
Alcohol related disorder	1 (88)	2 (20)	1 (68)	7.45	1	0.006

* $\chi 2$-test, except in age independent samples t-test (equal variance not assumed), two-tailed significance

5.3.2 Standardized mortality ratios by onset group (III)

In the study comparing mortality between the VLOSLP and the earlier onset group, overall SMR was 5.0 (95%Cl 4.6-5.5) in the former group and 2.9 (2.8-3.0) in the latter group. In the VLOSLP group, SMR was 8.3 (7.1-9.6; n=179) in men and 4.2 (3.8-4.7; n=364) in women. In the earlier onset group they were 2.9 (2.8-3.1, n=1316) and 2.9 (2.8-3.1, n=2055) respectively. The SMRs by age groups and gender are given in Figure 4.

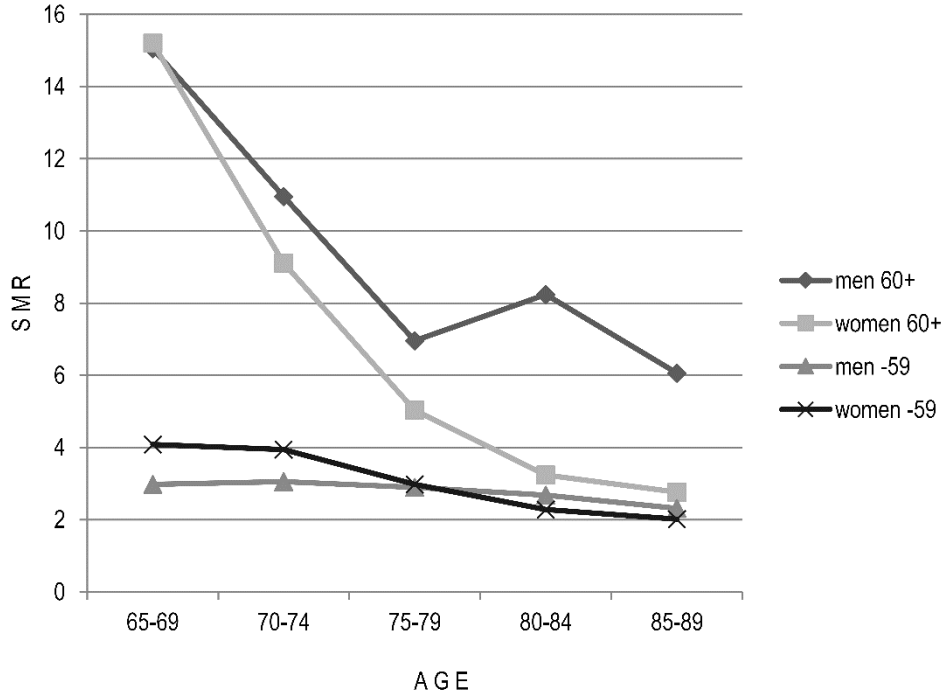


Figure 4. Total Standardized Mortality Ratios (SMR) by age, gender and onset group in schizophrenia cases over 65 years old. (Study III, reproduced with permission of Wiley.)

5.3.3 Causes of death by onset group (III)

The causes of death having most pronounced SMRs in older patients with schizophrenia in the VLOSLP group and in the earlier onset group are presented in Table 6. The most common causes of death were similar to those of Finnish general population of the same age and gender. The SMRs of this population were increased in most cause-of-death categories and were especially high in the VLOSLP group. When physical diseases at baseline were calculated by onset group, age and gender, men in the age group 80-84 with VLOSLP had significantly higher proportion of cardiovascular diseases at baseline than men belonging to the group of earlier onset of the disorder (58% vs. 41%, p=0.020) (unpublished data).

Table 6. Causes of death (ICD-9 and ICD-10) in older patients with schizophrenia. Standardized Mortality Ratios and 95%confidence intervals by onset group (60+, onset at 60 years or later; -59, onset before 60 years) and gender. (III)

Cause of death	Total				Men*				Women*			
	SMR	95% CI	OBS	EXP	SMR	95% CI	OBS	EXP	SMR	95% CI	OBS	EXP
60+ Accident	33.7	20.9-51.6	21	6.6	60.0	21.9-130.6	6	0.1	28.3	15.8-46.7	15	0.5
Respiratory	14.5	11.2-18.4	65	4.5	17.9	12.4-25.0	34	1.9	11.9	8.1-16.9	31	2.6
Dementia	8.6	6.7-10.8	71	8.3	23.2	13.9-36.2	19	0.8	7.0	5.2-9.1	52	7.5
Neoplasm	5.1	4.0-6.3	78	15.5	7.2	4.4-11.0	20	2.8	4.6	3.5-5.9	58	12.6
Circulatory	2.8	2.5-3.2	219	77.5	4.7	3.7-5.9	73	15.6	2.4	2.0-2.8	146	61.9
-59 Accident	8.9	7.5-10.6	137	15.4	8.6	6.5-11.1	58	6.8	9.2	7.3-11.5	79	8.6
Respiratory	6.2	5.6-6.8	435	70.4	5.9	5.1-6.7	221	37.6	6.5	5.7-7.5	214	32.7
Dementia	3.0	2.6-3.5	197	65.0	5.9	4.5-7.6	60	10.2	2.5	2.1-3.0	137	54.8
Neoplasm	1.8	1.6-1.9	547	312.4	1.8	1.6-2.0	222	125.0	1.7	1.6-1.9	325	187.4
Circulatory	2.3	2.1-2.4	1461	647.6	2.1	1.9-2.3	552	263.6	2.4	2.2-2.5	909	384.0

*Unpublished data.

5.3.4 Comparison of survival between onset groups (III)

Comparison between the VLOSLP group and patients with earlier onset illness resulted in only a minimal difference in survival after adjusting for the given variables, namely age, gender, physical illness (circulatory disease, respiratory disease, diabetes mellitus, neoplasm, dementia, high cholesterol level), alcohol related disorder, use of antipsychotics at baseline, and at least one psychiatric hospitalization in 1994-1998 (Hazard Ratio, HR, 1.16 95%CI 1.05-1.27, p=0.003) (Figure 5).

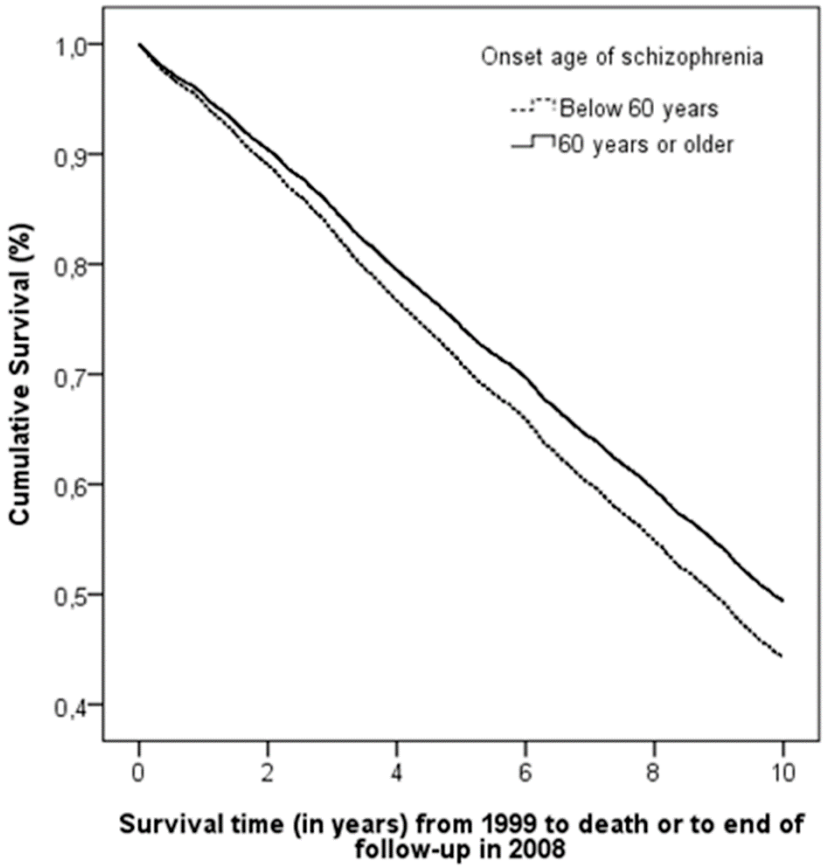


Figure 5. Survival time of older schizophrenia patients from entry into the study (1 January 1999) to death or to the end of follow-up (31 December 2008) if alive. (Study III, reproduced with permission of Wiley.)

5.4 Very-late-onset schizophrenia-like psychosis - psychiatric hospitalizations and long-term care (IV)

5.4.1 Rates of psychiatric hospitalizations between 1999 and 2003 (IV)

Examination of the rates of psychiatric admissions between 19992 and 2003 showed that 246/918 (27%) patients in the VLOSLP group and 1,430/6,142 (23%) patients in the earlier onset group had at least one psychiatric hospitalization (p=0.020): 64/254 (25%) and 448/2,050 (22%) (p=0.227) in men, and 182/664 (27%) and 982/4,092 (24%) (p=0.058) in women. When the rates of psychiatric hospitalization per year were compared, in the first year 141/918 (14%) patients in the VLOSLP group and 679/6,142 (11%) (p<0.001) in the earlier onset group had at least one day in psychiatric hospital, 40/254 (16%) and 232/2,050 (11%) (p=0.039) in men and 101/664 (15%) and 447/4,092 (11%) (p= 0.001) in women, respectively. No differences in hospitalization rates between onset groups were found during the second, third, fourth and fifth years of follow-up.

5.4.2 Durations of psychiatric hospitalizations with respect to time since onset (IV)

When the VLOSLP group was divided into four categories according to the time since onset of schizophrenia (1-3, 4-5, 6-10 and 11 or more years before the beginning of follow-up) in order to calculate durations of psychiatric hospitalizations, the number of days in psychiatric hospital in the first follow-up year differed between these subgroups (p=0.045). The mean number of days in psychiatric hospital was greater in the VLOSLP subgroup of patients 1-3 years after onset of the disease (19.1, sd 59.8) compared to patients having 11 years or more since illness onset (6.75, sd 32.1) (p=0.028). A corresponding difference was also found between the VLOSLP subgroup with 6-10 years since illness onset (19.7, sd 68.2) and with patients having 11 years or more (6.75, sd 32.1) since illness onset (p=0.037).

5.4.3 Predictors of ending up in long-term care (IV)

Between 1999 and 2002, patients in the VLOSLP group (those with dementias at baseline excluded) ended up more often in long-term care or long-lasting psychiatric hospitalization (LTC/LLP) than those in the earlier onset group in the third year [VLOSLP: n=151/749 (20%); earlier onset group: n=810/5,371 (15%); p<0.001] and in the fourth year of follow-up [n=141/707 (19%); n=773/4,987 (16%); p=0.003] respectively. Moreover, women in the VLOSLP group were more likely to end up in LTC/LLP than women with earlier onset of schizophrenia. Proportions of patients ending up only in LLP showed no differences between the onset groups.

The results of the logistic regression analysis showed that age was associated with ending up in LTC/LLP, but not the onset group of schizophrenia. Patients having some cardiovascular disease or a respiratory disease were less likely to end up in LTC/LLP than the rest of the patients (Table 7).

Further, in corresponding analyses conducted for both genders, being less likely to end up in LTC/LLP was true in male and female patients with cardiovascular disease (women: OR 0.62, 95%CI 0.49-0.78, p<0.001; men: OR 0.63, 0.54-0.73, p<0.001) and only in female patients with respiratory disease (OR 0.64, 0.47-0.87, p=0.004). Conversely, in female patients with diabetes (OR 1.30, 1.07-1.58, p=0.008) this risk was increased. Onset group of schizophrenia was associated weakly with the VLOSLP group in women (OR 1.23, 1.01-1.49, p=0.042) for likelihood of ending up in LTC/LLP.

Table 7. Predictors for ending up in long-term care or long-lasting psychiatric hospital care between 1999 and 2002, assessed using logistic regression analysis. (Study IV, reproduced with permission of Wiley.)

Variables	OR	95%CI	Sig
Background characteristics			
Age at 1999	1.10	1.09-1.12	p<0.001
Gender (women vs. men)	1.04	0.91-1.18	0.580
Onset group (60+ vs. 60-)	1.13	0.95-1.34	0.156
Physical illnesses			
Cardiovascular disease	0.63	0.55-0.71	p<0.001
Respiratory disease	0.73	0.58-0.92	0.008
Diabetes mellitus	1.16	0.98-1.37	0.081
Neoplasm	0.97	0.76-1.24	0.827
Hypercholesterolemia	0.57	0.28-1.16	0.121
Alcohol related disorder	0.83	0.46-1.50	0.545

* Note: the reference category in logistic regression analysis indicates negative response (no) unless otherwise stated.

6 Discussion

These studies included both older individuals with schizophrenia who had lived with the illness for decades and those who had recently received the diagnosis of schizophrenic disorder. The studies were based on the large data collected from Finnish nationwide registers. They included different late life aspects of elderly patients with schizophrenia e.g. mortality, medication, risk of psychiatric hospitalization, and rates of institutionalization.

6.1 Mortality in older patients with schizophrenia (I, III)

6.1.1 Overall mortality (I, III)

In the present register-based study of people with schizophrenia aged 65 years or more, the overall mortality rate was 2.7 that of with age- and gender-matched general population. This finding was in line with the findings of earlier studies, mostly on younger patients, in which the all-cause mortality rate varied on average from two- to three-fold on average (Laursen et al. 2014). Estimates of mortality, especially in specific causes of death, depend on various factors such as the length of follow-up, type of study, and cohort size and age (Bushe et al. 2010). The number of studies including older patients with schizophrenia is limited, or the results of this age group are not separately reported. In an earlier Finnish study on long-stay institutionalized psychiatric patients of whom 80% had schizophrenia, mortality was 3.0-3.7 times higher than in general population in the age group 65-84, but the number of older patients was limited (Räsänen et al. 2003). In another smaller three-year study of urban out- and inpatients, SMR in patients with schizophrenia older than 65 years was 1.6 and in schizoaffective people it was 2.1 (Chang et al. 2010). In a recent register-linked longitudinal study of community-dwelling older men with schizophrenia spectrum disorder, the hazard ratio of death varied between 1.9 and

2.3 after adjusting for different factors including lifestyle (Almeida at al. 2014). The most essential difference between these studies and the present one is the selection of study population – in the present study, the data covered all Finnish older schizophrenia patients who were alive at the beginning of the study. Kredentser et al. (2014) recently reported the 1.4-fold age-adjusted relative risk of death in people with schizophrenic disorder at 60 years or older, which is somewhat lower than in the present study.

Over-all mortality in patients with VLOSLP was five times higher than in general older population in the present study. SMR in the VLOSLP group was also twice as high as that in the earlier onset older patients with schizophrenia. As far as is known, this is the first study to compare mortality between very-late-onset and earlier onset patients in old age. However, there are some studies on mortality in VLOSLP patients where the estimates are lower than those presented here. In a Danish register-based study of first-admitted schizophrenia patients by Mortensen and Juel (1993), SMR of patients aged 65 or more increased in every age-group and in both genders except in that of men aged 85+. The highest mortality was in the age group 65-69 (2.0, 1.4-3.0) in men and in the age group 70-74 in women (2.2, 1.6-3.0). In a Swedish study by Ösby et al. (2000), SMR was significantly elevated (total SMR. 2.8 in males and 2.4 in females) in all first-onset age-groups, but lower in the oldest groups and the trend was for higher SMR within a year after first admission age, which may had decreased the SMR in the oldest group. The death rate in the VLOSLP group has also been reported to be more than three-fold that of patients with osteoarthritis (Kørner et al. 2009). Because of a lack of studies similar in study design to the present one, possible explanations for excess mortality must be sought from studies on younger people with schizophrenia.

Within-sample comparison adjusted for various factors such as age, physical illnesses, alcohol dependence and use of antipsychotics, hazard of death differed only minimally between the present VLOSLP group and the earlier onset group in ten-year follow-up. In a post-hoc analysis also including antidepressants as independent variables, the result of the within-sample comparison remained relatively unchanged (Hazard Ratio, HR, 1.14 95%CI 1.03-1.25, p=0.009, unpublished data). It therefore seems that the onset of schizophrenia itself does not substantially explain the higher death rate in patients with VLOSLP but rather the comorbid diseases and accidents. In a study on older patients with first onset

psychotic symptoms without dementia, psychosis did not in itself affect the mortality rate (Östling et al. 2007).

In the present study, mortality in men with VLOSLP was twice as high (8.3) as in women with VLOSLP (4.2). There was an exceptionally high peak in mortality among men with VLOSLP aged 80-84, which may be explained by the high proportion of cardiovascular diseases in this subgroup of patients. Mortality due to accidents was also high in men which probably somehow explains the difference in levels of overall SMRs. This finding, however, should be interpreted with caution when observing the SMRs by onset and gender because the subgroups were rather small. More than two thirds of the whole VLOSLP group were women as has also been the case in some earlier studies (Meesters et al. 2012; Palmer et al. 2001). The corresponding SMRs did not differ much between men and women in the earlier onset group (2.91 vs. 2.94) in that study. Men with schizophrenia in general have been reported to disappear easily from health services (Reeves et al. 2002). The illness in VLOSLP men may be more deleterious, resulting in difficulties in self-care and in compliance with ongoing treatments (Kreyenbuhl et al. 2009; Tan and Seng 2012). Unmarried men with schizophrenia seem to have poorer prognosis, especially in domains of social life (Salokangas et al. 2001). The response to antipsychotic therapy may also be poorer in men than in women (Smith 2010). All these propositions should serve to draw special attention to the needs of older men with schizophrenia, especially with VLOSLP.

6.1.2 Causes of death (I, III)

We found that mortality among all the present patients, including those collected from the pension registers, was elevated in the natural causes-of-death category (SMR 2.6) and also in every specific causes-of-death subcategory compared with the general population matched for age and gender. The present findings concur with the results of the longitudinal Danish study: the respective mortality rates of admitted patients for natural causes of death in patients with schizophrenia and schizoaffective disorder in the age-group of 55-79 years were 1.9 and 2.2 in women, and 1.7 and 2.3 in men compared to non-admitted patients respectively (Laursen et al. 2007). In mental disorders among all ages in general, the estimate of deaths due to natural causes has been 67% and due to unnatural causes 18% with the remainder

being unknown or unidentified (Walker et al. 2015). The most common specific cause of death in the present study was circulatory diseases (SMR 1.9) followed by neoplasms (1.9) and respiratory diseases (5.5). That means that older patients with schizophrenia seemed to die for similar reasons than general population although more often (Almeida et al. 2014).

6.1.2.1 Circulatory diseases (I, III)

Unwholesome lifestyle, genetic factors and adverse effects of antipsychotic drugs may predispose to a metabolic syndrome, which further predisposes to circulatory diseases (De Hert et al. 2006; Koponen et al. 2002; Suvisaari et al. 2007). In the CATIE study, metabolic syndrome was found in 35% of men and in more than 50% of women with chronic schizophrenia (McEvoy et al. 2005). A ten-year risk of coronary heart disease (79%) in schizophrenia (mean age 63 years) has been reported to be higher than that in general population and in other mental disorders (Jin et al. 2011). Also an association between the risk of an acute myocardial infarct and the use of antipsychotics in patients aged more than 65 years has been reported to be 2.5-3-fold and in patients with schizophrenia of all ages 2.6-fold (Lin et al. 2014). In a large retrospective study with 46,000 people with mental disorders and 300,000 controls, the hazard ratio of coronary heart disease mortality in schizophrenia in the age group of 55-75 was 2.0 and in those aged 75 or more it was 1.03. The corresponding figures for stroke were 2.0 and 1.3 respectively (Osborn et al. 2007). In a retrospective Swedish register study by Ösby et al., SMRs for cardiovascular diseases in patients in schizophrenia were 2.3 for males and 2.1 for females in all age groups (Ösby et al., 2000). There are some speculations that antidepressants may increase survival after a stroke by facilitating the neural mechanisms of recovery (Jorge et al. 2003; Mikami et al. 2011).

In patients with VLOSLP, mortality rates of all specific natural causes of death were elevated compared to those in general age- and gender matched population and also vis-à-vis the earlier onset group. Circulatory diseases were the most common cause of death in both of these onset groups and the difference between SMRs was small (2.8 in the VLOSLP group, 2.3 in the earlier onset group). There is some evidence that patients might have had unhealthy living habits even before the first psychosis (Ringen et al. 2014).

After starting the antipsychotic medication people may face severe weight gain. In a multi-centre open controlled randomized trial on patients with schizophrenia spectrum disorder at the age of 40 or younger, around 56% of the patients taking antipsychotics (haloperidol, amisulpride, olanzapine, quetiapine or ziprasidone) gained more than 7% of their baseline body weight within a year, but the difference between drugs was not significant (Kahn et al. 2008). Even if weight gain is less marked in older people than in younger ones and may sometimes even be a positive phenomenon, it is worth monitoring in older patients.

6.1.2.2 Cancer (I, III)

In the present study the mortality rate was higher in every specific cause-of-death category. Dying of neoplasm, i.e. cancer, was almost twice as common as in general older population. Cancer mortality in schizophrenia has varied, but has been reported to be more elevated in the most recent studies than in earlier studies (Hodgson et al. 2010). The proportion of older patients in these studies has usually been small or totally missing. In a meta-analysis by Saha et al. (2007) consisting of 37 studies, the median SMR for neoplasms in patients with schizophrenia was 1.4 for all ages, and in a longitudinal study by Tran et al. (2009) it was 1.5. In a large register-linked study on younger schizophrenia patients it was 1.6 (Nordentoft et al., 2013). By contrast, in a community-based study on older men with schizophrenia the hazard ratio for cancer mortality was lower than in non-schizophrenic subjects (HR 0.8) (Almeida et al. 2014). These different estimates of cancer mortality in schizophrenia may be due to different study designs, but some special reasons for excess mortality in schizophrenia have also been reported. In an Australian study by Lawrence et al. (2000), the incidence rate of cancer was equal to that in general population, but the mortality rate was significantly higher. Another US study also reported that excess cancer mortality could not be explained by illness incidence (Kisely et al. 2008). These findings support the notion that patients with schizophrenia have had inadequate access to appropriate screening, medical treatment and procedures.

Mortality rate in neoplasms found in the present VLOSLP group was also markedly elevated (5-fold) and was even higher than that in the earlier onset group (2-fold). Premorbid paranoid or schizoid personality in VLOSLP patients found in

earlier studies may have caused poorer access to health care services and a delay diagnosis in the physical diseases and consequent undertreatment (Jeste et al. 2011). In a nationwide population-based Australian register-linkage study of people with psychiatric illness including schizophrenia hazard ratio of metastases at time of cancer diagnosis was 1.6 (1.55-1.64). That is to say that cancers were diagnosed later than in general population, and patients were also less likely to be offered surgical treatment (HR 0.83), especially men (Kisely et al. 2013). These facts likely also concern older patients with psychiatric disorders, but do not explain the difference in SMRs between very-late-onset and earlier-onset schizophrenia patients.

6.1.2.3 Dementias (I, III)

In the present study, the patients with VLOSLP died from dementias nine times more often than people in general population and three times more often than the patients with onset of schizophrenia at earlier age. In baseline characteristics there was a significant difference between the proportions of patients having a diagnosis of any dementia (5.3% of VLOSLP, 1.4% of earlier onset patients). The risk of dementia in VLOSLP has been three-fold that of general population in earlier studies, although the estimates of risk vary considerably (Kohler et al. 2007). In general the number of deaths caused by dementia has doubled in ten years in Finland. Several reasons may explain this, such as more specific diagnostics, changes in the definitions of causes of death and above all ageing of the population (Statistics Finland 2014).

The mortality rate from dementia in the present VLOSLP patients may be overestimated. It is possible that some of these patients had initially been misdiagnosed as having schizophrenia instead of dementia if a sufficient period of early follow-up has been missed. On the other hand, some VLOSLP patients may also have been excluded from the original data due to possible misdiagnosis of dementia or other psychotic illnesses than schizophrenia. Of older patients with the first episode of any major psychiatric disorder admitted to a tertiary care psychogeriatric hospital, 23/71 had a diagnosis of unspecified nonorganic psychosis and 7/10 persistent delusional disorder (F22) which were later switched to a diagnosis of VLOSLP (Barak et al. 2011).

6.1.2.4 Respiratory diseases and some rarer causes of death (I,III)

We found that SMRs of respiratory diseases including COPD were 6.2 and 14.5 in patients with earlier onset schizophrenia and VLOSLP respectively. COPD has been one of the major causes of death in earlier studies and was probably related to smoking, because lifetime estimated cigarette consumption has been 70-80% in patients with schizophrenia under 67 years of age (Copeland et al. 2007). In a study on mortality among US veterans with an average age of 72 years at death, two thirds had a diagnosis of respiratory diseases in the last year of their lives, 38% had pneumonia and 46% had COPD (Copeland et al. 2007). Community-acquired pneumonias have also been associated with lower rates of vaccination in people with serious mental illness (Copeland et al. 2007). In addition, taking antipsychotics may increase the risk of pneumonia, which is a common cause of death in frail older patients (Trifiro et al. 2010).

The high SMR of infections (26.6) as a cause of death is at least partly explained by the assumption that patients died from unusual infections difficult to recognize. It is difficult to compare rates of infections as a cause of death in different areas of the world because of their diverse causes. In Finland for example, HIV or tuberculosis are extremely rare in older age groups in general and fortunately also in schizophrenia. In the Finnish Causes of Death Register pneumonias belonged mostly to a category of respiratory illnesses until 2005-2006. Since then pneumonias could not have been used as a main cause of death if a deceased person had any chronic disease impairing overall health. After the revision of the classification, the number of pneumonias as the main cause of death has decreased by one third and cases have switched to dementias and circulatory (cerebrovascular) diseases (Statistics Finland 2014).

Some rarer causes of death such as genitourinary diseases or digestive diseases also show surprisingly high SMRs in the present study (19.3 and 9.6). The median SMRs in these categories in the meta-analysis by Saha et al. (2007) were 3.7 and 2.4 respectively, but the vast majority of patients in the studies included in the meta-analysis were younger than the patients in the present study. Lack of insight into the illness in general may cause delayed treatments seeking, meaning that the stage of a physical illness may be more advanced at the time of diagnosis.

6.1.2.5 Theoretical explanations for natural causes of death (I, III)

Delayed diagnoses of physical disease may underlie premature death in people with schizophrenia in old age. This may be due to communication problems, patients' high tolerance of pain, and difficulties in reaching outpatient facilities (Potvin and Marchand 2008; Schoos and Cohen 2003). In addition, psychotic symptoms may impair the patient's ability to recognize physical symptoms and adhere to treatments (Brown and Mitchell 2012). Several studies have suggested undertreatment of physical illnesses in the mentally ill (Druss et al. 2001; Laursen et al. 2009). Treatment in end of life care has also been reported to be either better or inadequate in individuals with schizophrenia (Chochinov et al. 2012; Copeland et al. 2007; Ganzini et al. 2010). Patients with schizophrenia suffering from the same stage of cardiovascular disease have not undergone as many invasive procedures as those without schizophrenia (Laursen et al. 2009). Older patients with schizophrenia may be difficult to treat and understand or they may refuse the treatment proposed, but they also suffer from stigma. Regarding patients with VLOSLP, this diagnosis is still little known and these patients may not be recognized in health care, which easily leads to insufficient support and treatment.

6.1.2.6 Unnatural causes of death (I, III)

For unnatural causes of death, the SMR of the whole present sample was as high as 11. The finding concurs to some extent with the results of the Danish study in which the mortality rates for unnatural causes of death in patients with schizoaffective disorder and schizophrenia were respectively 13.2 and 8.9 in women, and 9.4 and 5.5 in men in the age-group 55-79 years compared to non-admitted people, respectively (Laursen et al. 2007).

A definition of accidental death is 'any person killed immediately or dying within 30 days as a result of an injury accident' (Crump et al. 2013). Risk of accidental death in any psychiatric disorder among aged 60 or older has been reported to be 4-5 –fold (Crumb 2013). In the present study, accidental falls were a major cause of death, in a category of unnatural causes of death, a finding which differs from that of younger people with schizophrenia, in whom suicidal deaths are the most common. Most of the accidents in older people occurred when falling at the same level or down stairs

(53% of all unnatural causes of death) followed by suicides (16%) and choking on food (14%). In the present study we had no information on the circumstances in which the accidents occurred. The present data does not specify if accidental falls or choking on food are a consequence of difficulties in moving or swallowing because of the extrapyramidal or other adverse effects of antipsychotics. Orthostatic hypotension, sedation or the anticholinergic properties of psychiatric medications may all contribute to falls. Choking on food may be a consequence of dry mouth or slowness of the swallowing followed by aspiration of food. In a Finnish review by Hartikainen et al. (2007), all psychotropic medications, including antipsychotics, were associated with an increased risk of falls in patients older than 60 years. In addition, some older patients with schizophrenia may have remarkable difficulties in mobility because of accelerated physical ageing and because they may be hasty in their every-day tasks such as in eating. These qualities predispose to fatal accidents.

In the present series of studies, 42 patients (0.8% of all deaths) committed a suicide and there were no suicides after the age of 81 years. SMRs for suicides were high for both genders, especially women, but this finding should be interpreted with caution because of a small number of suicides in the present sample. In a British community survey, risk of suicide in schizophrenia relative to the comparison group with no psychiatric disorders decreased towards older age groups but was still up to nine-fold between 50 and 70 years (Osborn et al. 2008). In a large register-based Danish cohort of older patients with schizophrenia the respective suicide rate ratios were 7.0 and 2.1 in men and 13.7 and 3.4 in women in ages 50-69 and 70+ with regard to hospital diagnosis of schizophrenia, respectively (Erlangsen et al. 2012). The risk of death by suicide was particularly high during the first three months after discharge compared with the risk after that time for both men (RR 24 vs. 4) and women (RR 78 vs. 11). Suicide attempts within the past 365 days also markedly increased the risk of death compared to those with no recent suicide attempts (RR 54 vs. 4 in men, 176 vs. 8 in women). Comorbid alcohol dependence and depressive symptoms also increased the relative risk of suicide, especially in women. In addition, exposure to childhood trauma, poor quality of life, and hopelessness has explained suicidality throughout the age continuum in earlier studies (Heilä et al. 1997).

In the present subjects with VLOSLP accidental falls were also a major specific unnatural cause of death (SMR 33, more than three-fold that of the earlier-onset group), but there were only three suicides in this group (unpublished data). People with VLOSLP are susceptible to the side effects of antipsychotics because they are

exposed to these medications presumably for the first time in their lives, and also due to age-related changes in central nervous system and multi-morbidity. There is evidence that some adverse effects of antipsychotics are either dose-related, for instance extrapyramidal side effects, or more evident at the beginning of treatment (Alexopoulos et al. 2004). In addition, other psychotropics such as benzodiazepines, widely used in agitation of schizophrenia, have been associated with serious adverse effects in old people e.g. impaired ability to function in the domains of cognition or mobility and balance. All these adverse effects increase the risk of falls which may sometimes be fatal. In a large Finnish nationwide study of the cumulative use of anticholinergic and sedative drugs in older community-dwelling people with and without dementia, adjusted HRs for mortality were 1.34 (1.13-1.60) and 1.75 (1.39-2.22) when taking at least two anticholinergic or sedative drugs at minimum effective dose when compared to the group with no exposure to these drugs (Gnjidic et al. 2014).

6.2 Relapse in older patients with schizophrenia (II, IV)

6.2.1 Psychiatric medications and risk of relapse (II)

6.2.1.1 Time trends in antipsychotics usage (II)

The use of antipsychotics changed distinctly during the years 1998-2003 in the patients of the present study. The proportion of SGAs used by outpatients quadrupled to 12% and combined usage of SGAs and FGAs doubled to 9%. At the same time, the use of FGAs decreased by one third, being 39% in the last year of follow-up. The trends in antipsychotics usage were as expected, because the second generation antipsychotics entered the market in the 1990's and the published guidelines at that time favoured them.

When analysing the data by age group, usage of antipsychotics was higher throughout in the younger group (64-79 years) than in the older group (80 years or more). The findings reported in earlier studies on this issue are contradictory, mainly due to differences in populations. In an earlier study on Finnish home care patients

the use of antipsychotics was also higher in younger people than in older ones (Alanen et al. 2008). In another Finnish study of mostly community-dwelling old people, the trend for increasing usage of antipsychotics was towards older age (Linjakumpu et al. 2002). In both these studies the proportion of people with schizophrenia was not reported and probably small. The reason for more frequent use of antipsychotic medication in younger older patients may be troublesome positive symptoms in younger years, which often diminish as patient gets older.

Two out of five of the present outpatients had not purchased any antipsychotic within a year. The present result is in line with a systematic review of 39 studies of schizophrenia, in which the mean rate of medication nonadherence was 41% (Lacro et al. 2002; Torniainen et al. 2015). The proportion of non-users of antipsychotics in an earlier study of older patients with schizophrenia was 19% which is lower than in the present study, but these patients were in long-term institutional care (Alanen et al. 2008). No gender differences were found in the present study in the analysis of trends in antipsychotics usage.

6.2.1.2 Antipsychotics, antidepressants and risk of relapse (II)

A broad definition of a relapse is "a return of a disease after partial recovery" (Lader, 1998). However, for research purposes, relapse in schizophrenia has been defined in different ways, such as a change in PANSS score or GAF score or as rate of hospitalizations, which has appeared to be the most common definition to describe it in the latest studies (Suzuki and Uchida 2014). In the present study, one-year risk of relapse was 9% when the definition criterion was psychiatric hospitalization (hospitalized in psychiatric hospitals for at least one day in 1999). This may be a slight underestimate due to some patients having exacerbation of symptoms but being treated in outpatient facilities and therefore not included here. However, underestimation may well be less in older patients because their ability to function deteriorates faster under the psychotic exacerbation than in younger patients.

Relapse rates in patients with schizophrenia taking antipsychotics have varied between 0% and 41% within a year depending on the clinical characteristics of the subjects, relapse criteria and study design (Kishimoto et al. 2013; Leucht et al. 2003). In a recent meta-analysis, no meaningful differences, despite clozapine, were found in the efficacy of 15 antipsychotics, but this review did not specifically concern older

people (Leucht et al. 2013). In the present study, combined FGAs and SGAs increased the risk of relapse, which probably means selection of the most severe patients in this group. Despite the evidence that relapse is more probable soon after the onset of illness, there is no plausible data to show that longer duration of antipsychotic medication protects patients even after discontinuation (Emsley et al. 2013). In a recent meta-analysis, SGAs were slightly superior to FGAs in preventing rehospitalization in middle-aged or younger patients with schizophrenia (Kishimoto et al. 2013). However, in an earlier study, the one-year rehospitalization rates of middle-aged patients (n = 195) taking olanzapine (34%) or risperidone (35%) were higher than those of the patients taking FGAs (20%), which may relate to the selection of patients into each group (Patel et al. 2002). Studies comparing efficacy in preventing psychiatric rehospitalizations between intramuscular and oral antipsychotics show variable results, but most of them report long-acting intramuscular antipsychotic treatment to be better in preventing relapse (Huang et al. 2013; Kampman et al. 2003; Kane et al. 2013; Olivares et al. 2009; Tiihonen et al. 2011).

Poor treatment adherence typical in schizophrenia increases the risk of psychiatric destabilization (Goff et al. 2010). In older people this phenomenon may be even more complex. Even partial medication nonadherence risks the general health of older patients more than in younger people, because fluctuation in drug concentrations may cause serious adverse effects, even confusion. Cognitive problems and sensory deficits further increase the risk of hospital treatment in old age schizophrenia. In a cross-sectional study by Pratt et al. (2006), better adherence in older patients with serious mental illnesses (mean age 61 years, 51% had schizophrenia or schizoaffective disorder) was associated with having a greater number of prescribed medications, superior levels of insight, better community functioning, and fewer negative symptoms. A lack of adherence was related to substance abuse and cognitive impairment (Patterson et al. 2002; Prince et al. 2008).

Of the present patients, 9% were on combined antipsychotic treatment at the end of follow-up. It is mainly in line with the finding of a recent study on patients (schizophrenia, bipolar disorder or dementia) admitted to a geriatric psychiatry unit in which the percentage of antipsychotic polypharmacy was 13% (Dolder and McKinsey 2011). In a European multi-centre study, the proportion of double medication was 10% in patients with schizophrenia older than 60 years. The patients taking concomitant SGAs and FGAs were usually more severely ill in all age groups

and had more side effects measured LUNSERS (Liverpool University Neuroleptic Side-Effect Rating Scale) than did the patients taking only one antipsychotic drug (Barbui et al. 2006). Polypharmacy has also been related to excessive total dose of antipsychotics which may lead to exacerbation of dose-related adverse effects, serious drug interactions, and complicated dosing regiments (Barbui et al. 2006; Fisher et al. 2014; Seppälä et al. 2015). All this may further impair motivation to continue treatment. Thus antipsychotic polypharmacy was associated with discontinuation more than was monotherapy in a recent one-year longitudinal study in which discontinuation of medication was defined as at least 90-day discontinuation of antipsychotic therapy. In the age group 56-64 years, 47% of patients taking only one antipsychotic drug and 74% of those having antipsychotic polypharmacy discontinued medication (Fisher et al. 2014). Antipsychotic polypharmacy has also been associated with a long index hospitalization, male gender, and longer duration of illness (Suokas et al. 2013).

However, in the present study, some of the patients in the group on antipsychotic polypharmacy may have been exposed to switching of antipsychotic medication. Withdrawal or change of antipsychotics are risk factors for relapse in older schizophrenia patients, even carefully prescribed and followed (Jeste et al. 1993). Reports on mortality in antipsychotic polypharmacy in patients with schizophrenia show both elevated and diminished risk (Joukamaa et al. 2006; Tiihonen et al. 2012). Finally, antipsychotic polypharmacy for older patients with schizophrenia cannot be recommended, because there is currently no good data or evidence to support it (Alexopoulos et al. 2004; Essali and Ali 2012; Gareri et al. 2014).

The risk of psychiatric hospitalization was also somewhat elevated in the present patients taking antidepressants (OR 1.27, 1.04-1.55). Whether this result is a consequence of comorbid depression or of the psychosis-inducing effects of antidepressants or harmful side effects remains open. Comorbid depression decreases treatment adherence and also the ability to function in every-day life and increases the risk of suicidal behaviour, all of which may increase the risk of hospitalization (Jin et al. 2001). On the other hand, antidepressants have been reported decrease suicides in patients with schizophrenia (Tiihonen et al. 2012). Depressive symptoms may also be associated with FGA-induced akinesia (Felmet et al. 2011).

6.2.2 Other factors related to risk of relapse (II)

Present patients whose data was based in the FHDR instead of the pension registers and patients with at least one psychiatric hospitalization during the five years before follow-up was started were more likely to relapse. This may mean that recent psychiatric hospitalizations predict hospital readmissions, which was also a case in a study of Prince et al. (2008) with non-psychotic psychiatric patients aged 65 years or more. This finding may also be valid in patients with very-late onset of illness (e.g. schizophrenia) having a higher risk of hospitalization because their recently diagnosed illness still needs stabilization.

According to the present results, diagnosis of any cardiovascular disease had a modestly decreased association with risk of psychiatric rehospitalization. This finding is in line with the results of the study on older patients by Prince et al. (2008), in which comorbid congestive heart failure (HR 0.83), as well as cancer, cerebrovascular disorder and dyslipidemia decreased the rate of psychiatric readmission within six months of the index hospitalization. It is possible that psychiatric patients having serious comorbid physical illness could have more contacts with health care professionals, where all their health problems are sufficiently noticed. Older patients may also be admitted to general hospital instead of psychiatric wards if they have problems with physical or mental health (Ettner 2001).

6.2.3 Relapse in patients with very-late-onset schizophrenia-like psychosis (IV)

Present patients with VLOSLP needed more psychiatric hospitalizations than patients with earlier onset of illness, especially in the first year of follow-up. In addition, the time since the illness onset influenced the length of hospitalization: the VLOSLP patients with shorter time since the first hospitalization due to psychosis had longer length of stay in psychiatric hospital. Fairly recent onset patients seemed to have the highest rates of rehospitalization, which often results from poor treatment adherence due to poor illness insight (Addington et al. 2007). Moreover, patients with recent onset may be more susceptible to stress and therefore admitted even if they commit well to the treatment.

The higher rate of psychiatric hospitalizations in the present relatively recent onset VLOSLP patients compared to those with earlier onset may also be explained by the different stage of the illness. The mean time between onset of schizophrenia and the beginning follow-up was several decades shorter in patients with VLOSLP than in patients with earlier onset. Ageing in early onset schizophrenia is often associated with improvement in fulminant psychotic symptoms and psychosocial functioning, better self-management and even reduction in rehospitalization rate (Jeste et al. 2011). The factors associated with longer length of stay in the geropsychiatric unit with mixed diagnoses (schizophrenia and other old-age psychoses 34%) included active psychotic symptoms, falling and pharmacological complications, and recent onset patients are probably more susceptible to these effects (Blank et al. 2005). VLOSLP patients are often still searching for a mental balance and a suitable treatment strategy while positive symptoms of patients with onset at earlier age have already burned out and some of them have found their way towards fairly successful psychological ageing. Moreover, the health care system fails to address the adequate care of very-late-onset patients because this diagnosis is not very well known.

6.3 Ending up in institutional care (IV)

Present patients in both onset groups ended up equally frequently in long-lasting psychiatric hospitalization and other long-term care (LLP and LTC). Older individuals were more likely to receive such care, which was surprising. Instead, having any cardiovascular or respiratory disease decreased the likelihood for LLP/LTC. Literature on this issue was difficult to find, but the present finding may concur to some extent with the results of Li et al. (2011), in which patients with schizophrenia had fewer diagnoses of cardiovascular diseases than patients with bipolar disease or patients without mental disorder when entering residential care (64% vs. 70% vs. 83%). In that study, patients with schizophrenia also had fewer musculoskeletal diseases, dementia and sensory diseases, better performance on activities of daily living, and were younger than the patients in the two other groups. However, the frequency of pulmonary diseases was higher than among the patients

with no mental disorder. The present finding is also supported to some extent by a study of Andrews et al. (2009) in which patients with schizophrenia ending up in institutional care had lower levels of disability and comorbidity than did older patients with no psychiatric disorder. In addition, in a study by Prince et al. (2008), having congestive heart failure or dyslipidaemia reduced the risk of any psychiatric reshopitalization (10% had schizophrenia) by 15% and cerebrovascular disease or cancer by 25% in patients aged 65 or more.

Older patients with schizophrenia may have other reasons associated with ending up prematurely in residential care than people with no psychotic disorder. Sometimes they even lack a clear indication for admission to institutional care because of a complexity of symptoms (Aschbrenner et al. 2011). Experienced loneliness, inadequate living circumstances and functional inability, typical also of older patients with schizophrenia, are general risk factors for premature long-term institutionalization in old age (Vaarama 2004). Mentally ill older patients with diverse symptoms and physical illness may be taken care of in a general hospital instead of a psychiatric ward (Prince et al. 2008). Thus it is possible that psychiatric patients with physical diseases are more connected to general health care, where both their physical and psychiatric problems attract attention which delays access to psychiatric hospital or long-term care.

Older patients with schizophrenia living in residential care facilities are more likely to be unmarried and to have impaired skills for daily living and building social network (Bartels et al. 1997). Cohen et al. (2000) reported that the most adequate predictors of abnormal functioning in schizophrenia may be negative symptoms, cognitive impairment, and abnormal movements. Thus a comprehensive care with social rehabilitation, e.g. social skills training, could help to avoid premature long-term care.

The older women with schizophrenia in the present study were slightly more likely to end up in long-lasting psychiatric care or long-term care than men, but this finding should be interpreted with caution because of a small numbers of patients in the subgroups. However, a similar conclusion was drawn in a recent Finnish study on a cohort of older people with various diagnoses. In that study, being a woman was a decisive factor for entering institutional care when compared with men (Martikainen et al. 2014). The average expectation of length of stay was also much longer in women than that in men (1,064 days vs. 686 days). Women may receive insufficient informal care from their spouses at the moment of exacerbation of

symptoms and they may be widowed earlier than men, which further decreases their support in old age. However, Reeves et al. (2002) reported no gender differences in rates of older schizophrenia patients' admission to psychiatric hospitals.

6.4 Strengths and limitations

6.4.1 Strengths of the study

The series of studies included in this thesis have several strengths. Firstly, the Finnish nationwide registers used for data collection are of high quality and reliable for research purposes. The accuracy and validity of the diagnoses in the psychosis category has also been shown to be excellent (Aro et al. 1990; Miettunen et al. 2011; Moilanen et al. 2003; Sund 2012). The vast majority of patients with schizophrenia are hospital-treated during their illness. Although outpatient services and antipsychotic medications have improved and more patients with recent onset psychotic symptoms can nowadays be treated without hospitalization, older patients having onset of schizophrenia decades ago have probably been admitted to psychiatric hospital at least once during their illness. This is also the case in most very-late-onset patients, because older people are usually hospital-treated when serious psychotic symptoms occur. In order to identify patients with schizophrenia who had never needed inpatient treatment, the data of the national pension registers were also included. With this sampling method it was also possible to determine the onset age in the case enjoying pensions before their first hospitalization (Miettunen et al. 2011). The data in the various registers were reliably collaged by the unique personal identification number assigned to every Finnish citizen. Private information on patients was not identifiable. The National Causes of Death register contains information on all deaths occurring in Finland. Deaths are certified by physicians and in cases of uncertain cause of death, post mortem examinations are performed. The quality of this register has also demonstrated to be very good (Lahti and Penttilä 2001). The data was collected and the requisite collation of register was done by the National Institute for Health and Welfare and the needed corrections to the data

were confirmed there. The statistical analyses of the final data were verified by a professional statistician.

Secondly, the study population is large enough and the follow-up time sufficiently long for producing reliable estimates of turning points in the lives of older patients with schizophrenia, and also for comparing the findings with those of general age- and gender matched population. In addition, the data covers almost all Finnish individuals with schizophrenia from different areas who were alive and at least 65 years old. In general, the considerable amount of research on schizophrenia excludes patients of that age. Therefore these studies produce valuable new information on older patients with schizophrenia.

Thirdly, to avoid selection bias, onset of schizophrenia was assessed from the first hospitalization due to psychotic symptoms, although the specific diagnosis of schizophrenia may have been set later. There are at least two studies to support this procedure. In a study by Munk-Jörgensen (1987), only half of patients later diagnosed as having schizophrenia received the diagnosis at their first hospitalization. In another recent study of first-onset brief psychosis in the older, the common diagnosis of psychosis was switched to a diagnosis of VLOSLP in more than every third patient over the ten year study period (Barak et al. 2011).

6.4.2 Limitations of the study

There are also some limitations in these studies. One limitation is that the registers used in the present series of studies were originally mostly collected for administrative purposes (Sund 2012). They include a great deal of information which is not always accurate and suitable for specific research purposes. The data submitted to the Institute for Health and Welfare (THL) may also be incomplete even if it is checked and corrected under the guidance of THL. Moreover, the number of variables that can be constructed from the basic variables is limited. In the present studies, potential intervening and confounding factors were taken into account when analysing the data wherever possible. However, checking the reliability of diagnoses and obtaining the information on basic characteristics of each study subject, such as living habits, marital status or income, were not feasible. Regarding register studies in general, the results obtained using them cannot be generalized directly and are essentially indicative (Erlangsen and Fedyszyn 2015; Sund 2012).

It is possible that some of the patients were misclassified as having a diagnosis of VLOSLP instead of dementia or vice versa. Symptoms in dementia e.g. in frontotemporal degeneration in its early phase, and those in schizophrenia may resemble each other. Alzheimer's disease usually begins with problems in short-term memory, or sometimes with visual or auditory hallucinations, but their quantity and content differ from those related to schizophrenia (Iglewicz et al. 2011; Reinhardt and Cohen 2015).

The FHDR begins in 1967 but the data in these studies begins from 1969. However, some identity codes from the very first years of the FHDR have included errors (Sund 2012). Therefore cases before 1972 were mostly omitted. There is a slight possibility that the first hospitalization due to psychosis of VLOSLP patients occurred before the inception of the FHDR. The patients classified into the VLOSLP group may also have had their first symptoms of schizophrenia long before the first hospitalization, which may confound the differentiation between the two onset groups. Because schizophrenia causes premature death in all age groups, it is possible that those older people with early-onset schizophrenia still alive in old age are healthier than were those people with schizophrenia who died before the follow-up. This selection may in part influence the results. In addition, some of the findings cannot be directly generalized to the present day, because the follow-up was at the beginning of 2000s.

The definition of relapse used in these present is synonymous with psychiatric hospitalization. However, not all the patients with increased severity of psychotic symptoms are admitted to psychiatric hospital. They may either be treated in outpatient facilities or in general hospitals especially when there are also physical comorbidities (Prince et al. 2008). Nevertheless, outpatient services for older psychiatric patients are often inadequate and psychiatric hospitalization is the only option during an eruption of psychotic symptoms or inability to function (Pylkkänen 2012).

When calculating the use of antipsychotics, it was not possible to take account of patients' individual doses. In the present data only the classes of antipsychotics (SGAs, FGAs) and antidepressants were available. The data did not specify if use of antidepressants or combined use of antipsychotics reflect a more severe cause of illness even if controlled for in a model. The use of medication was calculated on the basis of drugs purchased, but this does not necessarily mean that the patients actually took them, which may further confound the results.

Because these studies used many different statistical tests, the possibility of type I error cannot be excluded. Some subgroups were small and thus the findings (also negative) must be interpreted with caution due to a possibility of type II error.

Finally, despite the limitations, these studies succeed in pointing out some problems and flaws in the psychiatric and medical care of older patients with schizophrenia. The indicators, such as mortality or ending up in long-term care, revel some important objectives at which the resources of psychiatric and general health care should be targeted.

6.5 Implications for future research

Research on older patients with schizophrenia is still scanty, especially on those with very late onset illness. Studies on middle-aged people with schizophrenia are nowadays more frequent than before, which may be due to the rising mean age in Western societies. However, the number of oldest old schizophrenia patients is expected to increase in coming decades. In some estimates, patients older than 65 years cause the highest expenditures among all schizophrenia patients, mostly because of ending up in premature long-term care. Thus more research is urgently needed to evaluate how schizophrenia in old age affects overall health and what options are available for improving the prognosis of patients with schizophrenia in old age.

In Finland there is a trend to reduce the number of beds in psychiatric hospitals and allocate the resources to outpatient psychiatric care which is often next to primary health care. More patients with schizophrenic psychoses will then be diagnosed and treated in outpatient settings in the future. This may especially involve older people with considerable physical comorbidities. Outpatient visits in primary health care have been collected in Finland by the Institute of Health and Welfare since 2011. Hence, the opportunity to use this new register information could result in new information about the causes of excess mortality and the risk of relapse in this group of people. This information could help to assess the treatment strategies and evaluate if older people with schizophrenia access health care services. It would also enable comparison of real costs between treatment in hospital and outpatient settings. Including the personal characteristics of patients, such as living habits or

marital status, into a model would also yield valuable knowledge on the contributors to mortality or comorbidity.

Because of the limited amount of original research on old age schizophrenia, only a few review articles have been published in this field within the last ten years, mostly concerning cognitive performance or radiological findings. Review articles on very-late-onset schizophrenia are even rarer. In the future a meta-analysis of ageing either with early-onset or later onset schizophrenia is needed to spark interest among those working in geriatric psychiatry and to increase the author's own know-how.

7 Summary and conclusions

This large nationwide register-linkage study focused on mortality, psychiatric hospitalization and long-term care and psychiatric drug treatment of older patients with schizophrenia with different ages at onset. The principal conclusions of the present study are as follows:

1. During the period 1999-2008, overall mortality among elderly patients with schizophrenia was almost three-fold that of the general age- and gender matched population (Standardized Mortality Ratio, SMR: 2.7). In addition, the SMRs were elevated in the all causes-of-death category. For natural causes of death, i.e. physical illnesses, SMR was 2.6, whereas for unnatural causes of death, it was as high as 11-fold. (Study I)

2. The use of second generation antipsychotics (SGAs) and combined use of SGAs and first generation antipsychotics (FGAs) increased during the period 1998-2003, when at the same time decreasing percentage of old patients with schizophrenia used FGAs as monotherapy. Almost two out of five outpatients did not purchase any antipsychotics during the follow-up of six years. Antipsychotic polypharmacy and use of concomitant antidepressants seemed to increase but cardiovascular diseases in general modestly reduced the risk for psychiatric hospitalization in the first year of follow-up. (Study II)

3. The over-all mortality of patients with very-late-onset schizophrenia-like psychosis (VLOSLP) was five-fold that of general population and 40% higher than that of the group of patients with onset of schizophrenia before 60 years. In every specific causes-of-death category, SMRs were clearly elevated in the VLOSLP group. However, after adjusting for several variables such as gender, age, physical illness (cardiovascular disease, respiratory disease, diabetes mellitus, neoplasm, dementia, high cholesterol level), alcohol dependence, use of antipsychotics at baseline and at least one psychiatric

hospitalization in the period 1994-1998, there was no longer any significant difference in the hazard of death between the two subgroups by onset age of illness in the follow-up time period 1999-2008. (Study III)

4. More patients in the VLOSLP than in the earlier-onset group needed at least one psychiatric hospitalization (27% vs. 23%, p= 0.020) between 1999 and 2003. A shorter period of time between the onset of illness and the beginning of follow-up predicted longer length of psychiatric hospitalization. There were no differences in ending up in institutional care (psychiatric and somatic) between the two onset groups. Having comorbid cardiovascular or respiratory disease decreased the likelihood of ending up in any form of institutional care in both onset groups. (Study IV).

These findings support the earlier evidence of the risk of excess mortality in people with schizophrenia, but also provide new information that this risk persists into old age. Causes of death in older patients with schizophrenia are similar to those in general older population. More effort should be invested in the follow-up and treatment of medical illnesses in this patient group, because the risk of death is elevated in every natural causes-of-death category regardless of age at onset of schizophrenia. Moreover, by monitoring the effects of medication and supporting functional ability, the excess amount of fatal accidents could probably be reduced. Those older patients with schizophrenia who receive adequate comprehensive care for both psychiatric and medical illnesses are more likely to maintain their capacity and less likely to end up in early long-term care.

8 Acknowledgements

These studies were carried out in collaboration with the Department of Psychiatry at the University of Tampere, the Department of Psychiatry at the University of Oulu, the Department of Psychiatry at Oulu University Hospital, and the National Institute for Health and Welfare (THL), Centre for Health and Social Economics, as part of the PERFECT (PERFormance, Effectiveness and Cost of Treatment episodes) project.

First and most profoundly I thank my supervisor Professor Esa Leinonen for encouraging me to start and successfully finish this work. He has always supported me throughout this process and given his time when needed. He once inspired me to choose my career as an old age psychiatrist. I am going to miss the conversations with him concerning research and psychiatry but I am sure that this dialogue will continue.

I am also grateful to my other supervisor Hanna-Mari Alanen MD, PhD for sharing with me her outstanding expertise in geriatric psychiatry. She has also given me lots of good practical advice on how to live between science, work and family.

I express my gratitude to the National Institute for Health and Welfare and especially to Research Professor Unto Häkkinen for the opportunity to study this extraordinary data. He also gave me valuable suggestions and comments on my studies.

I am deeply grateful to Helinä Hakko PhD, because with her advice and ultimate expertise in statistical analysis I was able reach the goal. I also wish to thank Professor emeritus Matti Isohanni for giving me guidance and inspiring ideas for my research and scientific writing. I also highly appreciate the critical conversations with Associate Professor Olli Kampman, also a member of the follow-up team, who has taught me statistics and scientific thinking. My special thanks go also to another member of follow-up team Docent Harriet Finne-Soveri. I was lucky to have excellent co-authors.

I express my appreciation to the reviewers of the manuscript of my thesis, Professor emeritus Raimo K.R. Salokangas and Professor Sirpa Hartikainen. This

thesis is certainly of higher quality because of their constructive criticism and comments.

I want to thank Virginia Mattila MA for the important English language corrections. I admire her way of working - she always returned manuscripts sooner than expected. I also express my gratitude to Jari-Pekka Klemettilä MD and Kirsti Nurmela MD for giving their time for reading my texts and to Kirsti for her energizing friendship, as well as to other members of the scientific seminars for giving their interest to my studies. Professor emeritus Matti Joukamaa, Ritva Sundström MSc and many other people from the University of Tampere has greatly helped me in different ways, as well as Marjo Kiviniemi PhD from Oulu. Co-operation with Merja Juntunen MSc from THL was always pleasant and productive.

I am grateful for the financial support I have received from the Department of Psychiatry at Tampere University Hospital, the Department of Psychiatry at Helsinki University Central Hospital, the Uulo Arhio Foundation and the Finnish Psychiatric Association. My special thanks go to the National Graduate School of Clinical Investigation, and especially for Professor Hasse Karlsson, Docent Linnea Karlsson and the former and current coordinators Docent Jouni Lauronen and Nina Blom PhD for organizing support and the high validity seminars.

It is also my pleasure to thank many colleagues, especially Katariina Lahtinen MD, Docent Kati Juva and Jukka-Pekka Puutio MD, and other co-workers for their interest and support. Together with my wonderful every-day working team in Tikkurila Geropsychiatric Outpatient Unit I have realized why it is important to study this special research field. The heart of our group, Department Secretary Merja Taskinen, has helped me enormously in organizing my time table during these years. I also want to thank my former and current superiors from Helsinki University Central Hospital, Department of Psychiatry, and especially Docent Björn Appelberg for his positive attitude towards the time I have spent on this project.

I wish to thank Aino, Hille, Kirsti, Leena, Outi, Pia and Tarja for long-lasting friendship ever since we were medical students and I am happy to realize that we are still planning get-together journeys.

I have a great pleasure in thanking all my good friends. With them I have shared precious moments of life, which have brought me strength and happiness.

I am indebted to my loving parents, Ritva and Erkki, who have always encouraged me to believe in myself in a realistic way. Unfortunately my father did not live to see the final results and my mother is unable to be present on the occasion of the public

defense of my thesis, but I know that they would proud of me. I am also grateful to my parents-in-law, Pirkko and Esko, for their love and support. Thanks go also to my brother Antti and brother-in-law Janne and their families.

Finally, I express my deepest thanks to my husband Pekka for his love, patience and never-ending confidence in me and my project. Hilla, Väinö and Eino have completed our family, for which I am enormously grateful. Their energy, joy and incisive comments have shown me what is eventually best in life.

Klaukkala, September, 2015.

Tiina Talaslahti

9 References

Addington, D., Addington, M. D., & Patten, S. (2007). Relapse rates in an early psychosis treatment service. Acta Psychiatrica Scandinavica, 115(2), 126-131.

Alanen, H. M., Finne-Soveri, H., & Leinonen, E. (2008). Factors associated with non-use of antipsychotics among older residents with schizophrenia in long-term institutional care. International Journal of Geriatric Psychiatry, 23(12), 1261-1265.

Alanen, H. M., Finne-Soveri, H., Fialova, D., Topinkova, E., Jonsson, P. V., Soerbye, L. W., et al. (2008). Use of antipsychotic medications in older home-care patients. Report from nine European countries. Aging-Clinical & Experimental Research, 20(3), 260-265.

Alaräisänen, A., Miettunen, J., Räsänen, P., Fenton, W., Koivumaa-Honkanen, H. T., & Isohanni, M. (2009). Suicide rate in schizophrenia in the Northern Finland 1966 Birth Cohort. Social Psychiatry & Psychiatric Epidemiology, 44(12), 1107-1110.

Alexopoulos, G. S., Streim, J., Carpenter, D., Docherty, J. P., & Expert Consensus Panel for Using Antipsychotic Drugs in Older,Patients. (2004). Using antipsychotic agents in older patients. Journal of Clinical Psychiatry. 65(S2):5-99.

Alici-Evcimen, Y., Ertan, T., & Eker, E. (2003). Case series with late-onset psychosis hospitalized in a geriatric psychiatry unit in turkey: Experience in 9 years. International Psychogeriatrics, 15(1), 69-72.

Almeida, O. P., Howard, R. J., Levy, R., & David, A. S. (1995). Psychotic states arising in late life (late paraphrenia) psychopathology and nosology. British Journal of Psychiatry, 166(2), 205-214.

Almeida, O.P., Hankey, G.J., Yeap, B.B., Golledge, J., Norman, P.E., & Flicker, L. (2014). Mortality among people with severe mental disorders who reach old age: A longitudinal study of a community-representative sample of 37,892 men. PLoS ONE [Electronic Resource], 9(10), e111882.

Alwan, N.A., Johnstone, P., & Zolese, G. (2008). Length of hospitalisation for people with severe mental illness. Cochrane Database of Systematic Reviews, (1)-2008.

Andrews, A., Bartels, S. J., Xie, H., & Peacock, W. J. (2009). Increased risk of nursing home admission among middle aged and older adults with schizophrenia. American Journal of Geriatric Psychiatry, 17(8), 697-705.

Ansell, B. R. E., Dwyer, D. B., Wood, S. J., Bora, E., Brewer, W. J., Proffitt, T. M., et al. (2015). Divergent effects of first-generation and second-generation antipsychotics on cortical thickness in first-episode psychosis. Psychological Medicine, 45(3), 515-527.

Aro, S., Koskinen, R., & Keskimäki, I. (1990). Reliability of hospital discharge data concerning diagnosis, treatments and accidents. Duodecim 106(21), 1443–1450.

Aschbrenner, K. A., Cai, S., Grabowski, D. C., Bartels, S. J., & Mor, V. (2011). Medical comorbidity and functional status among adults with major mental illness newly admitted to nursing homes. Psychiatric Services, 62(9), 1098-1100.

Bankole, A., Cohen, C. I., Vahia, I., Diwan, S., Palekar, N., Reyes, P., et al. (2008). Symptomatic remission in a multiracial urban population of older adults with schizophrenia. American Journal of Geriatric Psychiatry, 16(12), 966-973.

Barak, Y., Knobler, C. Y., & Aizenberg, D. (2004). Suicide attempts amongst elderly schizophrenia patients: A 10-year case-control study. Schizophrenia Research, 71(1), 77-81.

Barak, Y., Levy, D., Szor, H., & Aizenberg, D. (2011). First-onset functional brief psychoses in the elderly. Canadian Geriatrics Journal, 14(2), 30-33.

Barak, Y., Aizenberg, D., Mirecki, I., Mazeh, D., & Achiron, A. (2002). Very late-onset schizophrenia-like psychosis: Clinical and imaging characteristics in comparison with elderly patients with schizophrenia. Journal of Nervous & Mental Disease, 190(11), 733-736.

Barbui, C., Nose, M., Mazzi, M.A., Bindman, J., Leese, M., Schene, A., et al. (2006). Determinants of first- and second-generation antipsychotic drug use in clinically unstable patients with schizophrenia treated in four European countries. International Clinical Psychopharmacology, 21(2), 73-79.

Barry, K. L., Blow, F. C., Dornfeld, M., & Valenstein, M. (2002). Aging and schizophrenia: Current health services research and recommendations. Journal of Geriatric Psychiatry & Neurology, 15(3), 121-127.

Bartels, S.J., Mueser, K.T., & Mills, K.M. (1997). A comparative study of elderly patients with schizophrenia and bipolar disorder in nursing homes and the community, 27(2-3), 181-90.

Blank, K., Hixon, L., Gruman, C., Robison, J., Hickey, G., & Schwartz, H.I. (2005). Determinants of geropsychiatric inpatient length of stay. Psychiatric Quarterly, 76(2), 195-212.

Bowie, C.R., Harvey, P.D., Moriarty, P.J., Parrella, M., White, L., & Davis, K.L. (2004). A comprehensive analysis of verbal fluency deficit in geriatric schizophrenia. Archives of Clinical Neuropsychology, 19(2), 289-303.

Boyer, L., Millier, A., Perthame, E., Aballea, S., Auquier, P., & Toumi, M. (2013). Quality of life is predictive of relapse in schizophrenia. BMC Psychiatry, 13, 15.

Breslow, N. E., & Day, N. E. (1987). Statistical methods in cancer research. Volume II--the design and analysis of cohort studies. IARC Scientific Publications, (82), 1-406.

Brown, S., & Mitchell, C. (2012). Predictors of death from natural causes in schizophrenia: 10-year follow-up of a community cohort. Social Psychiatry & Psychiatric Epidemiology, 47(6), 843-847.

Brown, S., Inskip, H., & Barraclough, B. (2000). Causes of the excess mortality of schizophrenia. British Journal of Psychiatry, 177, 212-217.

Brown, S., Kim, M., Mitchell, C., & Inskip, H. (2010). Twenty-five year mortality of a community cohort with schizophrenia. British Journal of Psychiatry, 196(2), 116-121.

Bushe, C. J., Taylor, M., & Haukka, J. (2010). Mortality in schizophrenia: A measurable clinical endpoint. Journal of Psychopharmacology, 24(4S), 17-25.

Castle, D.J. & Murray, R.M. (1991). The neurodevelopmental basis of sex differences in schizophrenia. Psychological Medicine, 21(3), 565-575.
Castle, D. J., & Murray, R. M. (1993). The epidemiology of late-onset schizophrenia. Schizophrenia Bulletin, 19(4), 691-700.
Chan, R.C., Di, X., McAlonan, G.M., & Gong, Q.Y. (2011). Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: An activation likelihood estimation meta-analysis of illness progression. Schizophrenia Bulletin, 37(1), 177-188.
Chang, C. K., Hayes, R. D., Broadbent, M., Fernandes, A. C., Lee, W., Hotopf, M., et al. (2010). All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: A cohort study. BMC Psychiatry, 10, 77.
Chen, L., Chen, X., Liu, W., Wang, Q., Jiang, T., Wang, J., et al. (2013). White matter microstructural abnormalities in patients with late-onset schizophrenia identified by a voxel-based diffusion tensor imaging. Psychiatry Research, 212(3), 201-207.
Chiapponi, C., Piras, F., Fagioli, S., Piras, F., Caltagirone, C., & Spalletta, G. (2013). Age-related brain trajectories in schizophrenia: A systematic review of structural MRI studies. Psychiatry Research, 214(2), 83-93.
Chochinov, H.M., Martens, P.J., Prior, H.J., & Kredentser, M.S. (2012). Comparative health care use patterns of people with schizophrenia near the end of life: A population-based study in Manitoba, Canada. Schizophrenia Research, 141(2-3), 241-246.
Ciompi, L. (1980). Catamnestic Long-term Study on the Course of Life and Aging of Schizophrenia. Schizophrenia Bulletin, 6(4), 606-618.
Cohen, C. I., & Talavera, N. (2000). Functional impairment in older schizophrenic persons: Toward a conceptual model. American Journal of Geriatric Psychiatry, 8(3), 237-244.
Cohen, C.I., Izediuno, I., Yadack, A.M., Ghosh, B., & Garrett, M. (2014). Characteristics of auditory hallucinations and associated factors in older adults with schizophrenia. American Journal of Geriatric Psychiatry, 22(5), 442-449.
Cohen, C. I., Vahia, I., Reyes, P., Diwan, S., Bankole, A. O., Palekar, N., et al. (2008). Focus on geriatric psychiatry: Schizophrenia in later life: Clinical symptoms and social well-being. Psychiatric Services, 59(3), 232-234.
Copeland, L. A., Mortensen, E. M., Zeber, J. E., Pugh, M. J., Restrepo, M. I., & Dalack, G. W. (2007). Pulmonary disease among inpatient decedents: Impact of schizophrenia. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 31(3), 720-726.
Cowling, D., Miettunen, J., Jääskeläinen, E., Koivumaa-Honkanen, H., Koponen, H., Pirkola, S., et al. (2012). Ageing in Schizophrenia – a review. Psychiatria Fennica, 43, 39-68.
Crump, C., Winkleby, M. A., Sundquist, K., & Sundquist, J. (2013). Comorbidities and mortality in persons with schizophrenia: A Swedish national cohort study. American Journal of Psychiatry, 170(3), 324-333.
Current Care Guideline. Skitsofrenian Käypä hoito –suositus. Suomalainen Lääkäriseura Duodecim [database online]. 2015. Available from http://www.kaypahoito.fi.

Dawes, S. E., Palmer, B. W., Meeks, T., Golshan, S., Kasckow, J., Mohamed, S., et al. (2012). Does antidepressant treatment improve cognition in older people with schizophrenia or schizoaffective disorder and comorbid subsyndromal depression? Neuropsychobiology, 65(3), 168-172.

De Hert, M. A., van Winkel, R., Van Eyck, D., Hanssens, L., Wampers, M., Scheen, A., et al. (2006). Prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotic medication. Schizophrenia Research, 83(1), 87-93.

Dipasquale, S., Pariante, C.M., Dazzan, P., Aguglia, E., McGuire, P., & Mondelli, V. (2013). The dietary pattern of patients with schizophrenia: A systematic review. Journal of Psychiatric Research, 47(2), 197-207.

Diwan, S., Cohen, C. I., Bankole, A. O., Vahia, I., Kehn, M., & Ramirez, P. M. (2007). Depression in older adults with schizophrenia spectrum disorders: Prevalence and associated factors. American Journal of Geriatric Psychiatry, 15(12), 991-998.

Dolder, C.R., & McKinsey, J. (2011). Antipsychotic polypharmacy among patients admitted to a geriatric psychiatry unit. Journal of Psychiatric Practice, 17(5), 368-374.

Douzenis, A., Seretis, D., Nika, S., Nikolaidou, P., Papadopoulou, A., Rizos, E.N., et al. (2012). Factors affecting hospital stay in psychiatric patients: The role of active comorbidity. BMC Health Services Research, 12, 166.

Druss, B. G., Bradford, W. D., Rosenheck, R. A., Radford, M. J., & Krumholz, H. M. (2001). Quality of medical care and excess mortality in older patients with mental disorders. Archives of General Psychiatry, 58(6), 565-572.

Emsley, R., Chiliza, B., Asmal, L., & Harvey, B. H. (2013). The nature of relapse in schizophrenia. BMC Psychiatry, 13, 50.

Erlangsen A., & Fedyszyn, I. (2015). Danish nationwide registers for public health and health-related research. Scandinavian Journal of Public Health. Mar 10. pii: 1403494815575193.

Erlangsen, A., Eaton, W. W., Mortensen, P. B., & Conwell, Y. (2012). Schizophrenia--a predictor of suicide during the second half of life? Schizophrenia Research, 134(2-3), 111-117.

Erlangsen, A., Zarit, S. H., Tu, X., & Conwell, Y. (2006). Suicide among older psychiatric inpatients: An evidence-based study of a high-risk group. American Journal of Geriatric Psychiatry, 14(9), 734-741.

Essali, A., & Ali, G. (2012). Antipsychotic drug treatment for elderly people with late-onset schizophrenia. Cochrane Database of Systematic Reviews, 2, 004162.

Ettner, S. L. (2001). The setting of psychiatric care for medicare recipients in general hospitals with specialty units. Psychiatric Services, 52(2), 237-239.

Felmet, K., Zisook, S., & Kasckow, J. W. (2011). Elderly patients with schizophrenia and depression: Diagnosis and treatment. Clinical Schizophrenia & Related Psychoses, 4(4), 239-250.

Fisher, M.D., Reilly, K., Isenberg, K., & Villa, K.F. (2014). Antipsychotic patterns of use in patients with schizophrenia: Polypharmacy versus monotherapy. BMC Psychiatry, 14(1), 341.

Fochtmann, L.J., Moitabai, R., & Bromet E.J. (2009). Schizophrenia and Other Psyhcotic Disorders: Other Psychotic Disorders. In Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 9th Edition, Kaplan, B., Sadock, V., & Ruiz, P. (Eds), Lippincott, Williams, & Wilkins, Philadelphia, PA, 1605-1628.

Fors, B.M., Isacson, D., Bingefors, K., & Widerlöf, B. (2007). Mortality among persons with schizophrenia in Sweden: An epidemiological study. Nordic Journal of Psychiatry, 61(4), 252-259.

Friedman, J.I., Harvey, P.D., Coleman, T., Moriarty, P.J., Bowie, C., Parrella, M. et al. (2001). Six-Year Follow-up Study of Cognitive and Functional Status Across the Lifespan in Schizophrenia: A Comparison With Alzheimer's Disease and Normal Aging. American Journal of Psychiatry, 158, 1441-1448.

Fusar-Poli, P., Smieskova, R., Kempton, M. J., Ho, B. C., Andreasen, N. C., & Borgwardt, S. (2013). Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neuroscience & Biobehavioral Reviews, 37(8), 1680-1691.

Ganzini, L., Socherman, R., Duckart, J., & Shores, M. (2010). End-of-life care for veterans with schizophrenia and cancer. Psychiatric Services, 61(7), 725-728.

Gareri, P., Segura-García, C., Manfredi, V. G. L., Bruni, A., Ciambrone, P., Cerminara, G., et al. (2014). Use of atypical antipsychotics in the elderly: A clinical review. Clinical Interventions in Aging, 9, 1363-1373.

Girard, C., & Simard, M. (2008). Clinical characterization of late- and very late-onset first psychotic episode in psychiatric inpatients. American Journal of Geriatric Psychiatry, 16(6), 478-487.

Gissler, M., & Haukka, J. (2004). Finnish health and social welfare registers in epidemiological research. Norwegian Journal of Epidemiology, 14(1), 113-120.

Gnjidic, D., Hilmer, S.N., Hartikainen, S., Tolppanen, A.M., Taipale, H., Koponen, M., et al. (2014). Impact of high risk drug use on hospitalization and mortality in older people with and without Alzheimer's disease: A national population cohort study. PLoS ONE [Electronic Resource], 9(1), e83224.

Goff, D. C., Hill, M., & Freudenreich, O. (2010). Strategies for improving treatment adherence in schizophrenia and schizoaffective disorder. Journal of Clinical Psychiatry, 71(Suppl 2), 20-26.

Haijma, S.V., Van Haren, N., Cahn, W., Koolschijn, P.C., Hulshoff Pol, H.E., & Kahn, R.S. (2013). Brain volumes in schizophrenia: A meta-analysis in over 18 000 subjects. Schizophrenia Bulletin, 39(5), 1129-1138.

Hanssen, M., van der Werf, M., Verkaaik, M., Arts, B., Myin-Germeys, I., van Os, J., et al. (2014). Comparative study of clinical and neuropsychological characteristics between early-, late and very-late-onset schizophrenia spectrum disorders. American Journal of Geriatric Psychiatry, 4, S1064-7481(14)00317-0, doi: 10.1016/j.jagp.2014.10.007.

Harding, C.M. (2003). Changes in Schizophrenia Across Time. Paradoxes, Patterns, and Predictors. In Textbook of Schizophrenia into Later Life. Cohen, C.I. (ed.), American Psychiatric Publishing, Washington, London, 19-41.

Hartikainen, S., Lönnroos, E., & Louhivuori, K. (2007). Medication as a risk factor for falls: Critical systematic review. Journals of Gerontology Series A-Biological Sciences & Medical Sciences, 62(10), 1172-1181.

Harvey, P. D., Reichenberg, A., & Bowie, C. R. (2006). Cognition and aging in psychopathology: Focus on schizophrenia and depression. Annual Review of Clinical Psychology, 2, 389-409.

Harvey, P. D., Parrella, M., White, L., Mohs, R. C., Davidson, M., & Davis, K. L. (1999). Convergence of cognitive and adaptive decline in late-life schizophrenia. Schizophrenia Research, 35(1), 77-84.

Heckers, S., Barch, D.M., Bustillo, J., Gaebel, W., Gur, R., Malaspina, D., et al. (2013). Structure of the psychotic disorders classification in DSM-5. Schizophrenia Research, 150(1), 11-14.

Heilä, H, Haukka, J., Suvisaari, J., & Lönnqvist, J. (2005). Mortality among patients with schizophrenia and reduced psychiatric hospital care. Psychological Medicine, 35, 725-732.

Heilä, H., Isometsä, E. T., Henriksson, M. M., Heikkinen, M. E., Marttunen, M. J., & Lönnqvist, J. K. (1997). Suicide and schizophrenia: A nationwide psychological autopsy study on age- and sex-specific clinical characteristics of 92 suicide victims with schizophrenia. American Journal of Psychiatry, 154(9), 1235-1242.

Hendrie, H. C., Lindgren, D., Hay, D. P., Lane, K. A., Gao, S., Purnell, C., et al. (2013). Comorbidity profile and healthcare utilization in elderly patients with serious mental illnesses. American Journal of Geriatric Psychiatry, 21(12), 1267-1276.

Hinterhuber, H. (1973). Zur Katamnese der Schizophrenien. Eine klinischestatistische Urtrersuchung Lebenslanger Verläufe. Catamnestic studies on schizophrenia. A clinical-statistical study of lifelong course. Fortschritte der Neurologie, Psychiatrie, und ihrer Grenzgebiete, 41(10):527-58.

Hiroeh, U., Appleby, L., Mortensen, P. B., & Dunn, G. (2001). Death by homicide, suicide, and other unnatural causes in people with mental illness: A population-based study. The Lancet, 358(9299), 2110-2112.

Hodgson, R., Wildgust, H. J., & Bushe, C. J. (2010). Cancer and schizophrenia: Is there a paradox? Journal of Psychopharmacology, 24(4 Suppl), 51-60.

Holden, N. L. (1987). Late paraphrenia or the paraphrenias? A descriptive study with a 10-year follow-up. British Journal of Psychiatry, 150, 635-639.

Honkonen, T., Saarinen, S., & Salokangas, R.K.R. (1999). Deinstitutionalization and Schizophrenia in Finland II: Discharged Patients and Their Psychosocial Functioning. Schizophrenia Bulletin, 25(3), 543-551.

Hor, K., & Taylor, M. (2010). Suicide and schizophrenia: A systematic review of rates and risk factors. Journal of Psychopharmacology, 24(4 Suppl), 81-90.

Howard, R., Rabins, P. V., Seeman, M. V., & Jeste, D. V. (2000). Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: An international consensus. The International Late-Onset Schizophrenia group. American Journal of Psychiatry, 157(2), 172-178.

Huang, S.S., Lin, C.H., Loh, el-W., Yang, H.Y, Chan, C.H., & Lan, T.H. (2013). Antipsychotic formulation and one-year rehospitalization of schizophrenia patients: A population-based cohort study. Psychiatric Services, 64(12), 1259-1262.

Huang, A. R., Mallet, L., Rochefort, C. M., Eguale, T., Buckeridge, D. L., & Tamblyn, R. (2012). Medication-related falls in the elderly: Causative factors and preventive strategies. Drugs & Aging, 29(5), 359-376.

Huber, R., Gross, G., & Schüttler, R. (1975). Late Schizophrenia. Archiv für Psychiatrie und Nervenkrankheiten, 221(1), 53-66.

Husa, A.P., Rannikko, I., Moilanen, J., Haapea, M., Murray, G.K., Barnett, J., et al. (2014). Lifetime use of antipsychotic medication and its relation to change of verbal learning and memory in midlife schizophrenia – An observational 9-year follow-up study. Schizophrenia Research, 158(1-3): 134-141.

Huttunen, M.O., Machon, R.A., & Mednick, S.A. (1994). Prenatal factors in the pathogenesis of schizophrenia. British Journal of Psychiatry, Suppl. (23):15-9.

Hymas, N., Naguib, M., & Levy, R. (1989). Late paraphrenia - a follow-up study. International Journal of Geriatric Psychiatry, 4, 23-29.

Iglewicz, A., Meeks, T.W., & Jeste, D.W. (2011). New Wine in Old Bottle: Late-Life Psychosis. Psychiatric clinics of North America, 34(2), 295-318.

Irani, F., Kalkstein, S., Moberg, E. A., & Moberg, P. J. (2011). Neuropsychological performance in older patients with schizophrenia: A meta-analysis of cross-sectional and longitudinal studies. Schizophrenia Bulletin, 37(6), 1318-1326.

Isohanni, M., Miettunen, J., Mäki P., Murray, GK., Ridler, K., Lauronen, E., et al. (2006). Risk factors for schizophrenia. Follow-up data from the Northern Finland 1966 Birth Cohort study. World Psychiatry, 5(3), 168-171.

Jääskeläinen, E., Juola, P., Hirvonen, N., McGrath J.J., Saha, S., Isohanni, M., et al. (2013). A systematic review and meta-analysis of recovery in schizophrenia. Schizophrenia Bulletin, 39(6), 1296-1306.

Jablensky, A. (2009). Schizophrenia and Other Psychotic Disorders: Burden of Schizophrenia. In Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 9th Edition, Kaplan, B., Sadock, V., & Ruiz, P. (Eds), Lippincott, Williams, & Wilkins, Philadelphia, PA, 1451-1462.

Jeste, D. V. (2004). Tardive dyskinesia rates with atypical antipsychotics in older adults. Journal of Clinical Psychiatry, 65(Suppl 9), 21-24.

Jeste, D.V., & Maglione, J.E. (2013). Treating older adults with schizophrenia: Challenges and opportunities. Schizophrenia Bulletin, 39(5), 966-968.

Jeste, D. V., Wolkowitz, O. M., & Palmer, B. W. (2011). Divergent trajectories of physical, cognitive, and psychosocial aging in schizophrenia. Schizophrenia Bulletin, 37(3), 451-455.

Jeste, D. V., Harris, M. J., Krull, A., Kuck, J., McAdams, L. A., & Heaton, R. (1995). Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. American Journal of Psychiatry, 152(5), 722-730.

Jeste, D. V., Twamley, E. W., Eyler Zorrilla, L. T., Golshan, S., Patterson, T. L., & Palmer, B. W. (2003). Aging and outcome in schizophrenia. Acta Psychiatrica Scandinavica, 107(5), 336-343.

Jin, H., Zisook, S., Palmer, B. W., Patterson, T. L., Heaton, R. K., & Jeste, D. V. (2001). Association of depressive symptoms with worse functioning in schizophrenia: A study in older outpatients. Journal of Clinical Psychiatry, 62(10), 797-803.

Jin, H., Folsom, D., Sasaki, A., Mudalia,r S., Henry, R., Torres, M., et al. (2011). Increased Framingham 10-year risk of coronary heart disease in middle-aged and older patients with psychotic symptoms. Schizophrenia Research, 125(2-3), 295-299.

Jones, D. K., Catani, M., Pierpaoli, C., Reeves, S. J., Shergill, S. S., O'Sullivan, M., et al. (2005). A diffusion tensor magnetic resonance imaging study of frontal cortex connections in very-late-onset schizophrenia-like psychosis. American Journal of Geriatric Psychiatry, 13(12), 1092-1099.

Jorge, R.E., Robinson, R.G., Arndt, S., & Starkstein, S. (2003). Mortality and Poststroke Depression: A Placebo-Controlled Trial of Antidepressants. American Journal of Psychiatry, 160, 1823-1829.

Joukamaa, M., Heliövaara, M., Knekt, P., Aromaa, A., Raitasalo, R., & Lehtinen, V. (2001). Mental disorders and cause-specific mortality. British Journal of Psychiatry, 179, 498-502.

Joukamaa, M., Heliövaara, M., Knekt, P., Aromaa, A., Raitasalo, R., & Lehtinen, V. (2006). Schizophrenia, neuroleptic medication and mortality. British Journal of Psychiatry, 188, 122-127.

Kampman, O., Illi, A., Poutanen, P., & Leinonen, E. (2003). Four-year outcome in non-compliant schizophrenia patients treated with or without home-based ambulatory outpatient care. European Psychiatry, 18(1), 1-5.

Kane, J.M., Kishimoto, T., & Correll, C.U. (2013). Assessing the comparative effectiveness of long-acting injectable vs. oral antipsychotic medications in the prevention of relapse provides a case study in comparative effectiveness research in psychiatry. Journal of Clinical Epidemiology, 66(8 Suppl), S37-41.

Karim, S., & Burns, A. (2003). The biology of psychosis in older people. Journal of Geriatric Psychiatry & Neurology, 16(4), 207-212.

Karvonen, K., Räsänen, P., Hakko, H., Timonen, M., Meyer-Rochow, V. B., Särkioja, T., et al. (2008). Suicide after hospitalization in the elderly: A population based study of suicides in northern Finland between 1988-2003. International Journal of Geriatric Psychiatry, 23(2), 135-141.

Kasckow, J. W., & Zisook, S. (2008). Co-occurring depressive symptoms in the older patient with schizophrenia. Drugs & Aging, 25(8), 631-647.

Kinon, B.J., Kollack-Walker, S., Jeste, D., Gupta, S., Chen, L., Case, M., Chen, J., et al. (2015). Incidence of Tardive Dyskinesia in Older Adult Patients Treated With Olanzapine or Conventional Antipsychotics. Journal of Geriatric Psychiatry and Neurology, 28(1), 67-79.

Kiosses, D.N., Szanto, K., & Alexopoulos, G.S. (2014). Suicide in older adults: The role of emotions and cognition. Current Psychiatry Reports, 16(11), 495.

Kisely, S., Crowe, E., & Lawrence, D. (2013). Cancer-related mortality in people with mental illness. JAMA Psychiatry, 70(2), 209-217.

Kisely, S., Cox, M., Campbell, L. A., Cooke, C., & Gardner, D. (2009). An epidemiologic study of psychotropic medication and obesity-related chronic illnesses in older psychiatric patients. Canadian Journal of Psychiatry - Revue Canadienne De Psychiatrie, 54(4), 269-274.

Kisely, S., Sadek J, MacKenzie A, Lawrence D, & Campbell LA. (2008). Excess cancer mortality in psychiatric patients. Canadian Journal of Psychiatry - Revue Canadienne De Psychiatrie, 53(11), 753-761.

Kishimoto, T., Agarwal, V., Kishi, T., Leucht, S., Kane, J.M., & Correll, C.U. (2013). Relapse prevention in schizophrenia: A systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. Molecular Psychiatry, 18(1), 53-66.

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.

Köhler, S., van Os, J., de Graaf, R., Vollebergh, W., Verhey, F., & Krabbendam, L. (2007). Psychosis risk as a function of age at onset: A comparison between early- and late-onset psychosis in a general population sample. Social Psychiatry & Psychiatric Epidemiology, 42(4), 288-294.

Kojo, K. (2010). Late-onset schizophrenic syndromes in socially isolated situations: A comparison of Janzarik's 'kontaktmangelparanoid' and late paraphrenia. Psychogeriatrics, 10(2), 83-89.

Koponen, H., Saari, K., Savolainen, M., & Isohanni, M. (2002). Weight gain and glucose and lipid metabolism disturbanses during antipsychotic medication: a review. European Archives of Psychiatry and Clinical Neuroscience., 252(6): 294-8.

Koponen, H., Alaräisänen, A., Saari, K., Pelkonen, O., Huikuri, H., Raatikainen, M.J., et al. (2008). Schizophrenia and sudden cardiac death: a review. Nordic Journal of Psychiatry, 62(5), 342-345.

Kørner, A., Lopez, A. G., Lauritzen, L., Andersen, P. K., & Kessing, L. V. (2009). Late and very-late first-contact schizophrenia and the risk of dementia--a nationwide register based study. International Journal of Geriatric Psychiatry, 24(1), 61-67.

Kredentser, M.S., Martens, P.J., Chochinov, H.M., & Prior, H.J. (2014). Cause and rate of death in people with schizophrenia across the lifespan: A population-based study in Manitoba, Canada. Journal of Clinical Psychiatry, 75(2), 154-161.

Lacro, J.P., Dunn, L.B., Dolder, C.R., Leckband, S.G., & Jeste, D.V. (2002). Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: A comprehensive review of recent literature. Journal of Clinical Psychiatry, 63(10), 892-909.

Lader, M. (1998). Pharmacological prevention of relapse. Kaohsiung Journal of Medical Sciences, 14(7), 448-457.

Lahti, R. A., & Penttilä, A. (2001). The validity of death certificates: Routine validation of death certification and its effects on mortality statistics. Forensic Science International, 115(1-2), 15-32.

Laursen, T.M., Nordentoft, M., & Mortensen, P.B. (2014). Excess early mortality in schizophrenia. Annual Review of Clinical Psychology, 10, 425-448.

Laursen, T. M., Munk-Olsen, T., Nordentoft, M., & Mortensen, P. B. (2007). Increased mortality among patients admitted with major psychiatric disorders: A register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. Journal of Clinical Psychiatry, 68(6), 899-907.

Laursen, T. M., Munk-Olsen, T., Agerbo, E., Gasse, C., & Mortensen, P. B. (2009). Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. Archives of General Psychiatry, 66(7), 713-720.

Laursen, T.M., Wahlbeck, K., Hallgren, J., Westman, .J, Ösby, U., Alinaghizadeh, H., et al. (2013). Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the nordic countries. PLoS ONE [Electronic Resource], 8(6), e67133.

Lavsa, S. M., Fabian, T. J., Saul, M. I., Corman, S. L., & Coley, K. C. (2010). Influence of medications and diagnoses on fall risk in psychiatric inpatients. American Journal of Health-System Pharmacy, 67(15), 1274-1280.

Leinonen, E., Santala, M., Hyötylä, T., Santala, H., Eskola M.N., & Salokangas, R. K.R. (2004). Elderly patients with major depressive disorder and delusional disorder are at increased risk of subsequent dementia. Nordic Journal of Psychiatry, 58(2), 161-164.

Leon, C., Gerretsen, P., Uchida, H., Suzuki, T., Rajji, T., & Mamo, D. C. (2010). Sensitivity to antipsychotic drugs in older adults. Current Psychiatry Reports, 12(1), 28-33.

Lesage, A. D., Trapani, V., & Tansella, M. (1990). Excess mortality by natural causes of Italian schizophrenic patients. European Archives of Psychiatry & Neurological Sciences, 239(6), 361-365.

Leucht, S., Burkard, T., Henderson, J., Maj, M., & Sartorius, N. (2007). Physical illness and schizophrenia: A review of the literature. Acta Psychiatrica Scandinavica, 116(5), 317-333.

Leucht, S., Barnes, T. R., Kissling, W., Engel, R. R., Correll, C., & Kane, J. M. (2003). Relapse prevention in schizophrenia with new-generation antipsychotics: A systematic review and exploratory meta-analysis of randomized, controlled trials. American Journal of Psychiatry, 160(7), 1209-1222.

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., et al. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. Lancet, 382(9896), 951-962.

Lewis, S., Escalona, P.R., & Keith, S. (2009). Schizophrenia and Other Psychotic Disorders: Phenomenology of Schizophrenia. In Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 9th Edition, Kaplan, B., Sadock, V. & Ruiz, P. (Eds), Lippincott, Williams, & Wilkins, Philadelphia, PA, 1433-1451.

Li, Y., Cai, X., & Cram, P. (2011). Are patients with serious mental illness more likely to be admitted to nursing homes with more deficiencies in care? Medical Care, 49(4), 397-405.

Lieberman, J.A. (2007). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia: efficacy, safety and cost outcomes of CATIE and other trials. Journal of Clinical Psychiatry, 68(2):e04.

Lin, S.T., Chen, C.C., Tsang, H.Y., Lee, C.S., Yang, P., Cheng, K.D., et al. (2014). Association between antipsychotic use and risk of acute myocardial infarction: A nationwide case-crossover study. Circulation, 130(3), 235-243.

Linjakumpu, T., Hartikainen, S., Klaukka, T., Koponen, H., Kivelä, S.L., & Isoaho, R. (2002). Psychotropics among the home-dwelling elderly--increasing trends. International Journal of Geriatric Psychiatry, 17(9), 874-883.

Loewenstein, D. A., Czaja, S. J., Bowie, C. R., & Harvey, P. D. (2012). Age-associated differences in cognitive performance in older patients with schizophrenia: A comparison with healthy older adults. American Journal of Geriatric Psychiatry, 20(1), 29-40.

Low, L. F., & Draper, B. (2009). Hospitalization patterns for psychiatric disorders across the lifespan in Australia from July 1998 to June 2005. Psychiatric Services, 60(1), 113-116.

Mäki, P., Veijola, J., Jones, P.B., Murray, G.K., Koponen, H., Tienari, P., et al. (2005). Predictors of schizophrenia - a review. British Medical Bulletin, 73-74, 1-15.

Malaspina, D., Owen, M.J., Heckers, S., Tandon, R., Bustillo, J., Schultz, S., et al. (2013). Schizoaffective disorder in the DSM-5. Schizophrenia Research, 150(1), 21-25.

Malhotra, D., & Sebat, J. (2012). CNVs: Harbingers of a rare variant revolution in psychiatric genetics. Cell, 148(6), 1223-1241.

Marriott, R. G., Neil, W., & Waddingham, S. (2006). Antipsychotic medication for elderly people with schizophrenia. Cochrane Database of Systematic Reviews, (1), 005580.

Martikainen, P., Moustgaard, H., Einiö, E., & Murphy, M. (2014). Life expectancy in long-term institutional care by marital status: Multistate life table estimates for older Finnish men and women. Journals of Gerontology Series B-Psychological Sciences & Social Sciences, 69(2), 303-310.

Mason, O., Stott, J., & Sweeting, R. (2013). Dimensions of positive symptoms in late versus early onset psychosis. International Psychogeriatrics, 25(2), 320-327.

Masters, G.A., Baldessarini, R.J., Ongur, D., & Centorrino, F. (2014). Factors associated with length of psychiatric hospitalization. Comprehensive Psychiatry, 55(3), 681-687.

Mazeh, D., Zemishlani, C., Aizenberg, D., & Barak, Y. (2005). Patients with very-late-onset schizophrenia-like psychosis: A follow-up study. American Journal of Geriatric Psychiatry, 13(5), 417-419.

McEvoy, J.P., Meyer, J.M., Goff, D.C., Nasrallah, H.A., Davis, S.M., Sullivan, L., et al. (2005). Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophrenia Research, 80(1), 19-32.

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: A concise overview of incidence, prevalence, and mortality. Epidemiologic Reviews, 30, 67-76.

McGurk, S.R., Moriarty, P.J., Harvey, P.D., Parrella, M., White, L., Friedman, J., et al. (2000). Relationship of cognitive functioning, adaptive life skills, and negative symptom severity in poor-outcome geriatric schizophrenia patients. Journal of Neuropsychiatry & Clinical Neurosciences, 12(2), 257-264.

Meesters, P. D., de Haan, L., Comijs, H. C., Stek, M. L., Smeets-Janssen, M. M., Weeda, M. R., et al. (2012). Schizophrenia spectrum disorders in later life: Prevalence and distribution of age at onset and sex in a Dutch catchment area. American Journal of Geriatric Psychiatry, 20(1), 18-28.

Mercer, G.T., Molinari, V., Kunik, M.E., Orengo, C.A., Snow, L., & Rezabek, P. (1999). Rehospitalization of older psychiatric inpatients: An investigation of predictors. Gerontologist, 39(5), 591-598.

Miettunen, J., Suvisaari, J., Haukka, J., & Isohanni, M. (2011). Use of register data for psychiatric epidemiology in the Nordic countries. In Textbook in Psychiatric Epidemiology, 3rd edition, Tsuang, M., Tohen, M., & Jones, P. (eds.), John Wiley & Sons: Chichester, West Sussex; 117–131.

Mikami, K., Jorge, R.E., Adams Jr, H.P., Davis, P.H., Leira, E.C., Jang, M. et al. (2011). Effect of Antidepressants on the Course of Disability Following Stroke. American Journal of Geriatric Psychiatry, 19(12), 1007-1015.

Mitford, E., Reay, R., McCabe, K., Paxton, R., & Turkington, D. (2010). Ageism in first episode psychosis. International Journal of Geriatric Psychiatry, 25(11), 1112-1118.

Moilanen, K., Veijola, J., Läksy, K., Mäkikyrö, T., Miettunen, J., Kantojärvi, L., et al. (2003). Reasons for the diagnostic discordance between clinicians and researchers in schizophrenia in the Northern Finland 1966 Birth Cohort. Social Psychiatry and Psychiatric Epidemiology, 38(6), 305-10.

Mortensen, P.B., & Juel, K. (1990). Mortality and causes of death in schizophrenic patients in Denmark. Acta Psychiatrica Scandinavica, 81(4), 372-377.

Nihtilä, E.K., Martikainen P.T., Koskinen, S.V., Reunanen, A.R., Noro, A.M., Häkkinen, U.T. (2008). Chronic conditions and the risk of long-term institutionalization among older people. European Journal of Public Health, 18(1): 77-84.

Nordentoft, M., Laursen, T. M., Agerbo, E., Qin, P., Høyer, E. H., & Mortensen, P. B. (2004). Change in suicide rates for patients with schizophrenia in Denmark, 1981-97: Nested case-control study. BMJ, 329(7460), 261.

Nordentoft, M., Wahlbeck, K., Hallgren, J., Westman, J., Ösby, U., Alinaghizadeh, H., et al. (2013). Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. PLoS ONE [Electronic Resource], 8(1), e55176.

Olivares, J.M., Rodriguez-Morales, A., Diels, J., Povey, M., Jacobs, A., Zhao, Z, et al. (2009). Long-term outcomes in patients with schizophrenia treated with risperidone long-acting injection or oral antipsychotics in Spain: Results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR). European Psychiatry: The Journal of the Association of European Psychiatrists, 24(5), 287-296.

Osborn, D., Levy, G., Nazareth, I., & King, M. (2008). Suicide and severe mental illnesses. Cohort study within the UK general practice research database. Schizophrenia Research, 99(1-3), 134-138.

Osborn, D., Levy, G., Nazareth, I., Petersen, I., Islam, A., & King, M.B. (2007). Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's general practice research database. Archives of General Psychiatry, 64(2), 242-249.

Ösby, U., Correia, N., Brandt, L., Ekbom, A., & Sparen, P. (2000). Mortality and causes of death in schizophrenia in Stockholm County, Sweden. Schizophrenia Research, 45(1-2), 21-28.

Östling, S., Palsson, S. P., & Skoog, I. (2007). The incidence of first-onset psychotic symptoms and paranoid ideation in a representative population sample followed from age 70-90 years. Relation to mortality and later development of dementia. International Journal of Geriatric Psychiatry, 22(6), 520-528.

Palmer, B.W., McClure, F.S., & Jeste, D.V. (2001). Schizophrenia in late life: Findings challenge traditional concepts. Harvard Review of Psychiatry, 9(2), 51-58.

Palmer, B. A., Pankratz, V. S., & Bostwick, J. M. (2005). The lifetime risk of suicide in schizophrenia: A re-examination. Archives of General Psychiatry, 62(3), 247-253.

Patel, N. C., Dorson, P. G., Edwards, N., Mendelson, S., & Crismon, M. L. (2002). One-year rehospitalization rates of patients discharged on atypical versus conventional antipsychotics. Psychiatric Services, 53(7), 891-893.

Patterson, T. L., Lacro, J., McKibbin, C. L., Moscona, S., Hughs, T., & Jeste, D. V. (2002). Medication management ability assessment: Results from a performance-based measure in older outpatients with schizophrenia. Journal of Clinical Psychopharmacology, 22(1), 11-19.

Perälä, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., et al. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. Archives of General Psychiatry, 64(1), 19-28.

Popovic, D., Benabarre, A., Crespo, J.M., Goikolea, J.M., Gonzalez-Pinto, A., Gutierrez-Rojas, L., et al. (2014). Risk factors for suicide in schizophrenia: Systematic review and clinical recommendations. Acta Psychiatrica Scandinavica, 130(6), 418-426.

Potvin, S., & Marchand, S. (2008). Hypoalgesia in schizophrenia is independent of antipsychotic drugs: A systematic quantitative review of experimental studies. Pain, 138(1), 70-78.

Pratt, N., Roughead, E.E., Salter, A., & Ryan, P. (2012). Choice of observational study design impacts on measurement of antipsychotic risks in the elderly: A systematic review. BMC Medical Research Methodology, 12, 72.

Pratt, S.I., Mueser, K.T., Driscoll, M., Wolfe, R., & Bartels, S.J. (2006). Medication nonadherence in older people with serious mental illness: Prevalence and correlates. Psychiatric Rehabilitation Journal, 29(4), 299-310.

Prince, J. D., Akincigil, A., Kalay, E., Walkup, J. T., Hoover, D. R., Lucas, J., et al. (2008). Psychiatric rehospitalization among elderly persons in the United States. Psychiatric Services, 59(9), 1038-1045.

Psarros, C., Theleritis, C. G., Paparrigopoulos, T. J., Politis, A. M., & Papadimitriou, G. N. (2009). Amisulpride for the treatment of very-late-onset schizophrenia-like psychosis. International Journal of Geriatric Psychiatry, 24(5), 518-522.

Pylkkänen, K. (2012). Finnish psychiatry--past and present. Nordic Journal of Psychiatry, 66(Suppl 1), 14-24.

Quin, R.C., Clare, L., Ryan, P., & Jackson, M. (2009). 'Not of this world': The subjective experience of late-onset psychosis. Aging & Mental Health, 13(6), 779-787.

Rajji, T.K., & Mulsant, B.H. (2008). Nature and course of cognitive function in late-life schizophrenia: A systematic review. Schizophrenia Research, 102(1-3), 122-140.

Ran, M. S., Chan, C. L., Chen, E. Y., Tang, C. P., Lin, F. R., Li, L., et al. (2008). Mortality of geriatric and younger patients with schizophrenia in the community. Suicide & Life-Threatening Behavior, 38(2), 143-151.

Rantanen, H., Koivisto, A. M., Salokangas, R.K.R., Helminen, M., Oja, H., Pirkola, S., et al. (2009). Five-year mortality of Finnish schizophrenia patients in the era of deinstitutionalization. Social Psychiatry & Psychiatric Epidemiology, 44(2), 135-142.

Reinhardt, M. M., & Cohen, C. I. (2015). Late-life psychosis: Diagnosis and treatment. Current Psychiatry Reports, 17(2).

Räsänen, S., Hakko, H., Viilo, K., Meyer-Rochow, V. B., & Moring, J. (2003). Excess mortality among long-stay psychiatric patients in Northern Finland. Social Psychiatry & Psychiatric Epidemiology, 38(6), 297-304.

Rasmussen, H. B., Timm, S., Wang, A. G., Soeby, K., Lublin, H., Fenger, M., et al. (2006). Association between the CCR5 32-bp deletion allele and late onset of schizophrenia. American Journal of Psychiatry, 163(3), 507-511.

Reeves, S., Stewart, R., & Howard, R. (2002). Service contact and psychopathology in very-late-onset schizophrenia-like psychosis: The effects of gender and ethnicity. International Journal of Geriatric Psychiatry, 17(5), 473-479.

Reeves, S., Hudson, S., Fletcher, H., Sauer, J., Stewart, R., & Howard, R. (2003). Are black Caribbean patients more likely to receive an incorrect diagnosis of very-late-onset schizophrenia-like psychosis than their white British counterparts? American Journal of Geriatric Psychiatry, 11(6), 674-677.

Reutfors, J., Brandt, L., Jonsson, E.G., Ekbom, A., Sparen, P., & Ösby, U. (2009). Risk factors for suicide in schizophrenia: Findings from a Swedish population-based case-control study. Schizophrenia Research, 108(1-3), 231-237.

Riecher-Rössler, A. (1999). Late Onset Schizophrenia: The German Concept and Literature. In Late Onset Schizophrenia, Howard, R., Rabins, P.V., & Castle, D.J. (eds), Wrightson Biomedical Publishing Ltd, Guildford, Petersfield, UK, 3-16.

Riecher-Rössler, A., Häfner, H., & Munk-Jørgensen, P. (1999). Validity of Late Onset Schizophrenia: A European View. In Late Onset Schizophrenia, Howard, R., Rabins, P.V., & Castle, D.J. (eds), Wrightson Biomedical Publishing Ltd, Guildford, Petersfield, UK, 55-78.

Riecher-Rössler, A., Loffler, W., & Munk-Jørgensen, P. (1997). What do we really know about late-onset schizophrenia? European Archives of Psychiatry & Clinical Neuroscience, 247(4), 195-208.

Ringen, P.A., Engh, J.A, Birkenaes, A.B., Dieset, I., & Andreassen, O.A. (2014). Increased mortality in schizophrenia due to cardiovascular disease - a non-systematic review of epidemiology, possible causes, and interventions. Frontiers in Psychiatry Frontiers Research Foundation, 5, 137.

Rodriguez-Ferrera, S., Vassilas, C. A., & Haque, S. (2004). Older people with schizophrenia: A community study in a rural catchment area. International Journal of Geriatric Psychiatry, 19(12), 1181-1187.

Roick, C., Fritz-Wieacker, A., Matschinger, H., Heider, D., Schindler, J., Riedel-Heller, S., et al. (2007). Health habits of patients with schizophrenia. Social Psychiatry & Psychiatric Epidemiology, 42(4), 268-276.

Roth, M., & Kay, D. W. (1998). Late paraphrenia: A variant of schizophrenia manifest in late life or an organic clinical syndrome? A review of recent evidence. International Journal of Geriatric Psychiatry, 13(11), 775-784.

Roth, M., & Morrissey, J. (1952). Problems in the diagnosis and classification of mental disorder in old age; with a study of case material. Journal of Mental Science, 98(410), 66-80.

Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? Archives of General Psychiatry, 64(10), 1123-1131.

Salokangas, R.K.R. (2009). Skitsofreniapotilaan somaattiset sairaudet. (English Summary: Somatic diseases of the schizophrenic patient). Duodecim, 125, 505-512.

Salokangas, R.K.R., & McGlashan, T.H. (2008). Early detection and intervention of psychosis. A review. Nordic Journal of Psychiatry, 62(2), 92-105.

Salokangas, R.K.R., Saarinen, S., & Stengård, E. (1996). Sairaalasta kotiutetut skitsofreniapotilaat (SKS-projekti) II: Aikatrenditutkimus vuosina 1982, 1986 ja 1990 kotiutettujen potilaiden kliinisen ja toiminnallisen tilan sekä hoito- ja tukipalveluiden käytön muutoksista. (English Summary: Schizophrenic patients discharged from hospital (DSP Project) II: A study of time trends in the clinical and functional status of Foundation for Psychiatric Research Publication Series Rep III. Helsinki.

Salokangas, R.K.R., Honkonen, T., Stengård, E., & Koivisto, A-M. (2001). To be or not to be married – that is the question of quality of life in men with schizophrenia. Social Psychiatry and Psychiatric Epidemiology, 36, 381-390.

Salokangas, R.K.R., Honkonen, T., Stengård, E., & Koivisto, A-M. (2002). Mortality in chronic schizophrenia during decreasing number of psychiatric beds in Finland. Schizophrenia Research, 54, 265-267.

Salokangas, R.K.R., Stengård, E., Honkonen, T., Koivisto, A-M., & Saarinen, S. (2000). Sairaalasta yhteiskuntaan (English Summary: From hospital to society. Seurantatutkimus sairaalasta kotiuttamisen vaikutuksista skitsofreniapotilaan elämään ja hoitotilanteeseen. STAKES, Raportteja 248, Helsinki.

Salokangas, R.K.R., Stengård, E., Räkköläinen, V., Alanen, Y.O., & Kaljonen, A. (1991). Uusien skitsofreniapotilaiden hoito ja ennuste (USP-projekti) V: Viiden vuoden ennuste. (English Summary: Treatment and prognosis of new schizophrenia patients. A five-year follow-up). Reports of Psychiatria Fennica No 95. Helsinki.

Salokangas, R.K.R., Helminen, M., Koivisto, A-M., Rantanen, H., Oja, H., Pirkola, S., et al. (2008). Skitsofreniapotilaiden kuolleisuus sairaanhoitopiireittäin. (English Summary: Mortality of patients with schizophrenia in health care districts.) Duodecim, 63(44), 3759-3766.

Schizophrenia Working Group of the Psychiatric Genomics, Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. Nature, 511(7510), 421-427.

Schneiderman, J. S., Hazlett, E. A., Chu, K., Zhang, J., Goodman, C. R., Newmark, R. E., et al. (2011). Brodmann area analysis of white matter anisotropy and age in schizophrenia. Schizophrenia Research, 130(1–3), 57-67.

Schoos, R., & Cohen, C.I. (2003). Medical Comorbidity in Older Persons with Schizophrenia. In Schizophrenia into Later Life. Cohen, C.I. (ed). American Psychiatric Publishing, Washington, London, 113-138.

Schurhoff, F., Golmard, J.L., Szoke, A., Bellivier, F., Berthier, A., Meary, A., et al. (2004). Admixture analysis of age at onset in schizophrenia. Schizophrenia Research, 71(1), 35-41.

Scott, J., Greenwald, B.S., Kramer, E., & Shuwall, M. (2010). Atypical (second generation) antipsychotic treatment response in very late-onset schizophrenia-like psychosis. International Geropsychiatrics, 23(5):742-8.

Selemon, L. D., Kleinman, J. E., Herman, M. M., & Goldman-Rakic, P. S. (2002). Smaller frontal gray matter volume in postmortem schizophrenic brains. American Journal of Psychiatry, 159(12), 1983-1991.

Seppälä, N., Leinonen, E., Viikki, M., Solismaa, A., Nuolivirta, T., & Kampman, O. (2015). Factors associated with subjective side-effects during clozapine treatment. Nordic Journal of Psychiatry, 69(3), 161-6.

Sharma, E.R, Debsikdar, A.V, Naphade, N.M, & Shetty, J.V. (2014). Very late-onset schizophrenia like psychosis: Case series and future directions. Indian Journal of Psychological Medicine, 36(2), 208-210.

Shelef, A., Mazeh, D., Berger, U., Baruch, Y., & Barak, Y. (2014). Acute electroconvulsive therapy followed by maintenance electroconvulsive therapy decreases hospital re-admission rates of older patients with severe mental illness. Journal of ECT, 31(2):125-8.

Shepherd, A.M., Laurens, K.R, Matheson, S.L, Carr, V.J., & Green, M.J. (2012). Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neuroscience & Biobehavioral Reviews, 36(4), 1342-1356.

Shepherd, S., Depp, C.A., Harris, G., Halpain, M., Palinkas, L.A., & Jeste, D.V. (2012). Perspectives on schizophrenia over the lifespan: A qualitative study. Schizophrenia Bulletin, 38(2), 295-303.

Smeets-Janssen, M. M., Meesters, P.D, Comijs, H.C, Eikelenboom, P., Smit, J.H., de Haan, L., et al. (2013). Theory of mind differences in older patients with early-onset and late-onset paranoid schizophrenia. International Journal of Geriatric Psychiatry, 28(11), 1141-46.

Smith, S. (2010). Gender differences in antipsychotic prescribing. International Review of Psychiatry, 22(5):472-84.

Social Insurance Institution of Finland - Kela. (2015). Statistics [database online]. Available from http://www.kela.fi/web/en/statistics.

Statistics Finland. Causes of Death. (2010, 2014). Available from http://tilastokeskus.fi/til/kuol/.

Stroup, T.S., Kraus, J.E, & Marder, S.R. (2006). Pharmacotherapies in Textbook of Schizophrenia, 1st Edition, Lieberman, J.A., Stroup, T.S., & Perkins, D.O. (Eds), American Psychiatric Publishing, Arlington, VA, 303-325.

Sund, R. (2012). Quality of the Finnish Hospital Discharge Register: A systematic review. Scandinavian Journal of Public Health, 40(6), 505-515.

Suokas, J.T, Suvisaari, J.M, Haukka, J., Korhonen, P., & Tiihonen, J. (2013). Description of long-term polypharmacy among schizophrenia outpatients. Social Psychiatry & Psychiatric Epidemiology, 48(4), 631-638.

Suvisaari, J., & Pietiläinen, O. (2015). Skitsofrenian geneettinen koodi purkautuu. Duodecim, 131(5), 407-409.

Suvisaari, J. M., Saarni, S. I., Perälä, J., Suvisaari, J. V., Härkänen, T., Lönnqvist, J., et al. (2007). Metabolic syndrome among persons with schizophrenia and other psychotic disorders in a general population survey. Journal of Clinical Psychiatry, 68(7), 1045-1055.

Suzuki, T., & Uchida, H. (2014). Successful withdrawal from antipsychotic treatment in elderly male inpatients with schizophrenia. Description of four cases and review of the literature. Psychiatry Research, 220(1-2), 152-157.

Tan, L.L., & Seng, K.H. (2012). First presentation psychosis among the elderly in Singapore. Singapore Medical Journal, 53(7), 463-467.

Tandon, R., Gaebel, W., Barch, D.M., Bustillo, J., Gur, R.E., Heckers, S., et al. (2013). Definition and description of schizophrenia in the DSM-5. Schizophrenia Research, 150(1), 3-10.

Tanskanen, P., Haapea, M., Veijola J., Miettunen, J., Järvelin, M.R., Pyhtinen, J., et al. (2009). Volumes of brain, grey and white matter and cerebrospinal fluid in schizophrenia in the Northern Finland 1966 Birth Cohort: an epidemiological approach to analysis. Psychiatry Research, 174(2), 116-20.

Tiihonen, J., Suokas, J. T., Suvisaari, J. M., Haukka, J., & Korhonen, P. (2012). Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Archives of General Psychiatry, 69(5), 476-483.

Tiihonen, J., Haukka, J., Taylor, M., Haddad, P.M., Patel, M.X., & Korhonen, P. (2011). A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. American Journal of Psychiatry, 168(6), 603-609.

Tiihonen, J., Lönnqvist, J., Wahlbeck, K., Klaukka, T., Niskanen, L., Tanskanen, A., et al. (2009). 11-year follow-up of mortality in patients with schizophrenia: A population-based cohort study (FIN11 study). Lancet, 374(9690), 620-627.

Torniainen, M., Mittendorfer-Rutz, E., Tanskanen, A., Björkenstam, C., Suvisaari, J., Alexanderson, K., et al. (2015). Antipsychotic treatment and mortality in schizophrenia. Schizophrenia Bulletin, 41(3), 656-63.

Tran, E., Rouillon, F., Loze, J. Y., Casadebaig, F., Philippe, A., Vitry, F., et al. (2009). Cancer mortality in patients with schizophrenia: An 11-year prospective cohort study. Cancer, 115(15), 3555-3562.

Trifiro, G., Gambassi, G., Sen, E. F., Caputi, A. P., Bagnardi, V., Brea, J., et al. (2010). Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: A nested case-control study. Annals of Internal Medicine, 152(7), 418-425.

Tsan, J. Y., Stock, E. M., Gonzalez, J. M., Greenawalt, D. S., Zeber, J. E., Rouf, E., et al. (2012). Mortality and guideline-concordant care for older patients with schizophrenia: A retrospective longitudinal study. BMC Medicine, 10, 147.

Uchida, H., Suzuki, T., Mamo, D. C., Mulsant, B. H., Tanabe, A., Inagaki, A., et al. (2008). Effects of age and age of onset on prescribed antipsychotic dose in schizophrenia spectrum disorders: A survey of 1,418 patients in Japan. American Journal of Geriatric Psychiatry, 16(7), 584-593.

Vahia, I. V., Palmer, B. W., Depp, C., Fellows, I., Golshan, S., Kraemer, H. C., et al. (2010). Is late-onset schizophrenia a subtype of schizophrenia? Acta Psychiatrica Scandinavica, 122(5), 414-426.

van Os J, Howard R, Takei N, & Murray R. (1995). Increasing age is a risk factor for psychosis in the elderly. Social Psychiatry & Psychiatric Epidemiology, 30(4), 161-164.

Veijola, J., Guo, J.Y., Moilanen, J.S., Jääskeläinen, E., Miettunen, J., & Kyllönen, M. (2014). Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication. PLoS One, 18;9(7), e101689.

Vita, A., De Peri, L., Deste, G., & Sacchetti, E. (2012). Progressive loss of cortical gray matter in schizophrenia: A meta-analysis and meta-regression of longitudinal MRI studies. Translational Psychiatry, 20;2:e190.

Voisey, J., Swagell, C.D., Hughes, I.P., Lawford, B.R., Young, R.M., & Morris, C.P. (2012). A novel DRD2 single-nucleotide polymorphism associated with schizophrenia predicts age of onset: HapMap tag-single-nucleotide polymorphism analysis. Genetic Testing & Molecular Biomarkers, 16(2), 77-81.

Walker, E.R., McGee, R.E., & Druss, B.G. (2015). Mortality in mental disorders and global disease burden implications: A systematic review and meta-analysis. JAMA Psychiatry, 72(4), 334-341.

Westman, J., Gissler, M., & Wahlbeck, K. (2012). Successful deinstitutionalization of mental health care: Increased life expectancy among people with mental disorders in Finland. European Journal of Public Health, 22(4), 604-606.

White, L., Friedman, J.I, Bowie, C.R, Evers, M., Harvey, P.D., Parrella, M., et al. (2006). Long-term outcomes in chronically hospitalized geriatric patients with schizophrenia: Retrospective comparison of first generation and second generation antipsychotics. Schizophrenia Research, 88(1-3), 127-134.

Wium-Andersen, M.K., Ørsted, D.D., & Nordestgaard, B.G. (2014). Elevated C-reactive protein associated with late- and very-late-onset schizophrenia in the general population: A prospective study. Schizophrenia Bulletin, 40(5), 1117-1127.

Xu, C., Aragam, N., Li, X., Villa, E.C., Wang, L., Briones, D., et al. (2013). BCL9 and C9orf5 are associated with negative symptoms in schizophrenia: Meta-analysis of two genome-wide association studies. PLoS ONE [Electronic Resource], 8(1), e51674.

Original publications

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Mortality and causes of death in older patients with schizophrenia

Tiina Talaslahti[1], Hanna-Mari Alanen[2], Helinä Hakko[3], Matti Isohanni[4], Unto Häkkinen[5] and Esa Leinonen[2,6]

[1]Helsinki University Central Hospital, Department of Psychiatry, Finland
[2]Tampere University Hospital, Department of Psychiatry, Finland
[3]Oulu University Hospital, Department of Psychiatry, Finland
[4]University of Oulu, Institute of Clinical Medicine, Department of Psychiatry, Finland
[5]National Institute for Health and Welfare, Helsinki, Finland
[6]University of Tampere, Medical School, Finland
Correspondence to: T. Talaslahti, E-mail: tiina.talaslahti@kolumbus.fi

Objective: The aim of this study was to evaluate mortality and causes of death in older patients with schizophrenia in comparison with the general population. The mortality of patients experiencing relapse was also compared with those in remission.

Methods: The study sample consists of patients ($n = 9461$) over 65 years by the first of January 1999, with schizophrenia or schizoaffective disorder (ICD-8, ICD-9: 295, ICD-10: F20, F25) as the main register diagnosis during the period 1969–1998. The sample was collected from nationwide registers in Finland and followed up between 1999 and 2008.

Results: Overall Standard Mortality Ratio (SMR) of the older schizophrenia patients was 2.69 [95% confidence interval, 2.62–2.76]. For natural causes of death, overall SMR was 2.58 (2.51–2.65; $n = 5301$), and for unnatural causes of death, it was 11.04 (9.75–12.47; $n = 262$). The most common causes of death matched those in the general population. Of patients who died during follow-up, 31% (1709/5596) had at least one psychiatric hospitalization within 5 years before follow-up. The SMR for this group was higher (3.92; 3.73–4.11) than in those patients (2.37; 2.29–2.44) with no such treatment during that time.

Conclusion: All-cause mortality of older patients with schizophrenia was almost threefold that of general population. They died for similar reasons to the general population; however, deaths for unnatural causes were especially common (accidents and suicides). Those patients still experiencing relapses in older age have an increased risk of death compared with those with schizophrenia in remission.

Key words: older patients; schizophrenia; mortality; causes of death; Standard Mortality Ratio (SMR)
History: Received 20 June 2011; Accepted 10 November 2011; Published online 17 January 2012 in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/gps.2833

Introduction

The number of older patients with schizophrenia is expected to double during the next two decades (Cohen *et al.*, 2008). Despite the elevated risk of premature death in this patient group, more patients will, nevertheless, reach older age. Studies concerning mortality of schizophrenia patients over 65 years old are rare, or detailed information is limited. Therefore, this issue needs special attention.

Excess mortality of younger patients with schizophrenia has mostly been associated with respiratory and cardiovascular diseases in addition to suicides (Joukamaa *et al.*, 2001; Brown *et al.*, 2010; Kiviniemi *et al.*, 2010). Unhealthy living habits such as smoking, limited diet, and lack of exercise increase the risk of these comorbidities. Furthermore, in addition to schizophrenia *per se*, some antipsychotics increase the risk of serious diseases such as metabolic syndrome, diabetes, and atherosclerosis (De Hert *et al.*, 2006; Suvisaari *et al.*, 2007). On the other hand, the use of antipsychotics has been reported to reduce mortality (Tiihonen *et al.*, 2009). The risk of premature

death may also be associated with delayed diagnosis of physical diseases and the specific difficulties in examining and treating patients with schizophrenia (Wildgust and Beary, 2010). The gap between the mortality of patients with schizophrenia and that of the general population has widened in recent decades (Saha *et al*., 2009).

Suicide is among the leading causes of death in patients with schizophrenia (Alaräisänen *et al*., 2009; Hor and Taylor, 2010). In a study by Cohen *et al*., as much as 75% of older patients with schizophrenia had depressive symptoms that may lead to suicidal ideation (Cohen *et al*., 2008). Positive symptoms of schizophrenia such as commanding hallucinations and somatic delusions as well as somatic symptoms and diseases may cause hopelessness and even suicidality in this vulnerable patient group. In addition, antipsychotic medication has been shown to be a risk factor for falls in mentally ill patients, especially among geriatric inpatients (Lavsa *et al*., 2010). The risk of death from unnatural causes and thus premature deaths is increased.

The primary aim of this study was to ascertain mortality and causes of death in older patients with schizophrenia in comparison with the general population. Secondly, mortality and causes of death were compared within the schizophrenia group in order to ascertain if they differ between patients in relapse and those in remission, for example no need for psychiatric admissions 5 years before follow-up.

Methods

Data

Data were obtained from the PERFormance, Effectiveness, and Cost of Treatment episodes (PERFECT) project, which is a collaboration between the National Institute for Health and Welfare, five university districts, and the Social Insurance Institution of Finland. The information from the different registers used was linked by the unique personal identification number allocated to every Finnish citizen.

Patients were first identified from the Finnish Hospital Discharge Register (FHDR), a register of all Finnish hospitalized patients maintained since 1969. Wards in mental and general hospitals, local health centers, military service, as well as prison and private hospitals are included in this register (Miettunen *et al*., 2011). At discharge, the days of treatment and the diagnoses go into this register. The reliability of the diagnoses of the FHDR has been shown in earlier studies (Aro *et al*., 1990; Moilanen *et al*., 2003). Secondly, the register of disability pensions from the Social Insurance Institution since 1982 was also used, likewise the register of the Pension Security Center. The latter contains information on pensions granted since 1969 by authorized Finnish pension providers. The National Causes-of-Death Register of Statistics Finland provided data on death certificates.

The National Causes-of-Death Register is a nationwide register including dates, places of death, and diagnoses. In most cases, the death certificate is based on the diseases known before death. However, every fifth death in the age group 65 or older necessitated a post mortem examination in the period 1999–2008 because the cause of death was unknown or unexpected. The validity of this register has been scientifically demonstrated (Lahti and Penttilä, 2001).

The classification of causes of death was that used by Statistics Finland (http://www.tilastokeskus.fi/til/ksyyt/2005/ksyyt_2005_2006-10-31_luo_001.html). In this study, the diagnoses have been divided into two main groups: the unnatural and natural causes of death. The former group includes the codes for suicides (ICD-10: X60–X84), accidents (ICD-10: V01–X59, Y10–Y86, Y972, and Y88–Y89) and homicide (ICD-10: 85–Y871), the latter includes all the other diagnoses such as various diseases.

The study protocol was approved by the National Research and Development Centre for Welfare and Ethics Committee.

Study population

The final sample to be analyzed was 9461 patients who were alive and have turned 65 years by 1 January 1999. Patients have had schizophrenia or schizoaffective disorder (ICD 8, ICD-9: 295, ICD-10: F20, F25) as the main diagnosis on hospitalization during the years 1969–1998. Detailed data on patients is given in Table 1. Patients retired because of schizophrenia or schizoaffective disorder were also included in order to identify those patients who never had had any psychiatric hospital treatment. Those living abroad or in the Åland Islands were removed from the data, the latter because of the likelihood of having received Swedish hospital care. The mortality and causes of death of this sample were followed up using the registers for the 10-year period (1999–2008).

Statistical analyses

The significance of group differences in categorical variables was assessed with Pearson's Chi-square test

Table 1 Baseline population: number of schizophrenia cases in different age groups and their basic health data

	Total ($n = 9461$)	Men ($n = 2957$)	Women ($n = 6504$)	Gender difference, p-value		
	% (n)	% (n)	% (n)	$\chi 2$	df	p
Age at baseline (years)						
65–69	35.0 (3314)	43.7 (1291)	31.1 (2023)	221.76	6	<0.001
70–74	29.0 (2739)	29.6 (875)	28.7 (1864)			
75–79	20.5 (1942)	17.5 (516)	21.9 (1426)			
80–84	9.4 (893)	6.2 (183)	10.9 (710)			
85–89	4.6 (439)	2.3 (69)	5.7 (370)			
90–94	1.2 (111)	0.6 (19)	1.4 (92)			
≥95	0.2 (23)	0.1 (4)	0.3 (19)			
Psychiatric hospital inpatients, 5 years before baseline*	29.2 (2766)	27.1 (801)	30.2 (1965)	9.59	1	0.002
Patients having any hospital care, 1 year before baseline	39.5 (3741)	38.0 (1125)	40.2 (2616)	4.03	1	0.045
Patients having antipsychotic drugs, 1 year before baseline	60.4 (5719)	59.4 (1756)	60.9 (3963)	2.03	1	0.156
Cardiovascular diseases**	39.8 (3765)	39.0 (1153)	40.2 (2612)	1.16	1	0.282
Diabetes**	14.3 (1356)	13.4 (395)	14.8 (961)	3.33	1	0.068
Neoplasms**	6.3 (598)	5.6 (165)	6.7 (433)	3.99	1	0.046
COPD**	7.7 (725)	9.3 (274)	6.9 (451)	15.62	1	<0.001
Dementia**	2.5 (240)	2.1 (63)	2.7 (177)	2.87	1	0.090
Hypercholesterolemia**	1.0 (96)	0.7 (20)	1.2 (76)	4.90	1	0.027
Alcoholism**	1.3 (120)	2.5 (74)	0.7 (45)	52.32	1	<0.001

COPD, chronic obstructive pulmonary disease.
*At least one psychiatric hospitalization between 1994 and 1998.
**Diagnosis in Finnish Hospital Discharge Register during the year 1998.

or Fisher's Exact test and in continuous variables with Student's t-test or Mann-Whitney U-test. Standard Mortality Ratios (SMRs) were used to describe the overall and cause-specific mortality of the older patients experiencing schizophrenia (Breslow and Day, 1987). The SMR is an epidemiologic ratio of the observed number of deaths in a study sample to the expected number of deaths calculated on the basis of the number of deaths in the reference population. The reference population used in the present study was general Finnish population matched for sex and age, and the data was obtained from Statistics Finland in 2010. SMRs were compared using rate ratio (RR) analysis and calculating 95% confidence intervals (CIs). All statistical tests were two-tailed, and the limit for statistical significance was a set at $p < 0.05$. Statistical analyses were conducted by using PASW for Windows, version 18 (SPSS Inc., Chicago, IL, USA), or SAS for Windows, version 9.2 (SAS Institute Inc., Cary, NC, USA), statistical programs.

Results

During the years 1999–2008, 59% (5596/9461) of the older patients died, 66% of men and 56% of women. The mean age at death was statistically significantly higher in women (79.9 ± 6.0) than in men (76.5 ± 6.1) ($p < 0.001$). Of all deaths, 4.7% (274) were unnatural: 5.1% in men and 4.5% in women.

The overall SMR of the older schizophrenia patients aged 65 or older was 2.69 (95%CI 2.62–2.76) and was significantly higher in men 3.00 (2.87–3.14) than in women 2.55 (2.47–2.63) (RR 1.18, 95%CI 1.11–1.24, $p < 0.05$) (Figure 1). For natural causes of death, overall SMR in these patients was 2.58 (2.51–2.65; $n = 5301$), in

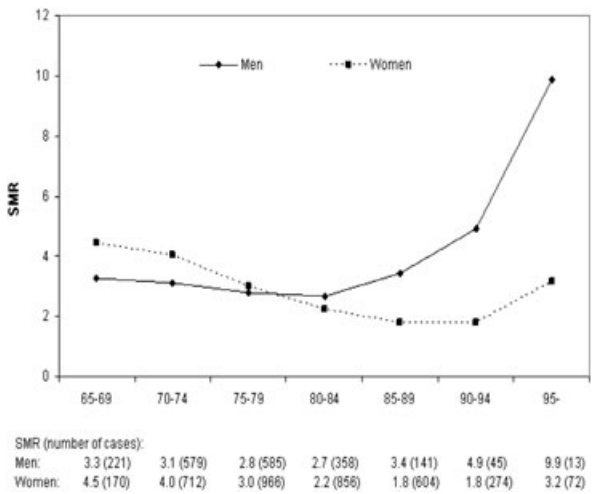


Figure 1 Total Standard Mortality Ratio (SMR) by age and gender in schizophrenia cases over 65 years old [total SMR for men was 3.00 (95% CI 2.87–3.14); total SMR for women was 2.55 (95%CI 2.47–2.63)].

men 2.87 (2.74–3.00; $n = 1832$) and in women 2.45 (2.37–2.53; $n = 3469$). For unnatural causes of death, overall SMR was 11.04 (9.75–12.47; $n = 262$); in men 11.52 (9.35-14.04; $n = 98$) and in women 10.78 (9.20–12.56; $n = 164$). The SMRs by age for natural and unnatural causes of death are given in Figure 2.

The most common causes of death matched those in the general population. However, SMRs in older patients with schizophrenia were increased even in circulatory diseases 1.89 (1.81-1.96), neoplasms 1.93 (1.80-2.07), and especially in dementias 2.79 (2.55-3.04). The causes of death having the highest SMRs in older patients with schizophrenia are presented in Table 2. In the category of unnatural causes of death, accidental falls ($n = 137$, at the same level or down the stairs) were the most common single cause of death followed by suicide ($n = 42$; hanging $n = 13$, drowning $n = 12$, other reasons $n = 17$), other accidents and sequelae of accidents ($n = 62$; choking on food $n = 37$, freezing to death $n = 9$, accidental poisoning $n = 8$, aspiration $n = 4$, burning to death $n = 4$), land transport accidents ($n = 7$), accidental drowning ($n = 6$), homicides ($n = 3$), and other causes of death ($n = 5$).

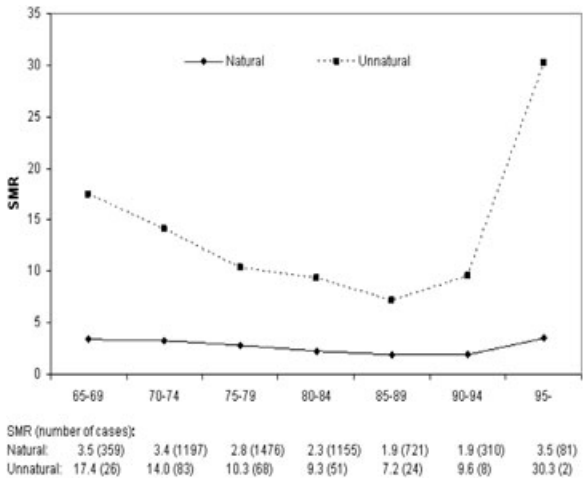


Figure 2 Standard Mortality Ratio (SMR) by age for natural and unnatural causes of death [total SMRs were 2.58 (95%CI 2.51–2.65) and 11.04 (95%CI 9.75–12.47)].

Of the patients who died during follow-up, 31% (1709/5596) had at least one psychiatric hospitalization 5 years before follow-up. The SMR for this relapsed group was higher (3.92; 3.73–4.11) than in those patients (2.37; 2.29–2.44) with no psychiatric hospitalization during that time (RR 1.66, 95%CI 1.56–1.75). This difference was found both in men [SMR 4.80 (4.41–5.22) in the hospital care group vs. 2.61 (2.47–2.75) in the no hospital care group in remission] (RR 1.84, 95% CI 1.67–2.03) and in women [SMR 3.60 (3.39–3.81) vs. 2.25 (2.16–2.34)] (RR 1.60, 95%CI 1.49–1.72).

Discussion

In the present study, mortality among the nearly 10,000 older patients with schizophrenia was almost three times higher than in age-matched and sex-matched general population. The excess mortality of patients with schizophrenia is well known (Saha *et al*., 2007), but the data on patients aged 65 years or more has been

Table 2 Causes of deaths (ICD-9 and ICD-10) in older patients with schizophrenia. Standardized Mortality Ratios and 95% confidence intervals by gender

Cause of death	Total				Men				Women			
	SMR	**95%CI**	**OBS**	**EXP**	**SMR**	**95%CI**	**OBS**	**EXP**	**SMR**	**95%CI**	**OBS**	**EXP**
Suicide	44.1	31.8–59.6	42	1.0	30.8	16.8–51.6	14	0.5	56.3	37.4–81.3	28	0.5
Infectious diseases	26.6	20.0–34.6	55	2.1	42.0	25.2–65.5	19	0.5	22.2	15.6–30.9	36	1.6
Genitourinary diseases	19.3	15.6–23.4	99	5.2	33.0	20.9–49.5	23	0.7	17.1	13.5–21.4	76	4.5
Endocrine diseases	15.3	12.2–18.9	86	5.6	19.8	11.7–31.3	18	0.9	14.4	11.2–18.3	68	4.7
Other nervous diseases	10.6	8.4–13.2	81	7.6	11.3	7.2–16.8	24	2.1	10.3	7.8–13.4	57	5.5
Accidents and violence	9.6	8.3–10.9	218	22.8	10.3	8.2–12.8	83	8.1	9.2	7.7–10.9	135	14.7
Digestive diseases	9.6	8.3–11.0	207	21.6	15.4	12.3–19.1	82	5.3	7.7	6.4–9.1	125	16.3
Respiratory diseases	5.5	5.1–6.0	696	125.6	5.9	5.3–6.6	322	54.6	5.3	4.8–5.8	374	71.0
Dementias	2.8	2.6–3.0	506	181.5	5.6	4.6–6.8	110	19.5	2.4	2.2–2.7	396	162.0
Circulatory diseases	1.9	1.8–2.0	2388	1275.6	2.1	2.0–2.3	817	387.8	1.8	1.7–1.9	1571	878.0
Neoplasms	1.9	1.8–2.0	827	427.7	1.9	1.7–2.1	316	165.4	2.0	1.8–2.1	511	262.4

SMR, Standardized Mortality Ratio; CI, confidence interval; OBS, observed number of deaths; EXP, expected number of deaths.

limited consisting of only small samples or otherwise insufficiently detailed information (Ösby *et al.*, 2000; Räsänen *et al.*, 2003; Chang *et al.*, 2010).

The SMR findings of the present study are in line with those of an earlier Finnish study on selected long-stay institutionalized psychiatric patients ($n = 253$) of whom 80% ($n = 203$) had schizophrenia. The SMR of the patients aged 65–84 years was 3.0–3.7 ($n = 32$) (Räsänen *et al.*, 2003). In that study, the mortality of patients 85 years or older ($n = 1$) was lower (SMR 1.6) and close to that of the general population. It is unclear how many patients aged 65 or more years really had schizophrenia. In a Swedish study, SMR was significantly elevated (total SMR was 2.8 in men and 2.4 in women) in all age-groups but also decreased with increasing age (Ösby *et al.*, 2000). In this study, patients were hospitalized for the first time with a diagnosis of schizophrenia and therefore, patients older than 65 years ($n = 770$) may have been a different group of patients with relatively late onset of schizophrenia. The trend was also for higher SMR within a year after first admission to hospital, which may have been a reason for the reduction in SMR with increasing age. In a recent 3-year register-based study, the total SMR of patients with schizophrenia aged 65 or more years was 1.63 ($n = 165$) and of those with schizoaffective disorder was 2.10 ($n = 21$)(Chang *et al.*, 2010).

The risk of death among schizophrenia patients has been reported to be highest some years after diagnosis (Mortensen and Juel, 1993; Palmer *et al.*, 2005). In their study of first-onset patients with schizophrenia aged less than 65 years, Kiviniemi and colleagues used the same PERFECT sample collected under the same criteria as in the present study (Kiviniemi *et al.*, 2010). They reported overall SMR 4.5 in these younger patients (mean age was 33.5 years) at 5 years follow-up, which was higher than in the present older population. The overall mortality due to natural causes did not differ much between that study (SMR 2.9) and the present one (SMR 2.7). The greatest differences between these studies in the SMRs of natural causes of death were in the endocrine, nutritional, and metabolic diseases (first-onset patients 3.9 vs. present patients 15.3) and in digestive diseases (1.9 vs. 9.6, respectively). In the present study, mortality decreased up to the age of 80–84 years in men and 85–89 years in women but after those ages started to increase again. Unnatural causes of death in particular increased markedly after the ages of 90–94 years.

The variation in SMRs reported in different studies may be explained by differences in study designs. In the present register study, both inpatients and outpatients were included regardless of the activity of the schizophrenic disorder. In the study by Räsänen and colleagues (65 or more years: $n = 33$), the long-term schizophrenia patients had been hospitalized for at least 6 months during follow-up. In the studies by Ösby *et al.* and Chang *et al.*, the numbers of patients aged 65 or more years were notably smaller ($n = 770$ and $n = 186$) compared with the present study of almost 10,000 older patients.

The findings of our study indicate that although older patients with schizophrenia die for similar reasons as the general age-adjusted population, their mortality is still higher in every cause-of-death category. The most common single cause of death was circulatory diseases, which in patients with schizophrenia can partly be explained at least by unhealthy living habits and long-term exposure to antipsychotic medication (De Hert *et al.*, 2006; Suvisaari *et al.*, 2007). According to a Danish study, the treatment of heart disease in patients with schizophrenia was ineffective and insufficient (Laursen *et al.*, 2009). Thus, undertreatment may be a partial explanation (Druss *et al.*, 2001). Circulatory diseases were also among the most common causes of death in younger patients with schizophrenia (Druss *et al.*, 2001; Leucht *et al.*, 2007; Saha *et al.*, 2007). For cancer, the mortality has varied across studies and has been reported to be even lower in patients with schizophrenia than in general population (Laursen *et al.*, 2007; Saha *et al.*, 2007; Bushe *et al.*, 2009). In the present older population, mortality from neoplasms was shown to be almost twice as high as in general population. The rarer causes of death such as genitourinary diseases or digestive diseases revealed unexpectedly high SMRs in the present older schizophrenia population.

The deteriorating cognition of older schizophrenia patients may cause difficulties in communicating and identifying the symptoms, possibly causing delay in the diagnosis and treating somatic illness (Schoos and Cohen, 2003a, 2003b). Unforeseen death is also more common in the group of older schizophrenia patients: in Copeland's study of war veterans with schizophrenia, 20 % died unexpectedly, the mean age being 69.7 years ($n = 943$). The risk for an unforeseen death was twofold in the group of people with schizophrenia compared with other veterans and even higher in schizophrenia patients without outpatient care (Odds ratio 4.9; 95% CI 3.6–6.8) (Copeland *et al.*, 2006). The reasons for unforeseen deaths may be undertreatment and exposure to antipsychotic drugs and also the nature of schizophrenic disorder, which leads to difficulties in reaching outpatient facilities.

The mortality from unnatural causes of death ($n = 262$) was 11 times higher in the present sample of older patients with schizophrenia than in general

population. Falls were a major cause of death in this category (53%; $n = 137$) followed by suicide (16%; $n = 42$) and choking on food (14%; $n = 37$). Most of these patients have been on antipsychotic medication for decades, and older patients are more vulnerable to extrapyramidal symptoms (Jeste, 2004). Consequently, antipsychotic drugs are associated with falls and fractures in general (Hartikainen *et al*., 2007). In the study by Kiviniemi, the SMR of younger first-onset schizophrenia patients for accidents and violence was 3.9, which is considerably lower than in the present patients (9.6). The difference in the mortality from unnatural causes between the present patients and general population diminished before the age of 85 years and increased thereafter. A recent Finnish pharmacoepidemiological study showed the use of antipsychotic medication to be associated with decreased mortality among patients with schizophrenia (Tiihonen *et al*., 2009), but the results were not described by age group after the age of 70 years. Impact of antipsychotic medication on excess mortality of older patients with schizophrenia is possible, but any conclusions about it cannot be made on the basis of the present study.

It has been reported that 4.9 % of patients with schizophrenia will commit suicide at some point (Palmer *et al*., 2005). In the present study, the SMR of suicide was as high as 44.1. However, suicide was still a relatively rare cause of death in the present older patients with schizophrenia (0.8%; total number, $n = 42$). No suicides were found after the age of 81 years in the present population. In a British study by Osborn *et al*. (2008), the risk of suicide persisted up to age 70 years. Suicide attempts at older age are often violent (Bazin, 2004; Karvonen *et al*., 2008) and therefore result more commonly in death. In the present study, violent suicide was used in 25 out of 42 suicides, 13 were hangings and 12 were drownings (intoxication, $n = 9$; jumping from a height or in front of a car, $n = 6$; self-harm by fire or object, $n = 2$). In studies on younger patients with schizophrenia, suicide tends to be the most noteworthy cause of death (Palmer *et al*., 2005; Limosin *et al*., 2007). In first-onset schizophrenia patients, the SMR of suicide was 14 (Kiviniemi *et al*., 2010).

In Finland, relapse into schizophrenic disorder, that is, positive psychotic symptoms, is usually the reason for hospitalization. Contact with psychiatric hospital care 5 years before follow-up predicted higher mortality among older schizophrenia patients. It is assumed that those patients who were inpatients at that time had more serious symptoms than those not needing hospitalization. Thus, the relapsed patients still experiencing from psychosis, that is, positive schizophrenic symptoms, were at elevated risk of dying. In men, this difference was even more pronounced.

The strength of this study is a population-based high-validity database of the FHDR. Because in Finland, about 95% of patients with schizophrenia are hospital-treated at some stage of their illness in addition to having entries in register sources, nearly all people with schizophrenia at the age of 65 or more years should be identifiable in national registers (Isohanni *et al*., 1997; Lahti and Penttilä, 2001). The present study sample is large and provides nationwide coverage of the older patients with schizophrenia. The follow-up study period of 10 years was also long and thus the mortality estimates can be considered to be reliable for mortality of older schizophrenia patients in relation to the general Finnish population of the same age and gender. The Finnish causes-of-death register is demonstrably a reliable tool for research purposes (Lahti and Penttilä, 2001). All deaths are diagnosed by physicians in addition with post mortem examinations if the cause of death is uncertain. The main limitation of this register-based data was that it was not possible to check the reliability of the schizophrenia diagnoses of study subjects. However, the validity and reliability of the data of FHDR has been reported elsewhere; for example, diagnoses are accurate and specific within psychosis category (Aro *et al*., 1990; Moilanen *et al*., 2003). In addition, no information was available on the living habits of the patients or on the exact age at onset of the disorder. From a methodological point of view, because several statistical tests were performed, some possibility of chance findings (type I error) exists, but because of the small number of cases in some of the subgroup analyses, a possibility of type II error to detect small differences may also have occurred.

Conclusion

According to this large register-based study, the risk of death seems to be significantly elevated among the older patients with schizophrenia. Nevertheless, some of these patients live unexpectedly long. As a whole, mortality is for the same natural reasons as in general population. However, mortality from unnatural causes (including accidents, violence, and suicides) is 11 times higher than in general population. Those patients still experiencing positive symptoms of schizophrenia are at increased risk of death compared with those patients with the disorder in remission. Therefore, in older patients with schizophrenia, both physical and psychiatric health as well as the adverse

Key points

- In this register-based study of nearly 10,000 older patients with schizophrenia, mortality was almost threefold compared with the general population.
- Although the mortality of older patients with schizophrenia was significantly elevated in every cause-of-death category, it was especially high (SMR 11.04) among unnatural causes (accidents, suicides).
- Relapse further increases the risk of death.

effects of medications should be carefully monitored and treated.

Conflict of interest

There are no conflicts of interest to declare.

References

Alaräisänen A, Miettunen J, Räsänen P, *et al*. 2009. Suicide rate in schizophrenia in the Northern Finland 1966 birth cohort. *Soc Psychiatry Psychiatr Epidemiol* **44**(12): 1107–1110.

Aro S, Koskinen R, Keskimäki I. 1990. Reliability of hospital discharge data concerning diagnosis, treatments and accidents. *Duodecim* **106**(21): 1443–1450.

Bazin N. 2004. Suicide and depression in the elderly. *Psychol Neuropsychiatr Vieil* **2**: S29–S33.

Breslow NE, Day NE. 1987. Statistical methods in cancer research. Volume II—the design and analysis of cohort studies. *IARC Sci Publ* **82**: 1–406.

Brown S, Kim M, Mitchell C, Inskip H. 2010. Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry* **196**(2): 116–121.

Bushe CJ, Bradley AJ, Wildgust HJ, Hodgson RE. 2009. Schizophrenia and breast cancer incidence: a systematic review of clinical studies. *Schizophr Res* **114**(1–3): 6–16.

Chang CK, Hayes RD, Broadbent M, *et al*. 2010. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. *BMC Psychiatry* **10**: 77.

Cohen CI, Vahia I, Reyes P, *et al*. 2008. Focus on geriatric psychiatry: schizophrenia in later life: clinical symptoms and social well-being. *Psychiatr Serv* **59**(3): 232–234.

Copeland LA, Zeber JE, Rosenheck RA, Miller AL. 2006. Unforeseen inpatient mortality among veterans with schizophrenia. *Med Care* **44**(2): 110–116.

De Hert MA, van Winkel R, Van Eyck D, *et al*. 2006. Prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotic medication. *Schizophr Res* **83**(1): 87–93.

Druss BG, Bradford WD, Rosenheck RA, *et al*. 2001. Quality of medical care and excess mortality in older patients with mental disorders. *Arch Gen Psychiatry* **58**(6): 565–572.

Hartikainen S, Lönnroos E, Louhivuori K. 2007. Medication as a risk factor for falls: critical systematic review. *J Gerontol A Biol Sci Med Sci* **62**(10): 1172–1181.

Hor K, Taylor M. 2010. Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol* **24**(4): S81–S90.

Isohanni M, Mäkikyrö T, Moring J, *et al*. 1997. A comparison of clinical and research DSM-III-R diagnoses of schizophrenia in a Finnish national birth cohort. Clinical and research diagnoses of schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* **32**(5): 303–308.

Jeste DV. 2004. Tardive dyskinesia rates with atypical antipsychotics in older adults. *J Clin Psychiatry* **65**(9): S21–S24.

Joukamaa M, Heliövaara M, Knekt P, *et al*. 2001. Mental disorders and cause-specific mortality. *Br J Psychiatry* **179**: 498–502.

Karvonen K, Räsänen P, Hakko H, *et al*. 2008. Suicide after hospitalization in the elderly: a population based study of suicides in Northern Finland between 1988–2003. *Int J Geriatr Psychiatry* **23**(2): 135–141.

Kiviniemi M, Suvisaari J, Pirkola S, *et al*. 2010. Regional differences in five-year mortality after a first episode of schizophrenia in Finland. *Psychiatr Serv* **61**(3): 272–279.

Lahti RA, Penttilä A. 2001. The validity of death certificates: routine validation of death certification and its effects on mortality statistics. *Forensic Sci Int* **115**(1–2): 15–32.

Laursen TM, Munk-Olsen T, Agerbo E, *et al*. 2009. Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. *Arch Gen Psychiatry* **66**(7): 713–720.

Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB. 2007. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry* **68**(6): 899–907.

Lavsa SM, Fabian TJ, Saul MI, *et al*. 2010. Influence of medications and diagnoses on fall risk in psychiatric inpatients. *Am J Health Syst Pharm* **67**(15): 1274–1280.

Leucht S, Burkard T, Henderson J, *et al*. 2007. Physical illness and schizophrenia: a review of the literature. *Acta Psychiatr Scand* **116**(5): 317–333.

Limosin F, Loze JY, Philippe A, *et al*. 2007. Ten-year prospective follow-up study of the mortality by suicide in schizophrenic patients. *Schizophr Res* **94**(1–3): 23–28.

Miettunen J, Suvisaari J, Haukka J, Isohanni M. 2011. Use of register data for psychiatric epidemiology in the Nordic countries. In Textbook in Psychiatric Epidemiology, 3rd edition, Tsuang M, Tohen M, Jones P (eds.) John Wiley & Sons: Chichester, West Sussex; 117–131.

Moilanen K, Veijola J, Läksy K, *et al*. 2003. Reasons for the diagnostic discordance between clinicians and researchers in schizophrenia in the Northern Finland 1966 birth cohort. *Soc Psychiatry Psychiatr Epidemiol* **38**(6): 305–310.

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

Osborn D, Levy G, Nazareth I, King M. 2008. Suicide and severe mental illnesses. Cohort study within the UK general practice research database. *Schizophr Res* **99**(1–3): 134–138.

Osby U, Correia N, Brandt L, *et al*. 2000. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res* **45**(1–2): 21–28.

Palmer BA, Pankratz VS, Bostwick JM. 2005. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry* **62**(3): 247–253.

Räsänen S, Hakko H, Viilo, K, *et al*. 2003. Excess mortality among long-stay psychiatric patients in Northern Finland. *Soc Psychiatry Psychiatr Epidemiol* **38**(6): 297–304.

Saha S, Chant D, McGrath J. 2007. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* **64**(10): 1123–1131.

Schoos R, Cohen CI. 2003a. Medical comorbidity in older persons with schizophrenia. In Schizophrenia into Later Life, Cohen CI (ed.). American Psychiatric Publishing: Washington, London; 113–138.

Schoos R, Cohen CI. 2003b. Medical comorbidity in older persons with schizophrenia. In Schizophrenia into Later Life, Cohen CI (ed.). American Psychiatric Publishing: Washington, London; 113–138.

Suvisaari JM, Saarni SI, Perälä J, *et al*. 2007. Metabolic syndrome among persons with schizophrenia and other psychotic disorders in a general population survey. *J Clin Psychiatry* **68**(7): 1045–1055.

Tiihonen J, Lönnqvist J, Wahlbeck K, *et al*. 2009. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* **374**(9690): 620–627.

Wildgust HJ, Beary M. 2010. Are there modifiable risk factors which will reduce the excess mortality in schizophrenia? *J Psychopharmacol Suppl* **24**(4): 37–50.

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Change in antipsychotic usage pattern and risk of relapse in older patients with schizophrenia

Tiina Talaslahti[1], Hanna-Mari Alanen[2], Helinä Hakko[3], Matti Isohanni[4], Unto Häkkinen[5] and Esa Leinonen[2,6]

[1]Department of Psychiatry, Helsinki University Central Hospital, Finland
[2]Department of Psychiatry, Tampere University Hospital, Finland
[3]Department of Psychiatry, Oulu University Hospital, Finland
[4]Institute of Clinical Medicine, Department of Psychiatry, University of Oulu, Finland
[5]National Institute of Health and Welfare, Helsinki, Finland
[6]Medical School, University of Tampere, Finland
Correspondence to: T. Talaslahti, MD, E-mail: tiina.talaslahti@kolumbus.fi

Objective: The aim of this study was to explore the use of first (FGAs) and second generation antipsychotics (SGAs) in older outpatients with schizophrenia and schizoaffective disorder. Factors associated with schizophrenic relapses were also studied.

Methods: The study sample consisting of 8792 patients aged 64 years or more was collected from Finnish nationwide registers. The register data on the use of FGAs and SGAs were followed up between 1998 and 2003. Factors associated with psychiatric hospitalization in 1999 indicating relapse were studied using logistic regression analysis.

Results: The use of SGAs increased from 2.8% to 12.4%, and the use of FGAs decreased from 57.5% to 39.4%. The use of a combination of SGAs and FGAs increased from 4.0% to 8.5%. The proportion of those who did not buy any antipsychotics varied between 35.8% and 39.7%. The number of patients hospitalized on psychiatric wards within a year (1999; relapsed) was 8.8%. Factors independently associated with relapse were use of combined FGAs and SGAs [odds ratio (OR) 1.70, $p = 0.001$] and use of antidepressants (OR 1.27, $p = 0.019$). Diagnosis of cardiovascular disease was negatively associated with risk of schizophrenic relapse (OR 0.84, $p = 0.040$).

Conclusion: The use of SGAs increased while the use of FGAs decreased in older outpatients with schizophrenia. Almost 40% of the study sample did not use any antipsychotic medication. The 1-year relapse rate was 8.8%. Several factors, such as combined use of FGAs and SGAs, or antidepressants, were associated with schizophrenic relapse, whereas cardiovascular disease showed a negative association with the relapse. Copyright © 2013 John Wiley & Sons, Ltd.

Key words: older patients; schizophrenia; antipsychotics; relapse
History: Received 18 September 2012; Accepted 6 February 2013; Published online 5 April 2013 in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/gps.3962

Introduction

Antipsychotics are essential treatments for patients with schizophrenia. For older patients, second generation antipsychotics (SGAs) are frequently recommended instead of first generation antipsychotics (FGAs) because of lower risk of extrapyramidal side effects, especially tardive dyskinesia (Alexopoulos *et al.*, 2004). The idea that lifelong medication is needed has been challenged in recent research (Moilanen *et al.*, 2011; Harrow *et al.*, 2012).

The vast majority of schizophrenia patients have a schizophrenic relapse during the course of their illness. Relapse rates in patients taking antipsychotics have varied between 0% and 41% within a year depending on study design, relapse criteria, and the clinical characteristics of the subjects (Leucht *et al.*, 2003; Kishimoto *et al.*, 2011). Patients are most likely

to suffer relapse a short time after the onset of their illness (Addington *et al*., 2007). Studies on relapse among patients aged 65 years or more are rare. The risk of schizophrenic relapse or exacerbation of psychotic symptoms has also been found to be associated with withdrawal or change of antipsychotics also in the older patients (Jeste *et al*., 1993). Failure to adhere to antipsychotic treatment increases the likelihood of relapse and causes patients' dropouts of psychiatric care (Goff *et al*., 2010). The most important factors found to be associated with lack of adherence include poor illness insight, substance abuse, and cognitive impairment (Patterson *et al*., 2002; Prince *et al*., 2008).

The aim of the present study was to explore the use of antipsychotic medication in Finnish older patients suffering from schizophrenia or schizoaffective disorder in the period 1998–2003. Risk and associated factors for schizophrenic relapses were also studied.

Methods

Data

Patients were identified from the Finnish Hospital Discharge Register ($n = 8227$) and the pension registers (the Register of Disability Pensions from the Social Insurance Institution and the register of the Finnish Center for Pensions) ($n = 1234$). Detailed information on study subjects was also compiled from the Registers of Medication from the Social Insurance Institution and the National Causes-of-Death Register of Statistics Finland, and linked by the unique personal identification number allocated to every Finnish citizen. The study protocol was approved by the National Research and Development Centre for Welfare and Ethics Committee.

Study population

The original sample to be analyzed consisted of 9461 patients aged 64 years or more who were followed up during the period 1998–2003. For the purposes of the present study, the patients had schizophrenia or schizoaffective disorder [International Classification of Diseases (ICD)-8, ICD-9: 295, ICD-10: F20, F25] as their main psychiatric diagnosis in the Finnish Hospital Discharge Register or in the registers on pensions. Schizophrenia and schizoaffective disorder were analyzed together because they were in the same category (295) in ICD-8 and ICD-9 and thus recorded together in national registers. Patients who were institutionalized in any units of health care systems for a whole year were excluded from the final sample ($n = 8792$) because all their drugs were provided by the institution, and thus, there were no record of medication purchased.

Psychotropic medication

The data on the purchased psychotropic medication during the years 1998–2003 were collected from the registers of the Social Insurance Institution with the help of Anatomical Therapeutic Chemical (ATC) classification codes. The data for antipsychotics were extracted from that register and were classified into FGAs [including N05AA01 (chlorpromazine), N05AA02 (levomepromazine), N05AA03 (promazine), N05AB02 (fluphenazine), N05AB03 (perphenazine), N05AC02 (tioridazine), N05AC01 (periciazine), N05AD03 (melperone), N05AD01 (haloperidol), N05AF01 (flupentixol), N05AF03 (chlorprothixene), N05AF05 (zuclopenthixol), N05AL01 (sulpiride)] or SGAs [including N05AX08 (risperidone), N05AH04 (quetiapine), N05AH03 (olanzapine), N05AE03 (sertindole), N05AH02 (clozapine)]. The use of antipsychotics was analyzed using the following categories: 0 = no antipsychotics, 1 = FGA only, 2 = SGA only, 3 = combined FGA and SGA. In addition, the use of antidepressants (yes/no, ATC code N06A) during 1998 was extracted from the Social Insurance Institution registers. Collection of register data has been described in more detail elsewhere (Talaslahti *et al*., 2012).

Relapse

A relapse was defined to have occurred if a patient had psychiatric hospitalization for at least 1 day in 1999. The patients who had been in psychiatric hospital for the whole year of 1999 were excluded from the study sample, because medication was provided by the institution. The relapse in 2000–2003 was not modeled because the source of errors would have increased because of the limited scope of the register data.

Physical illnesses

The diagnoses of physical illnesses were collected from the registers of the Finnish Hospital Discharge Register (main diagnosis between 1987 and 1998) and Social Insurance Institution in 1998 (reimbursement for medicine expenses and medicines purchased). The physical illnesses included in the analysis were high blood pressure (ICD-10: I10–I15), atrial fibrillation

(I48), congestive heart disease (I50), coronary artery disease (I20–I25), diabetes mellitus (E10–E14), chronic obstructive pulmonary disease (COPD) and asthma bronchiale (J44–J46), neoplasms (C00–C99), alcohol dependence (F10), dementia (F00–F03, G30), and high level of cholesterol (E78) (Peltola *et al.*, 2011).

Severity of schizophrenic illness

The severity of schizophrenic illness was assessed on the basis of the information on psychiatric hospitalizations prior to 1999. The patients were dichotomized according to having or not having psychiatric hospitalization(s) over a period of 5 years (1994–1998) before joining the study.

Causes of death

Time and causes of death of adoptees by the end of the year in 1998–2003 were obtained from the national death register maintained by Statistics Finland. The official death register includes personal information of the deceased (personal identification code), the date of death, and the diagnosis on the cause of death (certified cause of death, underlying cause of death, or other contributing causes of death). For the period 1987–95, statistics on the causes of death referred to the Finnish Classification of Diseases, which were based on ICD-9, but since 1996, the ICD-10 diagnostics codes have been used.

Statistical analysis

The significance of group differences in categorical variables was assessed with Pearson's Chi-square test or Fisher's exact test and in continuous variables with Student's *t*-test Q1 or Mann–Whitney *U* test. The likelihood for relapse in 1999 was analyzed using logistic regression analysis with age, gender, source of data, use of medication (FGAs, SGAs, FGAs plus SGAs, or antidepressants) during the previous year, somatic illnesses (cardiovascular diseases, diabetes, dementia, COPD/asthma bronchiale, neoplasms, and high level of cholesterol), alcohol dependence, and severity of illness as independent variables. When calculating time trends in the use of antipsychotics, the annual sample size was papered off because of deaths of the patients during the follow-up. All statistical tests were two tailed, and the limit for statistical significance was set at $p < 0.05$. Statistical analyses were conducted using PASW for Windows, version 18 statistical program (SPSS Inc., Chicago, IL, USA).

Results

Time trends in the use of antipsychotics

The proportion of SGAs used increased from 2.8% (244/8792) to 12.4% (800/6444) ($p < 0.001$) during the period 1998–2003 in older patients with schizophrenia. At the same time, the use of FGAs decreased from 57.5% (5054/8792) to 39.4% (2538/6444) ($p < 0.001$). The use of combined FGAs and SGAs increased from 4.0% (350/8792) to 8.5% (550/6444) ($p < 0.001$) (Figure 1).

When these analyses were repeated by age group (64–79 years, 80 years or over), use of SGAs increased from 3.0% (226/7564) to 12.7% (738/5809) among 65–79 year olds and from 1.5% (18/1228) to 7.8% (62/635) in patients aged 80 years or over. Conversely, the use of FGAs decreased from 60.0% (4540/7564) to 41.0% (2383/5809) in patients aged 65–79 years and from 41.9% (514/1228) to 24.4% (155/635) in the older group. Among those taking combined FGAs and SGAs, an increase from 4.2% (319/7564) to 9.1% (531/5809) was found in the younger group and from 2.5% (31/1228) to 3.0% (19/635) in the older group. There were no differences between genders in the frequency of antipsychotic class taken (FGAs vs. SGAs).

Patients not taking antipsychotic medication

The share of patients not taking antipsychotics increased from 35.8% (3144/8792) to 39.7% (2556/6444) ($p < 0.001$) (Figure 2). Detailed information on each age group is given in Figure 2.

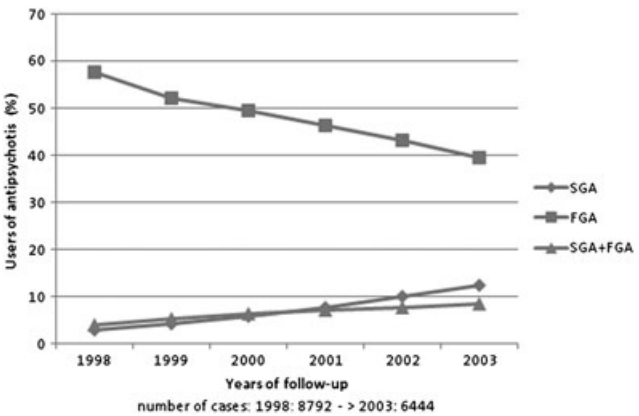


Figure 1 Usage of antipsychotics in Finnish older schizophrenia patients in 1998–2003. FGA, first generation antipsychotic; SGA, second generation antipsychotic.

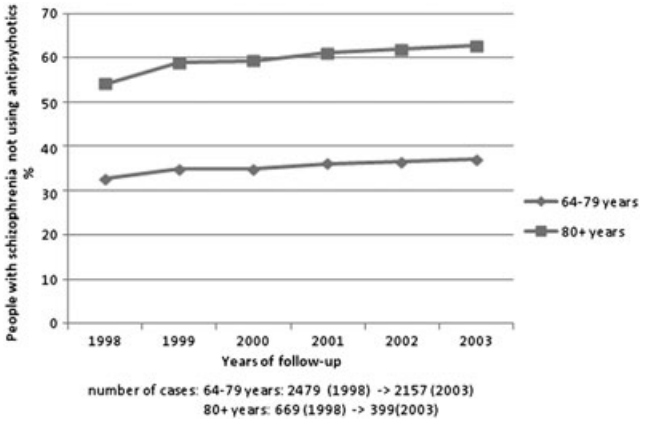


Figure 2 Non-usage of antipsychotics in Finnish older schizophrenia patients in 1998–2003.

Predictors for relapse

The proportion of the older schizophrenia patients hospitalized in psychiatric hospitals for at least 1 day in 1999 (relapsed) was 8.8% ($n = 780$). According to the results of the logistic regression analysis, the risk was increased either in those patients taking combined FGAs and SGAs or in those taking antidepressants. The risk was higher in the age group 65–79 years, in those whose data was based in the Finnish Hospital Discharge Register (instead of the register of Social Insurance Institution or Finnish Center for Pensions, indicating no prior psychiatric hospitalizations), and in those with at least one psychiatric hospitalization during the 5 years prior to joining the study. In contrast, the risk of relapse was modestly decreased in the group of patients with any diagnosis of cardiovascular disease (high blood pressure, atrial fibrillation, congestive heart disease, or coronary artery disease) (Table 1).

Discussion

The use of SGAs increased and the use of FGAs decreased in the present older patients with schizophrenia during the period 1998–2003. At the end of follow-up, 12.4% of 6444 patients were on SGAs and 39.4% on FGAs. This was an expected finding as Wang *et al.* (2005) also reported that the proportion of new users of SGAs among patients with psychotic disorders aged 65 years or more during the years 1994–2003 was 24.7%. In the present study, there were likewise no gender differences in the use of different classes of antipsychotics, which concurs with the findings of Sajatovic *et al.* (2002).

The numbers of those older patients not taking any antipsychotics was 36–40%. Indeed, the idea of

Table 1 Estimation results of the logistic regression model (dependent variable: likelihood for relapse in 1999)

	Likelihood for relapse		
Variables	OR	95% CI	Sig.
Antipsychotic medication during previous year			
No antipsychotic medication	Ref.		
First generation antipsychotics (FGAs)	0.94	0.78–1.13	0.496
Second generation antipsychotics (SGAs)	1.29	0.91–1.84	0.158
Combined FGAs and SGAs[a]	1.70	1.25–2.31	0.001
Use of antidepressants during previous year	1.27	1.04–1.55	0.019
Background characteristics			
Age group of 64–79 years (ref. 80 years or more)	2.18	1.62–2.95	$p < 0.001$
Data source, FHDR[b] (ref. pension registers)	1.58	1.16–2.16	0.004
Male gender (ref. female)	0.99	0.83–1.17	0.887
Severity of schizophrenic illness[c]	7.39	6.22–8.79	$p < 0.001$
Somatic illnesses			
Cardiovascular disease	0.84	0.71–0.99	0.040
Diabetes	0.83	0.65–1.06	0.134
Dementia	0.87	0.51–1.46	0.585
COPD, asthma bronchiale	0.83	0.61–1.13	0.231
Carcinoma	0.79	0.56–1.12	0.186
Cholesterol	0.95	0.42–2.14	0.894
Alcohol dependence	1.25	0.70–2.22	0.446

Note: The reference category in logistic regression analysis indicates negative response (no) unless otherwise stated. COPD, chronic obstructive pulmonary disease.

[a]Combined first generation antipsychotics plus second generation antipsychotics.

[b]Finnish Hospital Discharge Register.

[c]At least one psychiatric hospitalization in 1994–1998.

lifelong medication has recently been challenged (Moilanen *et al.*, 2011; Harrow *et al.*, 2012). The course of schizophrenia in later life varies within and between individuals. The positive symptoms usually diminish over time and are replaced by negative symptoms. Some individuals, however, suffer from delusions and hallucinations until old age (Cohen *et al.*, 2008). In a study of long-term institutional care, Alanen *et al.* found that the prevalence of older schizophrenia residents not receiving any antipsychotic medication was 18.5%. Severe functional impairment and dementia were associated with non-use of antipsychotics (Alanen *et al.*, 2006).

The recommendations on the use of antipsychotics in the older patients are primarily based on studies including younger patients (Marriott *et al.*, 2006). In addition, there is no trial-based evidence for guidelines on medication in late-onset schizophrenia (Arunpongpaisal *et al.*, 2003; Suzuki *et al.*, 2011; Essali and Ali, 2012). Despite the shortage of studies, SGAs, after their introduction, have been widely recommended as a treatment of choice for older psychotic patients instead of FGAs, mainly because of a better side-effect profile (Alexopoulos *et al.*, 2004). Jeste *et al.* (2003)also found a significant improvement in psychopathology of older schizophrenia patients when FGAs were changed to SGAs. However, in some reports, SGAs were not beneficial compared with FGAs for physical health, long-term manifestation of symptoms, cognition, or self-care outcome (White *et al.*, 2006; Kisely *et al.*, 2009).

The 1-year schizophrenia relapse rate in these older subjects was around 9%, and the risk was higher in the age group of 65–79 years than in those 80 years or over. The readmission rates in any age group are highest among fairly new-onset patients, which often results from poor treatment compliance due to poor illness insight (Addington *et al.*, 2007). However, most of the present patients, even those in the age group 65–79 years, had suffered from schizophrenia for decades. In our earlier registration study, 31% of schizophrenia patients aged 65 years or more had had at least one psychiatric hospitalization in the preceding 5 years (Talaslahti *et al.*, 2012).

In the present study, the risk of relapse was increased in those patients taking combined FGAs and SGAs when adjusting the results of logistic regression analysis for severity of illness. Of the present patients, 4% ($n = 350$) were on combined antipsychotic treatment, whereas in a recent study on patients admitted to a geriatric psychiatry unit (patients with schizophrenia, dementia, or bipolar disorder), the percentage of antipsychotic polypharmacy was 13% (Dolder and McKinsey, 2011). In an earlier study, 1-year rehospitalization rates of middle-aged patients ($n = 195$) taking olanzapine (34%) or risperidone (35%) were higher than those of the patients taking conventional antipsychotics (20%), which may relate to the selection of patients to each group (Patel *et al.*, 2002). The present patients taking a combination of FGAs and SGAs may have had some kind of treatment difficulties or adverse events and therefore had a need for augmentation.

The risk for relapse rate was also somewhat elevated in patients taking antidepressants. Comorbid depression has been reported to be associated with increased rehospitalization (Jin *et al.*, 2001). Whether the present result is a consequence of comorbid depression or of the psychosis-inducing effects of antidepressants remains open. Prevalence rates of depression in older schizophrenia patients have varied from 11% to 75%, depending on population and the depression severity (Diwan *et al.*, 2007). Depressive symptoms may also be associated with FGA-induced akinesia (Felmet *et al.*, 2011). Augmentation with a selective serotonin reuptake inhibitor (SSRI) is advised in cases where subsyndromal or major depression persists (Kasckow and Zisook, 2008).

In the present study, the risk for relapse was decreased in the group of patients with a diagnosis of some cardiovascular disease. This finding corroborates the results of Prince *et al.* (2008), where patients with congestive heart failure had decreased readmission rates for a psychiatric illness. In that study, patients with cancer, cerebrovascular disorder, or dyslipidemia were also less likely than other patients to experience psychiatric rehospitalization. The explanation for the lower rehospitalization rates in those patients with concomitant severe physical illnesses could relate to their increased contacts with healthcare professionals, who may also pay attention to patients' mental health in addition to their physical illnesses. Older psychiatric patients with serious cardiovascular illness might primarily be hospitalized in general hospitals (in spite of some psychiatric symptoms) if they are in need for intensive care.

There are some limitations in the present study. Relapse and rehospitalization are not necessarily synonymous. Relapse means a clinically significant increased severity of psychotic symptoms. Not all patients experiencing relapse may be hospitalized. In addition, if older people have other health problems, too, general hospital may be primary instead of a psychiatric ward (Prince *et al.*, 2008). However, in Finland, re-emergence or exacerbation of positive psychotic symptoms is the most important reason for psychiatric hospitalization. This is especially true

of older patients with schizophrenia, because the outpatient services are insufficient and their functioning ability soon deteriorates as psychotic symptoms increase (Pylkkänen, 2012). It was also impossible to check the reliability of the diagnoses of the present subjects. However, the validity and reliability of the data of the Finnish Hospital Discharge Register or other registers used have been reported in earlier studies (Aro *et al*., 1990; Moilanen *et al*., 2003; Miettunen *et al*., 2011). All diagnoses on the causes of death have to pass a routine validation procedure carried out by Statistics Finland. Therefore, the Finnish death certificate, in conjunction with death certification practices, has been shown to be adequate for statistical research into mortality and causes of death (Lahti and Penttilä, 2001). In addition, it was possible to calculate the use of antipsychotics in classes (FGAs, SGAs) only, without knowledge of individual medications or doses. Finally, we cannot completely exclude the possibility that the combination use of antipsychotics might somehow reflect more severe psychiatric symptoms even though controlled in statistical model. The strengths of this study are the high validity and large sample size of these population-based databases. The Finnish Hospital Discharge Register contains almost all the patients with schizophrenia, because in Finland, about 95% of patients have been treated in psychiatric hospital at some stage of the illness (Isohanni *et al*., 1997). The data were also supplemented with outpatients found through the National Pension Registers. The unique personal identification numbers assigned to every Finnish citizen makes it possible to collate the register data.

Conclusion

In this large register-based study, the use of SGAs increased as expected during the 6-year follow-up in older patients with schizophrenia. At the same time, the use of FGAs decreased, but at the end of follow-up, they were still the most prescribed antipsychotics. There were no gender differences in the use of different antipsychotics classes, but surprisingly, two fifths of the patients took no antipsychotic medication at all. Antidepressants and the use of combined FGAs and SGAs were associated with schizophrenic relapse, whereas there was a negative association between cardiovascular disease and relapse. It may be that contacts with healthcare professionals also improve the treatment of schizophrenic disorder. Therefore, it is important to pay attention to both physical and psychiatric health in the treatment of older schizophrenia patients.

Key points

- In this large register-based study, the use of second generation antipsychotics increased while the use of first generation antipsychotics decreased during the 6-year follow-up in older outpatients with schizophrenia.
- Almost 40% did not use any antipsychotic medication.
- The 1-year risk of schizophrenic relapse (8.8%) was associated with antidepressants and combined use of first and second generation antipsychotics, whereas cardiovascular disease showed a negative association with the relapse.

Conflict of interest

There are no conflicts of interest to declare. The manuscript was supported by the National Graduate School of Clinical Investigation.

References

Addington D, Addington MD, Patten S. 2007. Relapse rates in an early psychosis treatment service. *Acta Psychiatr Scand* **115**(2): 126–131.

Alanen H-M, Finne-Soveri H, Noro A, Leinonen E. 2006. Use of antipsychotic medications among elderly residents in long-term institutional care: a three-year follow-up. *Int J Geriatr Psychiatr* **21**(3): 288–295.

Alexopoulos GS, Streim J, Carpenter D, *et al*. 2004. Using antipsychotic agents in older patients. *J Clin Psychiatry* **65**(S2): 5-99. Discussion: 100-102, quiz 103-104.

Aro S, Koskinen R, Keskimäki I. 1990. Reliability of hospital discharge data concerning diagnosis, treatments and accidents. *Duodecim* **106**(21): 1443–1450.

Arunpongpaisal S, Ahmed I, Aqeel N, Suchat P. 2003. Antipsychotic drug treatment for elderly people with late-onset schizophrenia. *Cochrane Database Syst Rev* **2**: 004162.

Cohen CI, Vahia I, Reyes P, *et al*. 2008. Focus on geriatric psychiatry: schizophrenia in later life: clinical symptoms and social well-being. *Psychiatr Serv* **59**(3): 232–234.

Diwan S, Cohen CI, Bankole AO. 2007. Depression in older adults with schizophrenia spectrum disorders: prevalence and associated factors. *Am J Geriatr Psychiatr* **15**(12): 991–998.

Dolder CR, McKinsey J. 2011. Antipsychotic polypharmacy among patients admitted to a geriatric psychiatry unit. *J Psychiatr Pract* **17**(5): 368–374.

Essali A, Ali G. 2012. Antipsychotic drug treatment for elderly people with late-onset schizophrenia. *Cochrane Database Syst Rev* **2**: 004162.

Felmet K, Zisook S, Kasckow JW. 2011. Elderly patients with schizophrenia and depression: diagnosis and treatment. *Clin Schizophr Relat Psychoses* **4**(4): 239–250.

Goff DC, Hill M, Freudenreich O. 2010. Strategies for improving treatment adherence in schizophrenia and schizoaffective disorder. *J Clin Psychiatry* **71**(S2): 20–26.

Harrow M, Jobe TH, Faull RN. 2012. Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study. *Psychol Med* **17**: 1–11.

Isohanni M, Mäkikyrö T, Moring J, *et al*. 1997. A comparison of clinical and research DSM-III-R diagnoses of schizophrenia in a Finnish national birth cohort. Clinical and research diagnoses of schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* **32**(5): 303–308.

Jeste DV, Lacro, JP, Gilbert PL, *et al*. 1993. Treatment of late-life schizophrenia with neuroleptics. *Schizophr Bull* **19**(4): 817–830.

Jeste DV, Barak Y, Madhusoodanan S, *et al*. 2003. International multisite double-blind trial of the atypical antipsychotics risperidone and olanzapine in 175 elderly patients with chronic schizophrenia. *Am J Geriatr Psychiatr* **11**(6): 638–647.

Jin H, Zisook S, Palmer BW, *et al*. 2001. Association of depressive symptoms with worse functioning in schizophrenia: a study in older outpatients. *J Clin Psychiatry* **62**(10): 797–803.

Kasckow JW, Zisook S. 2008. Co-occurring depressive symptoms in the older patient with schizophrenia. *Drugs Aging* **25**(8): 631–647.
Kisely S, Cox M, Campbell LA, *et al*. 2009. An epidemiologic study of psychotropic medication and obesity-related chronic illnesses in older psychiatric patients. *Can J Psychiatry* **54**(4): 269–274.
Kishimoto T, Agarwal V, Kishi T, *et al*. 2011. Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. *Mol Psyhciatr* **29** doi: 10.1038/mp.2011.143.
Lahti RA, Penttilä A. 2001. The validity of death certificates: routine validation of death certification and its effects on mortality statistics. *Forensic Sci Int* **115**(1–2): 15–32.
Leucht S, Barnes TR, Kissling W, *et al*. 2003. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. *Am J Psychiatry* **160**(7): 1209–1222.
Marriott RG, Neil W, Waddingham S. 2006. Antipsychotic medication for elderly people with schizophrenia. *Cochrane Database Syst Rev* **1**: 005580.
Miettunen J, Suvisaari J, Haukka J, *et al*. 2011. Use of register data for psychiatric epidemiology in the Nordic countries. In Textbook in Psychiatric Epidemiology, 3rd edition, Tsuang M, Tohen M, Jones P (eds.) John Wiley & Sons: Chichester, West Sussex; 117–131.
Moilanen K, Veijola J, Läksy K, *et al*. 2003. Reasons for the diagnostic discordance between clinicians and researchers in schizophrenia in the Northern Finland 1966 Birth Cohort. *Soc Psychiatry Psychiatr Epidemiol* **38**(6): 305–310.
Moilanen J, Haapea M, Miettunen J, *et al*. 2011. Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication — a 10-year follow-up of the Northern Finland 1966 Birth Cohort Study. *Eur Psychiatry* **13**.
Patel NC, Dorson PG, Edwards N, *et al*. 2002. One-year rehospitalization rates of patients discharged on atypical versus conventional antipsychotics. *Psychiatr Serv* **53**(7): 891–893.
Patterson TL, Lacro J, McKibbin CL, *et al*. 2002. Medication management ability assessment: results from a performance-based measure in older outpatients with schizophrenia. *J Clin Psychopharmacol* **22**(1): 11–19.
Peltola M, Juntunen M, Häkkinen U, *et al*. 2011. A methodological approach for register-based evaluation of cost and outcomes in health care. *Ann Med* **43**(1): 4–13.
Prince JD, Akincigil A, Kalay E, *et al*. 2008. Psychiatric rehospitalization among elderly persons in the United States. *Psychol Serv* **59**(9): 1038–1045.
Pylkkänen K. 2012. Finnish psychiatry—past and present. *Nord J Psychiatry* **66**(S1): 14–24.
Sajatovic M, Sultana D, Bingham CR, *et al*. 2002. Gender related differences in clinical characteristics and hospital based resource utilization among older adults with schizophrenia. *Int J Geriatr Psychiatr* **17**(6): 542–548.
Suzuki T, Remington G, Uchida H, *et al*. 2011. Management of schizophrenia in late life with antipsychotic medications: a qualitative review. *Drugs Aging* **28**(12): 961–980.
Talaslahti T, Alanen HM, Hakko H, *et al*. 2012. Mortality and causes of death in older patients with schizophrenia. *Int J Geriatr Psychiatr* **17** doi: 10.1002/gps.2833.
Wang PS, Schneeweiss S, Avorn J, *et al*. 2005. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* **353**(22): 2335–2341.
White L, Friedman JI, Bowie CR, *et al*. 2006. Long-term outcomes in chronically hospitalized geriatric patients with schizophrenia: retrospective comparison of first generation and second generation antipsychotics. *Schizophr Res* **88**(1-3): 127–134.

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Patients with very-late-onset schizoprhenia-like psychosis have higher mortality rates than elderly patients with earlier onset schizophrenia

Tiina Talaslahti[1], Hanna-Mari Alanen[2], Helinä Hakko[3], Matti Isohanni[4], Unto Häkkinen[5] and Esa Leinonen[2,6]

[1]Helsinki University Central Hospital, Department of Psychiatry, Finland
[2]Tampere University Hospital, Department of Psychiatry, Finland
[3]Oulu University Hospital, Department of Psychiatry, Finland
[4]University of Oulu, Institute of Clinical Medicine, Department of Psychiatry, Finland
[5]National Institute of Health and Welfare, Helsinki, Finland
[6]Medical School, University of Tampere, Finland
Correspondence to: T. Talaslahti, E-mail: tiina.talaslahti@kolumbus.fi

Objective: In this register-based study of schizophrenia patients aged 65 years or above, mortality and causes of death diagnosed at age of 60+ (very-late-onset schizophrenia-like psychosis, VLOSLP) were studied in comparison with sex- and age-matched general Finnish population. Standardized Mortality Ratios (SMRs) of VLOSLP patients were also compared with those of earlier onset (below 60 years) schizophrenia patients, and hazard of death was calculated between these patient groups.

Methods: The data was obtained from Finnish nationwide registers and consisted of 918 VLOSLP patients and 6142 earlier onset patients who were at least 65 years on 1 January 1999. The register-based follow-up for mortality covered 10 years between 1999 and 2008.

Results: Overall SMR was 5.02 (4.61–5.46) in the group of VLOSLP patients and 2.93 (2.83–3.03) in the group of earlier onset patients. In men, SMRs were 8.31 (7.14–9.62; $n = 179$) and 2.91 (2.75–3.07, $n = 1316$) and in women 4.21 (3.78–4.66; $n = 364$) and 2.94 (2.82–3.07, $n = 2055$). In the VLOSLP group, SMRs were higher in most causes-of-death categories such as accidents, respiratory diseases, dementias, neoplasms and circulatory diseases. However, in direct comparison adjusted for several variables, the difference between these groups was minimal (Hazard Ratio, HR, 1.16 95%CI 1.05–1.27, $p = 0.003$).

Conclusion: Patients with VLOSLP, especially men, are at even higher risk of death than schizophrenia patients with earlier onset. Physical comorbidities and accidents in the VLOSLP group mostly explained this result. Targeted clinical interventions with effective collaboration between psychiatry and primary and specialist-level somatic care are crucial to reduce their excess mortality. Copyright © 2014 John Wiley & Sons, Ltd.

Key words: schizophrenia; aged; age at onset; mortality; cause of death
History: Received 05 December 2013; Accepted 28 May 2014; Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/gps.4159

Introduction

People with schizophrenia have 15–20 years shorter life expectancy than non-schizophrenic population (Cowling *et al.*, 2012; Laursen *et al.*, 2013). According to our earlier study, mortality in patients with schizophrenia is also increased in older patients compared with general population. It is high in every cause-of-death category, especially in unnatural causes of death, but the causes of death still resemble those of the general population (Talaslahti *et al.*, 2012). Excess mortality in old age groups with this disease may be a consequence of comorbidities caused by unhealthy living habits, of exposure to antipsychotics or of unnatural causes such as suicides or accidents (Ran *et al.*, 2007; Suvisaari *et al.*, 2007). Furthermore, problems in psychiatric and medical compliance and possibly inadequate outpatient psychogeriatric services may hamper treatment interventions.

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Psychiatric hospital admission and long-term care in patients with very-late-onset schizophrenia-like psychosis

Tiina Talaslahti[1], Hanna-Mari Alanen[2], Helinä Hakko[3], Matti Isohanni[4], Olli Kampman[5,6], Unto Häkkinen[7] and Esa Leinonen[2,6]

[1]Helsinki University Central Hospital, Department of Psychiatry, Finland
[2]Tampere University Hospital, Department of Psychiatry, Finland
[3]Oulu University Hospital, Department of Psychiatry, Finland
[4]University of Oulu, Institute of Clinical Medicine, Department of Psychiatry, Finland
[5]Seinäjoki Hospital District, Department of Psychiatry, Seinäjoki, Finland
[6]School of Medicine, University of Tampere, Finland
[7]National Institute for Health and Welfare, Helsinki, Finland
Correspondence to: T. Talaslahti, MD, E-mail: tiina.talaslahtiat@kolumbus.fi

Objective: In this register-based study the rates and durations of psychiatric hospitalizations were compared between patients with very-late-onset schizophrenia-like psychosis (VLOSLP, n = 918) and elderly patients with illness onset before 60 years (n = 6142). The proportion of patients ending up in long-term care (LTC) or long-lasting psychiatric hospital care (LLP) was also studied.

Methods: A sample of patients with schizophrenia aged 65 or over was collected from the Finnish Hospital Discharge Register. Psychiatric hospitalizations were calculated per year, and logistic regression was used to compare onset groups and factors associated with ending up in LTC/LLP.

Results: Between 1999 and 2003, 27% of patients with VLOSLP and 23% of patients with earlier onset had at least one psychiatric hospitalization ($p = 0.020$). When the rates of patients' stays in psychiatric hospital per year were compared, the only difference was that in the first year 14% (141/918) and 11% (679/6142) had at least one day in psychiatric hospital ($p < 0.001$) respectively. In logistic regression onset group of schizophrenia was not associated with LTC/LLP, except weakly the VLOSLP group in women ($p = 0.042$, OR 1.23). Patients having any cardiovascular disease ($p < 0.001$, OR 0.63) or a respiratory disease ($p = 0.008$, OR 0.73) were less likely to end up in LTC/LLP.

Conclusion: The patients with VLOSLP needed more psychiatric hospital care than those with earlier illness onset. Ending up in LTC/LLP was equally common in both onset groups, but some physical diseases, such as cardiovascular and respiratory, diminished the likelihood of this.

Key words: elderly; schizophrenia; very-late-onset schizophrenia-like psychosis; psychiatric hospital care; long-term care
History: Received 06 February 2015; Accepted 07 July 2015; Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/gps.4333

Introduction

Schizophrenia patients with onset at 60 years or later (very-late-onset schizophrenia-like psychosis, VLOSLP) is a small group among elderly patients with schizophrenia, but they require attention and their number is expected to increase in coming decades (Cohen *et al.*, 2008). Even though VLOSLP patients receive a diagnosis of schizophrenia in old age, their illness differs only slightly from that of elderly earlier onset patients and it is characterized by such clinical features as more positive symptoms or better treatment response to antipsychotic medication (Howard *et al.*, 2000; Rodriguez-Ferrera *et al.*, 2004; Hanssen *et al.*, 2014).

Most studies have concentrated on young or midlife first-episode patients with schizophrenia which has resulted in a lack of treatment algorithms applicable to elderly patients. Research comparing patients

with later onset of schizophrenia with those diagnosed at a younger age is also rare. In our recent studies, mortality in the VLOSLP group was increased because of physical comorbidities and accidents when compared with earlier onset age-matched elderly schizophrenia patients and general population samples (Talaslahti *et al.*, 2012, 2015). VLOSLP patients are more often female, married or widowed and have had more years of education than patients with early-onset schizophrenia which may support them to cope better with everyday life (Barak *et al.*, 2002; Mazeh *et al.*, 2005). Late-onset patients have even more prominent cognitive deficits than earlier onset elderly schizophrenia patients which according to present understanding seldom leads to dementia (Girard *et al.*, 2011). The risk of ending up in a residential home care as well as the need for hospital care or home health care has been found to be increased in all elderly patients with schizophrenia compared with people without this severe mental illness (Andrews *et al.*, 2009; Hendrie *et al.*, 2014). However, very little is known about the need for hospital care of VLOSLP patients. As far as we know, this is the first large and nationwide register-based study on psychiatric hospitalizations and long-term care in VLOSLP patients.

The present register sample included 918 VLOSLP patients and 6142 earlier onset patients. The primary aim of the study was to compare the rates and durations of psychiatric hospitalizations between these groups, and also within the VLOSLP group for a five-year period between 1999 and 2003. The secondary aim was to ascertain what proportion of old schizophrenia patients ended up in long-term care or in long lasting psychiatric hospital care in four-year follow-up, and which factors contributed this.

Methods

Data

The Finnish Hospital Discharge Register (FHDR, also known as the Care Register for Health Care since 1994) administrated by the National Institute for Health and Welfare offered the data for present research purposes. The FHDR was supplemented by the National Causes-of-Death Register of Statistics Finland and linked by the unique personal identification number of every resident in Finland. These data has been described in detail elsewhere (Talaslahti *et al.*, 2012, 2015). The study protocol was approved by the Ethics Committee of the National Institute for Health and Welfare.

Study population

The data consisted of all Finnish in- and outpatients aged 65 years or older by 1 January 1999 with a present main diagnosis of schizophrenia or schizoaffective disorder [International Classification of Diseases ICD-8, ICD-9: 295, ICD-10: F20, F25]. The sample was first divided into two groups: the group of patients with very-late-onset schizophrenia-like psychosis (VLOSLP), e.g. those with disease onset at 60 years or later (n = 918), and the group of earlier onset patients, e.g. those with disease onset at younger than 60 years (n = 6142) i.e. after 1978. The time of illness onset was approximated from the first hospitalization because of any psychosis. The mean time from illness onset to the beginning of follow-up was on average 7.1 years (SD ±4.8) in the VLOSLP group and 25.6 years (SD ±6.9) in the earlier onset group. As the recent onset of illness may have influenced hospitalization rates, the VLOSLP group was further divided into four subgroups depending on how many years had elapsed since the onset of illness (1–3, 4–5, 6–10 and 11 or more years) before the beginning of follow-up.

The numbers of days in psychiatric hospital were followed up for five years and calculated per year from the registers. The data concerning long-term care (other than psychiatric care, LTC) and long-lasting psychiatric hospitalization (LLP) was available only for a time period of for four years. Patients with any dementia (ICD-10: F00–F03, G30) at the beginning of follow-up were excluded from this analysis [VLOSLP: n = 49 (5.3%); earlier onset group: n = 89 (1.4%); total: n = 138 (2%)].

In Finland long-term patients refers to all patients for whom a decision has been made on a need for long-term care in sheltered accommodation, residential homes or health centres (usually permanent residence) or who have been in continuous care in any health care institution for more than 90 days. Patients in long-lasting psychiatric hospitalization have stayed in hospital for more than 180 days. Proportions of patients ending up in LTC/LLP were compared between the VLOSLP and the earlier onset group.

Statistical analyses

The significance of group differences in categorical variables was assessed with Pearson's Chi-square test or Fisher's exact test and in continuous variables with Student's *t*-test Q1 or Mann–Whitney *U*-test. The likelihood for ending up in long-term care/long-lasting psychiatric hospital care was analysed using

logistic regression analysis with onset of illness (before 60 years/60 years or older), age, gender or physical disease [cardiovascular disease (high blood pressure ICD-10: I10–I15, atrial fibrillation I48, congestive heart disease I50, coronary artery disease I20–I25), diabetes mellitus E10–14, neoplasm C00–C99, respiratory disease (chronic obstructive pulmonary disease COPD and asthma bronchiale J44–J46)], high level of cholesterol E78 or alcohol-related disorder F10 as independent variables (Peltola *et al.*, 2011). Corresponding analyses were made for both genders separately. Deaths were taken into account when calculating annual proportions of hospitalization or long-term care. All statistical tests were two-tailed, and the limit for statistical significance was set at $p < 0.05$. Statistical analyses were conducted using SPSS for Windows, version 22 statistical programme (IBM SPSS, Armonk, NY).

Results

The sociodemographic and main clinical characteristics of the sample (n = 7060) of elderly patients with schizophrenia are given in Table 1. Between 1999 and 2003, 30.4% of them (VLOSLP 32.6%/earlier onset 30.0%) died.

Psychiatric hospitalizations

During the five-year follow-up, 246/918 (27%) patients in the VLOSLP group and 1430/6142 (23%) patients in the earlier onset group had at least one psychiatric hospitalization ($p = 0.020$). The corresponding figures for men were 64/254 (25%) and 448/2050 (22%) ($p = 0.227$), and 182/664 (27%) and 982/4092 (24%) ($p = 0.058$) for women.

When the rates of psychiatric hospitalization per year were compared, in the first year 141/918 (14%) patients in the VLOSLP group and 679/6142 (11%) in the earlier onset group had at least one day in psychiatric hospital ($p < 0.001$), 40/254 (16%) and 232/2050 (11%) ($p = 0.039$) in men and 101/664 (15%) and 447/4092 (11%) ($p = 0.001$) in women respectively. No differences in hospitalization rates between onset groups were found during the second, third, fourth and fifth years of follow-up.

When the VLOSLP group was divided into four categories according to the time since onset of schizophrenia (1–3, 4–5, 6–10 and 11 or more years before the beginning of follow-up), the number of days in psychiatric hospital in the first follow-up year differed between these subgroups ($p = 0.045$). The mean number of days in psychiatric hospital was greater in the VLOSLP subgroup of patients having 1–3 years since illness onset (19.1 days, sd 59.8) compared with those having 11 years or more since illness onset (6.75 days, sd 32.1) ($p = 0.028$). A corresponding difference was also found between the VLOSLP subgroup with 6–10 years since illness onset (19.7 days, sd 68.2) and those having 11 years or more since illness onset (6.75 days, sd 32.1) ($p = 0.037$).

Long-term care or long-lasting psychiatric hospital care

Patients in the VLOSLP group ended up more often in LTC/LLP than those in the earlier onset group in the

Table 1 Baseline characteristics of elderly patients with schizophrenia by onset groups (onset at 60 years or later and onset before 60 years)

	Onset age for schizophrenia					
	Total (n = 7060) % (n)	60+ (n = 918) % (n)	−59 (n = 6142) % (n)	P-value		
				t-test or $\chi 2$	df	p*
Socio-demographics						
Age in 1999 (years, ± SD)	71.2	73.1 (±4.3)	71.0 (±4.2)	−14.4	1189	<0.001
Gender, women	67.4 (4756)	72.3 (664)	66.6 (4092)	11.8	1	0.001
Physical or other illnesses at baseline						
Cardiovascular disease	39.0 (2753)	47.9 (440)	37.7(2313)	35.4	1	<0.001
Diabetes mellitus	14.5 (1024)	14.9 (137)	14.4 (887)	0.15	1	0.699
Neoplasm	6.1 (428)	7.2 (66)	5.9 (362)	2.35	1	0.125
Respiratory disease	8.4 (591)	9.8 (90)	8.2 (501)	2.82	1	0.093
Dementia	2.0 (138)	5.3 (49)	1.4 (89)	63.02	1	<0.001
High cholesterol level	1.1 (81)	1.4 (13)	1.1 (68)	0.67	1	0.412
Alcohol-related disorder	1.2 (88)	2.2 (20)	1.1 (68)	7.45	1	0.006
Long-term care (LTC) or long lasting psychiatric hospital care (LLP) during 1999–2002						
Ending up in LTC/LLP	22.9 (1617)	28.0 (257)	22.1 (1360)	15.4	1	<0.001

*$\chi 2$-test, except in age independent samples t-test (equal variance not assumed), two-tailed significance patients' data collected from pension registers were excluded.

third year [VLOSLP: n = 151/749 (20.2%); earlier onset group: n = 810/5371 (15.1%); $p < 0.001$] and in the fourth year of follow-up [n = 141/707 (19.9%); n = 773/4987 (15.5%); p = 0.003] respectively. Moreover, women in the VLOSLP group were more likely to end up in LTC/LLP than women with earlier onset. Proportions of patients ending up only in LLP showed no differences between the onset groups.

Predictors of ending up in long-term care or long-lasting psychiatric hospital care

The results of the logistic regression analysis (Table 2) suggested that age was associated with ending up in LTC/LLP, but onset group of schizophrenia was no longer associated with it. Patients having any cardiovascular disease or a respiratory disease were less likely to end up in LTC/LLP. Further, in corresponding analysis made for both genders, ending up less likely in LTC/LLP was true in male and female patients with cardiovascular disease (female: $p < 0.001$, OR 0.62, 95%CI 0.49–0.78, and male: $p < 0.001$, OR 0.63, 95% CI 0.54–0.73) and only in female patients with respiratory disease (p = 0.004, OR 0.64, 95%CI 0.47–0.87). Conversely, in female patients with diabetes (p = 0.008, OR 1.30, 95%CI 1.07–1.58) this risk was increased. Onset group of schizophrenia was associated weakly for the VLOSLP group in women (p = 0.042, OR 1.23, 95%CI 1.01–1.49).

Discussion

The main finding of the present study was that VLOSLP patients needed for more psychiatric hospitalizations than patients with earlier onset. This difference was more pronounced in the most recently diagnosed VLOSLP patients. In the total sample both VLOSLP and earlier onset patients ended up in LTC/LLP equally although the risk was modestly elevated in VLOSLP women. Surprisingly, higher age increased and physical diseases, such as cardiovascular or respiratory diseases, decreased the likelihood. In earlier studies, we reported that elderly patients with schizophrenia, especially those in the VLOSLP group, had higher mortality rates than age-matched general population (Talaslahti *et al.*, 2012, 2015).

Table 2 The predictors of ending up in long-term care or long-lasting psychiatric hospital care (LTC/LLP) between 1999 and 2002, assessed using logistic regression

Variables	OR	95%CI	Sig
Background characteristics			
Age at 1999	1.10	1.09–1.12	$p < 0.001$
Gender (women vs. men)	1.04	0.91–1.18	0.580
Onset group (60+ vs. 60−)	1.13	0.95–1.34	0.156
Physical illnesses			
Cardiovascular disease	0.63	0.55–0.71	$p < 0.001$
Respiratory disease	0.73	0.58–0.92	0.008
Diabetes mellitus	1.16	0.98–1.37	0.081
Neoplasm	0.97	0.76–1.24	0.827
High cholesterol level	0.57	0.28–1.16	0.121
Alcohol-related disorder	0.83	0.46–1.50	0.545

*Note: the reference category in logistic regression analysis indicates negative response (no) unless otherwise stated.
OR: odds ratio; CI: confidence interval; Sig: significance.

Although there were more psychiatric hospitalizations in the present VLOSLP group than in the earlier onset group in the first year of follow-up, the difference between these groups was rather small (4%). However, this finding concurs with the study by Mitford *et al.* (2010) where first episode very-late-onset patients with psychotic disorder had more hospital days in the first year than younger late-onset patients. Older people with schizophrenia (mixed groups of very-late-onset and earlier onset schizophrenia) have also been reported to have fewer admissions to psychiatric hospital, but their length of stay was longer than that of younger patients with schizophrenia (Barry *et al.*, 2002; Low and Draper, 2009; Mitford *et al.*, 2010; Hendrie *et al.*, 2013). The lower frequency of admissions has been explained with older schizophrenia patients' better coping with their illness, and longer length of stay with difficulties in finding an adequate residence after hospitalization. The slightly higher rate of psychiatric hospitalizations in the present relatively recent onset VLOSLP patients may be a result of imbalance in symptoms before a suitable treatment strategy has been found. The manifestation of the illness may be more severe in its early years. In addition, the health care system fails to address the adequate care of very-late-onset patients because this diagnosis is not very well known.

In the study by Prince *et al.* physical comorbidity decreased the likelihood for psychiatric rehospitalization in older patients with schizophrenia (Prince *et al.*, 2008). In another study, patients with schizophrenia ending up in institutional care had lower levels of disability and comorbidity than elderly patients without a mental illness (Andrews *et al.*, 2009). The results of these studies concur to some extent with the present findings that certain physical illnesses decreased the risk for ending up in long-term stay among elderly patients with schizophrenia. In the present study, however, the decreased risk was not explained by deaths occurring in more severely ill patients. Although cardiovascular and respiratory diseases may be fatal, they

did not seem to be a critical factor for ending up in long-term care. Problems in activities of daily living, experienced loneliness and inadequate living circumstances may be risk factors for premature long-term institutionalization in elderly people in general (Vaarama, 2004). However, the older schizophrenia patients having some physical disease may receive more effective overall care and support that help them also to cope with schizophrenic symptoms and thus avoid psychiatric hospitalizations. In addition, if older patients with schizophrenia have physical health problems, general hospital care may sometimes be offered instead of the psychiatric ward (Prince *et al.*, 2008).

The risks of long-lasting care in general were equal in the present VLOSLP group and patients with earlier disease onset. However, women with VLOSLP were more likely to end up in LTC/LLP, but this finding should be interpreted with caution because of the small numbers included in the subgroup analyses. In the study by Reeves *et al.* (2002), no gender differences were found between different onset groups concerning admittance to psychiatric hospitals.

As a post-hoc analysis using 40 years as a cut point, risk of ending up in LTC/LLP was also calculated. Twenty-seven percent of the patients in younger onset group (less than 40 years) and 22% in older onset group (40 years or more) were admitted to LTC/LLP (OR 0.52, 95%CI 0.44–0.60, $p < 0.001$). However, when using this cut point, the onset of illness may no more be reliable because of the fact that the earliest hospitalizations are not available in the data.

In the present study, 16.1% of the sample (19.9% of the VLOSLP and 15.3% of the earlier onset group) were in LTC/LLP by the end of follow-up. Of all Finnish adults aged 75 years or older, 10.4% were living in long-term facilities in 2002 (Ailasmaa *et al.*, 2003). In an earlier study, 25% of very-late-onset patients with functional psychoses, including schizophrenia and related disorders, were institutionalized within ten years of index admission (Holden, 1987). Patients with schizophrenia have been reported to start living in institutional care at younger age than adults with mental problems other than schizophrenia or general population and they sometimes even lack a clear indication for admittance (Aschbrenner *et al.*, 2009). Median age on admission to residential care was 65 years for patients with schizophrenia and 80 years for individuals with no mental illness (Andrews *et al.*, 2009). As summarized, it seems that schizophrenia predisposes for earlier need for long-term care in old age.

The strengths of this study are large and population-based databases with high validity and reliability for research purposes, as well as the accuracy and validity of diagnoses in the psychoses category, as demonstrated in several previous Finnish studies (Aro *et al.*, 1990; Moilanen *et al.*, 2003; Lahti and Penttilä, 2001; Miettunen *et al.*, 2011; Sund, 2012). In Finland the vast majority of patients with schizophrenia are treated in hospital at some stage of their illness, and therefore nearly all elderly people with this diagnosis should be identifiable in national registers and according to the personal identification code (Isohanni *et al.*, 1997; Lahti and Penttilä, 2001; Perälä *et al.*, 2007).

The main limitation in this register-based data was that it was the lack of any opportunity to check the reliability of individual schizophrenia diagnoses or background data such as living habits or use of outpatient health services among the study subjects. It is possible that some of the patients were misclassified as having a diagnosis of VLOSLP instead of dementia or vice versa. Some identity codes after the establishment of the FHDR could be incorrect (Sund, 2012). Therefore the inclusion for this study was practically started from 1972. Some of the patients assigned to the VLOSLP group may have had a hospitalization before 1972 and no hospitalizations thereafter before the age of 60 years. There may also be considerable gaps between onset of symptoms and first hospitalizations, which may confound differentiation also between very late onset and other schizophrenia patients.

Conclusions

In this large register-linkage study of elderly patients with schizophrenia, the patients diagnosed at 60 years or later needed more psychiatric hospitalizations than earlier onset patients. It seems that schizophrenia is a predisposing factor for substantially earlier need for long-term care in old age. Although patients from both onset groups ended up in long-lasting psychiatric hospital care or long-term residential care equally, physical diseases seemed surprisingly to relate to less prevalent early institutional care. Patients with very-late-onset schizophrenia-like psychosis would probably benefit most from long time and comprehensive outpatient care with observations of physical illnesses in reducing the need for psychiatric hospital care and the risk of premature long-term care.

Conflict of interest

None declared.

Key points

- In this large register-linkage study of elderly patients with schizophrenia, the patients with very-late-onset schizophrenia-like psychosis needed more psychiatric hospitalizations than the patients with earlier illness onset.
- Physical diseases such as cardiovascular or respiratory disease diminished the likelihood for ending up in long-term care.

Acknowledgements

This work was supported by the National Graduate School of Clinical Investigation (CLIGS, Finland) and the Finnish Psychiatric Association. None of them had a role in study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the paper for publication.

References

Ailasmaa R, Kuronen R, Lehtonen J, Kauppinen S. 2003. Institutional Care and Housing Services in Social Welfare 2002. National Research and Development Centre for Welfare and Health. Statistical Summary 19/2003. Available from: https://www.julkari.fi/handle/10024/76359 (Accessed 15/6/2015).

Andrews AO, Bartels SJ, Xie H, Peacock WJ. 2009. Increased risk of nursing home admission among middle aged and older adults with schizophrenia. *Am J Geriatr Psychiatry* **17**(8): 697–705.

Aro S, Koskinen R, Keskimäki I. 1990. Reliability of hospital discharge data concerning diagnosis, treatments and accidents. *Duodecim* **106**(21): 1443–1450.

Aschbrenner KA, Cai S, Grabowski DC, *et al.* 2009. Medical comorbidity and functional status among adults with major mental illness newly admitted to nursing homes. *Psychiatr Serv* **62**(9): 1098–1100.

Barak Y, Aizenberg D, Mirecki I, *et al.* 2002. Very late-onset schizophrenia-like psychosis: clinical and imaging characteristics in comparison with elderly patients with schizophrenia. *J Nerv Ment Dis* **190**(11): 733–736.

Barry KL, Blow FC, Dornfeld M, *et al.* 2002. Aging and schizophrenia: current health services research and recommendations. *J Geriatr Psychiatry Neurol* **15**(3): 121–127.

Cohen CI, Vahia I, Reyes P, *et al.* 2008. Focus on geriatric psychiatry: schizophrenia in later life: clinical symptoms and social well-being. *Psychiatr Serv* **59**(3): 232–234.

Girard C, Simard M, Noiseux R, *et al.* 2011. Late-onset-psychosis: cognition. *Int Psychogeriatr* **23**(8): 1301–1316.

Hanssen M, van der Werf M, Verkaaik M, *et al.* 2014. Comparative study of clinical and neuropsychological characteristics between early-, late and very-late-onset schizophrenia-spectrum disorders. *Am J Geriatr Psychiatry* **4**S1064-7481(14)00317.

Hendrie HC, Lindgren D, Hay DP, *et al.* 2013. Comorbidity profile and healthcare utilization in elderly patients with serious mental illnesses. *Am J Geriatr Psychiatry* **21**(12): 1267–1276.

Hendrie HC, Tu W, Tabbey R, *et al.* 2014. Health outcomes and cost of care among older adults with schizophrenia: a 10-year study using medical records across the continuum of care. *Am J Geriatr Psychiatry* **22**(5): 427–436.

Holden NL. 1987. Late paraphrenia or the paraphrenias? A descriptive study with A 10-year follow-up. *Br J Psychiatry* **150**: 635–639.

Howard R, Rabins PV, Seeman MV, Jeste DV. 2000. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The international late-onset schizophrenia group. *Am J Psychiatry* **157**(2): 172–178.

Isohanni M, Mäkikyrö T, Moring J, *et al.* 1997. A comparison of clinical and research DSM-III-R diagnoses of schizophrenia in a Finnish national birth cohort. Clinical and research diagnoses of schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* **32**(5): 303–308.

Lahti RA, Penttilä A. 2001. The validity of death certificates: routine validation of death certification and its effects on mortality statistics. *Forensic Sci Int* **115**(1–2): 15–32.

Low LF, Draper B. 2009. Hospitalization patterns for psychiatric disorders across the lifespan in Australia from July 1998 to June 2005. *Psychiatr Serv* **60**(1): 113–116.

Mazeh D, Zemishlani C, Aizenberg D, Barak Y. 2005. Patients with very-late-onset schizophrenia-like psychosis: a follow-up study. *Am J Geriatr Psychiatry* **13**(5): 417–419.

Miettunen J, Suvisaari J, Haukka J, *et al.* 2011. Use of register data for psychiatric epidemiology in the Nordic countries. In Textbook in Psychiatric Epidemiology, Tsuang M, Tohen M, Jones P (eds.). 3rd edn.John Wiley & Sons: Chichester, West Sussex; 117–131.

Mitford E, Reay R, McCabe K, *et al.* 2010. Ageism in first episode psychosis. *Int J Geriatr Psychiatry* **25**(11): 1112–1118.

Moilanen K, Veijola J, Läksy K, *et al.* 2003. Reasons for the diagnostic discordance between clinicians and researchers in schizophrenia in the northern Finland 1966 birth cohort. *Soc Psychiatry Psychiatr Epidemiol* **38**(6): 305–310.

Peltola M, Juntunen M, Häkkinen U, *et al.* 2011. A methodological approach for register-based evaluation of cost and outcomes in health care. *Ann Med* **43**(1): 4–13.

Perälä J, Suvisaari J, Saarni SI, *et al.* 2007. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry* **64**(1): 19–28.

Prince JD, Akincigil A, Kalay E, *et al.* 2008. Psychiatric rehospitalization among elderly persons in the United States. *Psychiatr Serv* **59**(9): 1038–1045.

Reeves S, Stewart R, Howard R. 2002. Service contact and psychopathology in very-late-onset schizophrenia-like psychosis: the effects of gender and ethnicity. *Int J Geriatr Psychiatry* **17**(5): 473–479.

Rodriguez-Ferrera S, Vassilas CA, Haque S. 2004. Older people with schizophrenia: a community study in a rural catchment area. *Int J Geriatr Psychiatry* **19**(12): 1181–1187.

Sund R. 2012. Quality of the Finnish hospital discharge register: a systematic review. *Scand J Publ Health* **40**: 505–515.

Talaslahti T, Alanen HM, Hakko H, *et al.* 2012. Mortality and causes of death in older patients with schizophrenia. *Int J Geriatr Psychiatry* **27**(11): 1131–1137.

Talaslahti T, Alanen HM, Hakko H, *et al.* 2015. Patients with very-late-onset schizophrenia-like psychosis have higher mortality rates than elderly patients with earlier onset schizophrenia. *Int J Geriatr Psychiatry* **30**(5): 453–459.

Vaarama M. 2004. Ikääntyneiden toimintakyky ja hoivapalvelut—nykytila ja vuosi 2015 (Ability to function and services in care for older people—present state and the year 2015, in Finnish). Tulevaisuusselonteon liiteraportti 5. Valtioneuvoston kanslian julkaisusarja 33/2004.

Onset of schizophrenia at 60 years or later, so-called very-late-onset schizophrenia-like psychosis (VLOSLP), is a rare disease with a prevalence of 0.05 (Meesters *et al.*, 2012), and little is known about mortality in these patients. According to an international expert consensus panel, a diagnosis of VLOSLP is valid and useful when assessing medical treatment plans for older psychotic patients (Howard *et al.*, 2000). In terms of psychopathology, treatment response and neuropsychological aspects, VLOSLP and earlier onset schizophrenia differ distinctly from each other (Howard *et al.*, 2000; Rodriguez-Ferrera *et al.*, 2004; Mazeh *et al.*, 2005; Girard and Simard, 2008). In earlier studies, onset of schizophrenia after the age of 45 increased the risk of death compared with those with earlier onset (Ran *et al.*, 2007). There is a lack of studies comparing mortalities among older patients with schizophrenia with differing ages at onset, including VLOSLP (Healey, 2013).

In this register study consisting of 7060 patients (aged 65 or above) with schizophrenia, there were 918 (13%) patients whose probable age of onset of schizophrenia was 60 years or later. The first aim of this study was to ascertain mortality and causes of death in patients with VLOSLP as compared to general population (Standard Mortality Ratios). The second aim was to compare mortality between VLOSLP patients and those with earlier onset of schizophrenia. The register data was followed up for 10 years after entry into the study in 1999.

Methods

Data

The data was collected from Finnish nationwide registers: the Finnish Hospital Discharge Register (FHDR) and the National Causes-of-Death Register of Statistics Finland. The data was linked by the unique personal identification number of every Finnish resident. Collection of register data has been described in more detail in the earlier study (Talaslahti *et al.*, 2012). The study protocol was approved by the National Research and Development Centre for Welfare and Ethics Committee.

Study population

The original sample to be analysed was 7060 inpatients and outpatients with prevalent schizophrenia, who were at least 65 years old by 1 January 1999. From the very first original sample, consisting of all the patients of that age, those collected from pension registers were excluded because the time of probable onset of schizophrenia was impossible to check. The patients had schizophrenia or schizoaffective disorder [International Classification of Diseases (ICD)-8, ICD-9: 295, ICD-10: F20, F25] as their main psychiatric diagnosis in the Finnish Hospital Discharge Register. Schizoaffective disorder was also included because both diagnoses (F20 and F25) are under the same diagnostic category in ICD-8 and ICD-9. The onset of the disease was approximated from the first hospitalization due to any psychosis. The final sample ($n = 918$) consisted of patients given this diagnosis (or other "non-organic" psychosis which later was converted into schizophrenia) for the first time at the age of 60 years or later (very-late-onset schizophrenia-like psychosis, VLOSLP) after 1978. The mortality and causes of death of these patients were followed up from the registers for a 10-year period (1999–2008) and compared with those with onset of schizophrenia before the age of 60 years ($n = 6{,}142$). The mean time from onset of the disease to the beginning of follow-up was 7.1 years (±4.8 SD) in the VLOSLP group and 25.6 years (±6.9 SD) in the earlier onset group.

Causes of death

Time and causes of death were obtained from the official national death register maintained by Statistics Finland. This includes personal information on the deceased, the date of death, and the diagnosis on the cause of death according to the ICD-10 classification system (certified cause of death, underlying cause of death or other contributing causes of death). The validity of this register has been scientifically demonstrated elsewhere (Lahti and Penttilä, 2001).

Statistical analyses

The significance of group differences in categorical variables was assessed with Pearson's Chi-square test or Fisher's exact test, and in continuous variables with Student's *t*-test or Mann–Whitney *U*-test. Overall and cause-specific mortality were described by Standardized Mortality Ratios (SMRs) (Breslow and Day, 1987). The SMR is an epidemiologic ratio of the observed number of deaths in a study sample to the expected number of deaths calculated on the basis of the number of deaths in the reference population, which was the general Finnish population matched for sex and age, and obtained from Statistics Finland in 2010. SMRs were compared using rate ratio (RR) analysis and calculating 95% confidence intervals (CIs). Cox proportional hazard model was used to examine the difference between onset groups (below 60 years, 60 years and

over) in time from entry to the study to the death of patients or to the end of follow-up (31 December 2008) if alive. The Hazard Ratio (HR) for death and its 95% confidence interval (95%CI) was adjusted for gender, age, physical illness (circulatory disease, respiratory disease, diabetes mellitus, neoplasm, dementia, hypercholesterolemia), alcohol dependence, use of antipsychotics at baseline and at least one psychiatric hospitalization in 1994–1998. All statistical tests were two tailed. The limit for statistical significance was $p < 0.05$. Statistical analyses were conducted using PASW for Windows, version 18 (SPSS Inc., Chicago, IL, USA), or SAS for Windows, version 9.2, statistical programs (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of older patients with schizophrenia

Among the patients with schizophrenia aged 65 years or older on 1 January 1999, 543/918 (59%) of those with onset of disease at 60 years or older (VLOSLP) and 3371/6142 (55%) of those with disease onset at less than 60 years died during the 10-year follow-up from 1999 to 2008. The corresponding figures for men were 179/254 (70%) and 1316/2050 (64%), and among women 364/664 (55%) and 2055/4092 (50%). The mean age at death was higher in the VLOSLP group (78.2 ± 4.8) than in the group with earlier onset (76.0 ± 4.8) ($p < 0.001$). At the beginning of follow-up, the patients in the VLOSLP group had more diagnoses of circulatory diseases, dementias and alcoholism (Table 1).

Standardized Mortality Ratios (SMRs)

The Standardized Mortality Ratios (SMRs) were calculated to evaluate the mortality of elderly patients with schizophrenia in relation to age, gender and year of death matched to the general Finnish population. The SMRs by age and gender in both groups are given in Figure 1. The overall SMR was 5.02 (95%Cl 4.61–5.46) in the VLOSLP group and 2.93 (2.83–3.03) in the earlier onset group. In the VLOSLP group, SMR was 8.31 (7.14–9.62; $n = 179$) in males and 4.21 (3.78–4.66; $n = 364$) in females. In the earlier onset group, they were 2.91 (2.75–3.07, $n = 1316$) and 2.94 (2.82–3.07, $n = 2055$) respectively.

The causes of death having most pronounced SMRs in elderly patients with schizophrenia in both groups are presented in Table 2. The most common causes of death were similar to those of the general Finnish population of the same age and sex. Some groups of causes-of-death were too small for comparison. The SMRs of this population were increased in most cause-of-death categories and were especially high in the VLOSLP group. Unnatural causes-of-death corresponded to the highest SMR, and within this the single causes in the VLOSLP group were: accidental falls ($n = 18$), choking on food ($n = 2$) and accidental drowning ($n = 1$).

Comparison of survival between onset groups

Figure 2 illustrates the sample comparison, in which the difference in hazard of death during ten-year follow-up was assessed. Direct comparison between the VLOSLP group and those with earlier onset resulted in only a minimal difference when adjusted for the given variables (HR, 1.16 95%CI 1.05–1.27, $p = 0.003$).

Discussion

Around 1% of patients with schizophrenia are diagnosed at 60 years or older, and prevalence of schizophrenia and

Table 1 Basic health data (diagnoses in Finnish Hospital Discharge Register in 1998) of older patients with schizophrenia by onset groups (onset at 60 years or later before 60 years)

	Total ($n = 9461$)	60+[a] ($n = 918$)	60−[b] ($n = 6142$)	*P*-value		
Diagnosis at baseline	% (n)	% (n)	% (n)	χ^2	*df*	*p*
Circulatory diseases	39.9 (2753)	47.9 (440)	37.7(2313)	35.4	1	<0.001
Diabetes mellitus	14.5 (1024)	14.9 (137)	14.4 (887)	0.15	1	0.699
Neoplasm	6.1 (428)	7.2 (66)	5.9 (362)	2.35	1	0.125
Respiratory disease	8.4 (591)	9.8 (90)	8.2 (501)	2.82	1	0.093
Dementia	2.0 (138)	5.3 (49)	1.4 (89)	63.02	1	<0.001
Hypercholesterolemia	1.1 (81)	1.4 (13)	1.1 (68)	0.67	1	0.412
Alcoholism	1.2 (88)	2.2 (20)	1.1 (68)	7.45	1	0.006

[a]Onset at 60 years or later.
[b]Onset before 60 years.

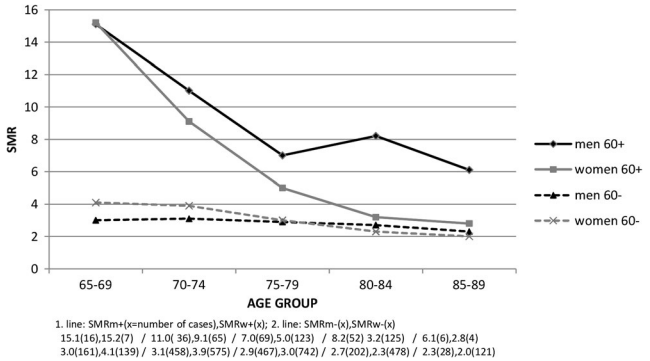


Figure 1 Total Standard Mortality Ratio (SMR) by age, gender and onset groups in schizophrenia cases over 65 years old.

schizoaffective disorder together in the age-group of 65+ is about 1% (Howard *et al.*, 2000; Perälä *et al.*, 2007). In Finland, a fifth of the population of 5.4 million is over 65 years old, and this age group is growing rapidly, as well as the number of elderly patients with schizophrenia. Therefore, studies on this issue are important.

According to the present results, mortality in older patients with schizophrenia diagnosed later in life (very-late-onset schizophrenia-like psychosis, VLOSLP) was five-fold compared to that of the age-matched general population and almost twice as high as in patients with earlier onset. Risk of death in the VLOSLP group was increased in most single causes-of-death categories such as respiratory diseases, dementias, neoplasms and circulatory diseases, but especially in unnatural causes-of-death. Various other reasons may contribute to these findings such as selection in early onset patients (only exceptionally healthy patients are still alive at the age of 65 or over). Within-sample comparison adjusted for different variables such as gender, age, physical illnesses, alcohol dependence and use of antipsychotic medication at baseline, hazard of death differed only minimally between the groups during 10 years of follow-up. Therefore, it seems that schizophrenia itself increases mortality equally in old age regardless of the time of onset of illness.

In previous studies, overall mortality in older patients with schizophrenia has been reported to be increased around three-fold and active psychosis may have a negative impact on survival time (Brown and Mitchell, 2012; Talaslahti *et al.*, 2012). As far as we know, there are no reports so far on mortality and causes of death in schizophrenia comparing patients with VLOSLP and those with earlier onset.

Gender differences and mortality

The present results also reveal clear gender differences in SMRs within the VLOSLP group: the mortality in men was around double that of women (8.31 vs. 4.21). At baseline, 72% of these patients were women. In some studies, women have also been over-represented among those who developed their first psychosis after the age of 40 or 60 (Palmer *et al.*, 2001; Meesters *et al.*, 2012). Schizophrenia has been reported to have an even more deteriorating (and perhaps more lethal) course in men leading to inability to take care of themselves and refusal to accept health care services (Kreyenbuhl *et al.*, 2009). Accordingly, in two studies on VLOSLP patients, men were reported to easily drop out of service delivery (Reeves *et al.*, 2002; Tan and Seng, 2012).

Circulatory diseases and mortality

As expected, circulatory diseases were the most common cause of death in both the VLOSLP and earlier onset group. This finding matches that in general population, but there was only a modest difference in SMRs between these subgroups of schizophrenia. Treatment with antipsychotics has been associated with an elevated risk of metabolic syndrome, diabetes mellitus and cardiovascular disease and excess mortality with unhealthy lifestyle in schizophrenia (De Hert *et al.*, 2006; Suvisaari *et al.*, 2007; Brown and Mitchell, 2012). The VLOSLP patients have no such a long history of exposure to antipsychotics as earlier onset patients;

Table 2 Causes of deaths (ICD-9 and ICD-10) in older patients with schizophrenia. Standardized Mortality Ratios and 95%confidence intervals by onset groups (onset at 60 years or later or before 60 years)

	Onset at 60 years or later ($n = 918$)				Onset before 60 years ($n = 6142$)			
Variables	SMR	95%CI	obs	exp	SMR	95%I	obs	exp
Accidents and violence	33.74	20.88–51.58	21	0.62	8.93	7.50–10.55	137	15.35
Respiratory disease	14.46	11.16–18.43	65	4.50	6.18	5.61–6.79	435	70.37
Dementia	8.57	6.69–10.81	71	8.29	3.03	2.62–3.49	197	64.99
Neoplasm	5.05	3.99–6.30	78	15.45	1.75	1.61–1.90	547	312.41
Circulatory disease	2.83	2.46–3.23	219	77.52	2.26	2.14–2.38	1461	647.57

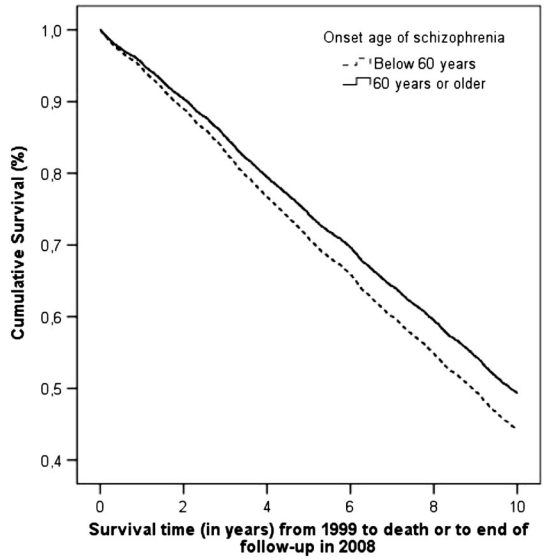


Figure 2 Survival time of elderly schizophrenia patients from the entry to the study (1 January 1999) to death or to the end of follow-up (31 December 2008) if alive.

thus, this exposure may not account for increased SMRs in VLOSLP patients. However, VLOSLP patients are often reported to have premorbid paranoid or schizoid personality, which may result in poorer access to medical care and therefore long lasting undertreatment of, e.g. circulatory illnesses.

Accidents and respiratory diseases as causes of death

Accidents leading to death occurred almost 30 times more often to VLOSLP patients than to the general age-matched population and almost three times more commonly than in old schizophrenia patients with earlier onset. There is ample data that antipsychotics as well as benzodiazepines may cause fatal falls in the elderly (Hartikainen *et al.*, 2007; Huang *et al.*, 2012), and VLOSLP may also be as patients more vulnerable to extrapyramidal symptoms than EOS patients. Thus, the impact of antipsychotics or benzodiazepines on the excess accident mortality in these patients is possible, but further conclusions cannot be drawn from this data.

SMR for respiratory diseases was more than twice as high in the present VLOSLP group as in the earlier onset group. Similarly to patients with dementia, taking antipsychotics may also be a risk factor for pneumonia in frail older patients with schizophrenia (Trifiro *et al.*, 2010). Ageing for patients with early onset schizophrenia often means some improvement in psychotic symptoms and reduction in relapses leading to hospitalizations (Jeste *et al.*, 2011). Instead, VLOSLP patients with recently diagnosed illness may require forced doses of psychotropic medication and consequently be exposed to related drug adverse effects. Even though the use of antipsychotics apparently did not increase mortality in elderly psychotic patients in some studies, antipsychotics for older patients with schizophrenia should always be administrated with caution (Suvisaari *et al.*, 2013).

Cancer mortality

In studies considering almost solely younger patients, cancer mortality in schizophrenia has been varied but generally increased (Hodgson *et al.*, 2010). In the present study, neoplasms were a more common risk of death for the present VLOSLP patients than for the other old schizophrenia patients with earlier onset. Psychiatric patients including those with schizophrenia have been reported to have more metastases at the time of diagnosis (Kisely *et al.*, 2013). Thus, cancer in VLOSLP patients may have not been found early enough perhaps due to premorbid personality traits.

Dementias

In the present study, a total of 16% of deaths were caused by dementias, and the SMR of VLOSLP group was almost three times higher than that of the earlier onset group. The International Late-Onset Schizophrenia Group has stated that there is enough evidence to justify that VLOSLP and late-onset schizophrenia (diagnosed between 40 and 59 years) can obtain independent classifications (Howard *et al.*, 2000). VLOSLP has been characterized by typical psychotic but few negative symptoms, little thought disorder, female preponderance and minor cognitive defects with widespread functional deficits and better learning capacity than in early onset schizophrenia in old age (Howard *et al.*, 2000; Palmer *et al.*, 2001). In earlier longitudinal studies, 23–35% of very late onset patients with paranoid or schizophrenic symptoms have shown stronger global cognitive deterioration than normal controls (Hymas *et al.*, 1989; Reeves *et al.*, 2002). People with late and very late onset schizophrenia have also been reported to have a three times higher risk of developing dementia compared with the general population (Korner *et al.*, 2009). The association of more rapid cognitive decline and long term care has also been reported on late onset paranoid or schizophrenic patients (Holden, 1987; Mazeh *et al.*, 2005). Behavioral symptoms of dementia and psychotic symptoms of

schizophrenia may resemble each other, but the core symptoms are usually different, and misdiagnosing may be avoided with painstaking examination and follow-up. In this study, changes in cognition could be evaluated only through mortality from dementias.

Imaging studies have reported only nonspecific changes such as higher ventricle-to-brain ratio or third ventricle volume, lower volume in the left temporal lobe or superior temporal gyrus compared with age peers and cortical and focal white-matter abnormality (Howard *et al.*, 2000; Jones *et al.*, 2005). In a recent study on the first presentation non-organic psychosis in the elderly, CT/MRI findings (those of VLOSLP patients 58.2%) were in the mild to normal range in 81.4% and the most common changes in brain structure were white matter diseases or vascular lesions (Tan and Seng, 2012).

Probably the etiology in the background of VLOSLP is multidimensional. Those becoming demented later may have originally been misdiagnosed or their schizophrenic disorder may have caused a neurodegenerative process as a consequence. The possibility of an incorrect diagnosis of schizophrenia at the very beginning of dementia might be one explanation for why the patients with VLOSLP diagnosis had higher dementia SMR rates than the other old patients with schizophrenia.

Strengths and limitations

The strength of this study is high quality Finnish national registers offering nationwide data that cover all citizens (Aro *et al.*, 1990; Lahti and Penttilä, 2001; Moilanen *et al.*, 2003). The register-based data was reliably linked with each other by using a unique personal identification code given to every Finnish citizen. About 95% of patients with schizophrenia have been hospitalized at some stage of their illness, and all the hospitalizations can be found in the Finnish Hospital Discharge Register (Isohanni *et al.*, 1997). All deaths are diagnosed by physicians, and post mortem examinations are performed if the cause of death remains uncertain. The follow-up time was long covering 10 years after entry into the study, and the sample size was large enough for reliable estimates of SMRs.

As limitations, background data such as living habits or usage of open care health services could not be obtained from these registers. The register data did not allow us to compare patients with VLOSLP and patients with other old age psychiatric conditions because the data was limited. Furthermore, it was impossible to check the reliability of the diagnoses in this register data, and the possibility that some patients have undiagnosed dementia cannot be excluded. However, the accuracy and validity of diagnosis in the psychosis category in the FHDR have been reported in earlier studies (Aro *et al.*, 1990; Moilanen *et al.*, 2003; Miettunen *et al.*, 2011; Sund, 2012). Some identity codes in the very first years of the system could be incorrect. Therefore, the inclusion for this study practically started from 1972 (Sund, 2012). There is also a slight possibility that some of the patients classified here into the VLOSLP group may have had a hospitalization before 1972 at a very young age (and no hospitalization thereafter before the age of 60 years). There may also be a considerable gap between onset of symptoms and first hospitalization, which may confound a differentiation between very late onset and other schizophrenia patients.

Conclusion

Patients, especially men, with very-late-onset schizophrenia-like psychosis (VLOSLP) are at even higher risk of death than other old patients with this disease. In the present study, overall mortality in the VLOSLP group was more than 60% higher than among the patients with earlier onset of schizophrenia. SMRs in VLOSLP patients were higher in most causes-of-death categories: accidents and violence, respiratory diseases, neoplasms, dementias and circulatory diseases. The reasons for such an excess mortality can probably be found in physical comorbidities and susceptibility to accidents. More attempts should be made to strengthen collaboration between psychiatry and primary and specialist-level somatic care and to retain old patients with schizophrenia in the health care services.

Conflict of interest

None declared.

Key points

- In this large register-based study of older patients with schizophrenia, mortality of very-late-onset schizophrenia-like psychosis (VLOSLP) was five-fold that of general sex- and age-matched population.
- In the VLOSLP patients, a higher risk of death compared with the earlier onset patients with schizophrenia seems to be a consequence of physical comorbidities and accidents.

References

Aro S, Koskinen R, Keskimäki I. 1990. Reliability of hospital discharge data concerning diagnosis, treatments and accidents. *Duodecim* **106**(21): 1443–1450.

Breslow NE, Day NE. 1987. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. *IARC Sci Publ* **82**: 1–406.

Brown S, Mitchell C. 2012. Predictors of death from natural causes in schizophrenia: 10-year follow-up of a community cohort. *Soc Psychiatry Psychiatr Epidemiol* **47**(6): 843–847.

Cowling D, Miettunen J, Jääskeläinen E, *et al*. 2012. Ageing in schizophrenia: a review. *Psychiatr Fennica* **43**: 39–68.

De Hert MA, van Winkel R, Van Eyck D, *et al*. 2006. Prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotic medication. *Schizophr Res* **83**(1): 87–93.

Girard C, Simard M. 2008. Clinical characterization of late- and very late-onset first psychotic episode in psychiatric inpatients. *Am J Ger Psychiatr* **16**(6): 478–487.

Hartikainen S, Lönnroos E, Louhivuori K. 2007. Medication as a risk factor for falls: critical systematic review. *J Gerontol A Biol Sci Med Sci* **62**(10): 1172–1181.

Healey D. 2013. Commentary. *Evid Based Ment Health* **16**(35). doi: 10.1136/eb-2012-101173

Hodgson R, Wildgust HJ, Bushe CJ. 2010. Cancer and schizophrenia: is there a paradox? *J Psychopharmacol Suppl* **24**(4): 51–60.

Holden NL. 1987. Late paraphrenia or the paraphrenias? A descriptive study with a 10-year follow-up. *Br J Psychiatry* **150**: 635–639.

Howard R, Rabins PV, Seeman MV, Jeste DV. 2000. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group. *Am J Psychiatr* **157**(2): 172–178.

Huang AR, Mallet L, Rochefort CM, *et al*. 2012. Medication-related falls in the elderly: causative factors and preventive strategies. *Drugs Aging* **29**(5): 359–376.

Hymas N, Naguib M, Levy R. 1989. Late paraphrenia - a follow-up study. *Int J Ger Psychiatr* **4**: 23–29.

Isohanni M, Mäkikyrö T, Moring J, *et al*. 1997. A comparison of clinical and research DSM-III-R diagnoses of schizophrenia in a Finnish national birth cohort. Clinical and research diagnoses of schizophrenia. *Soc Psychiatr Psychiatr Epidemiol* **32**(5): 303–308.

Jeste DV, Wolkowitz, OM, Palmer PV. 2011. Divergent trajetories of physical, cognitive and psychosocial aging in schizophrenia. *Rev Schizophr Bull* **37**(3): 451–455.

Jones DK, Catani M, Pierpaoli C, *et al*. 2005. A diffusion tensor magnetic resonance imaging study of frontal cortex connections in very-late-onset schizophrenia-like psychosis. *Am J Ger Psychiatr* **13**(12): 1092–1099.

Kisely S, Crowe E, Lawrence D. 2013. Cancer-related mortality in people with mental illness. *JAMA Psychiatr* **70**(2): 209–217.

Korner A, Lopez AG, Lauritzen L, *et al*. 2009. Late and very-late first-contact schizophrenia and the risk of dementia--a nationwide register based study. *Int J Ger Psychiatr* **24**(1): 61–67.

Kreyenbuhl J, Nossel IR, Dixon LB. 2009. Disengagement from mental health treatment among individuals with schizophrenia and strategies for facilitating connections to care: a review of the literature. *Schizophr Bull* **35**(4): 696–703.

Lahti RA, Penttilä A. 2001. The validity of death certificates: routine validation of death certification and its effects on mortality statistics. *Forensic Sci Int* **115**(1–2): 15–32.

Laursen TM, Wahlbäck K, Hällgren J, *et al*. 2013. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophreniain the Nordic countries. *PLoS One* **24**(8): e67133. DOI: 10.1371/journal.pone.0067133

Mazeh D, Zemishlani C, Aizenberg D, Barak Y. 2005. Patients with very-late-onset schizophrenia-like psychosis: a follow-up study. *Am J Ger Psychiatr* **13**(5): 417–419.

Meesters PD, de Haan L, Comijs HC, *et al*. 2012. Schizophrenia spectrum disorders in later life: prevalence and distribution of age at onset and sex in a Dutch catchment area. *Am J Ger Psychiatr* **20**(1): 18–28.

Miettunen J, Suvisaari J, Haukka J, *et al*. 2011. Use of register data for psychiatric epidemiology in the Nordic countries. In Textbook in Psychiatric Epidemiology, 3rd edn., Tsuang M, Tohen M, Jones P (eds.) John Wiley & Sons: Chichester, West Sussex; 117–131.

Moilanen K, Veijola J, Läksy K, *et al*. 2003. Reasons for the diagnostic discordance between clinicians and researchers in schizophrenia in the Northern Finland 1966 Birth Cohort. *Soc Psychiatry Psychiatr Epidemiol* **38**(6): 305–310.

Palmer BW, McClure FS, Jeste DV. 2001. Schizophrenia in late life: findings challenge traditional concepts. *Harv Rev Psychiatry* **9**(2): 51–58.

Perälä J, Suvisaari J, Saarni SI, *et al*. 2007. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatr* **64**(1): 19–28.

Ran MS, Chen EY, Conwell Y, *et al*. 2007. Mortality in people with schizophrenia in rural China: 10-year cohort study. *Br J Psychiatry* **190**: 237–242.

Reeves S, Stewart R, Howard R. 2002. Service contact and psychopathology in very-late-onset schizophrenia-like psychosis: the effects of gender and ethnicity. *Int J Ger Psychiatr* **17**(5): 473–479.

Rodriguez-Ferrera S, Vassilas CA, Haque S. 2004. Older people with schizophrenia: a community study in a rural catchment area. *Int J Ger Psychiatr* **19**(12): 1181–1187.

Sund R. Quality of the Finnish hospital discharge register: a systematic review. 2012. *Scan J Public Health* **40**: 505–515.

Suvisaari JM, Saarni SI, Perälä J, *et al*. 2007. Metabolic syndrome among persons with schizophrenia and other psychotic disorders in a general population survey. *J Clin Psychiatry* **68**(7): 1045–1055.

Suvisaari JM, Partti K, Perälä J, *et al*. 2013. Mortality and its determinants in people with psychotics disorders. *Psychosom Med* **75**(1): 60–67.

Talaslahti T, Alanen HM, Hakko H, *et al*. 2012. Mortality and causes of death in older patients with schizophrenia. *Int J Ger Psychiatr* **27**(11): 1131–1137.

Tan LL, Seng KH. 2012. First presentation psychosis among the elderly in Singapore. *Singapore Med J* **53**(7): 463–467.

Trifiro G, Gambassi G, Sen EF, *et al*. 2010. Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. *Ann Intern Med* **152**(7): 418–425.