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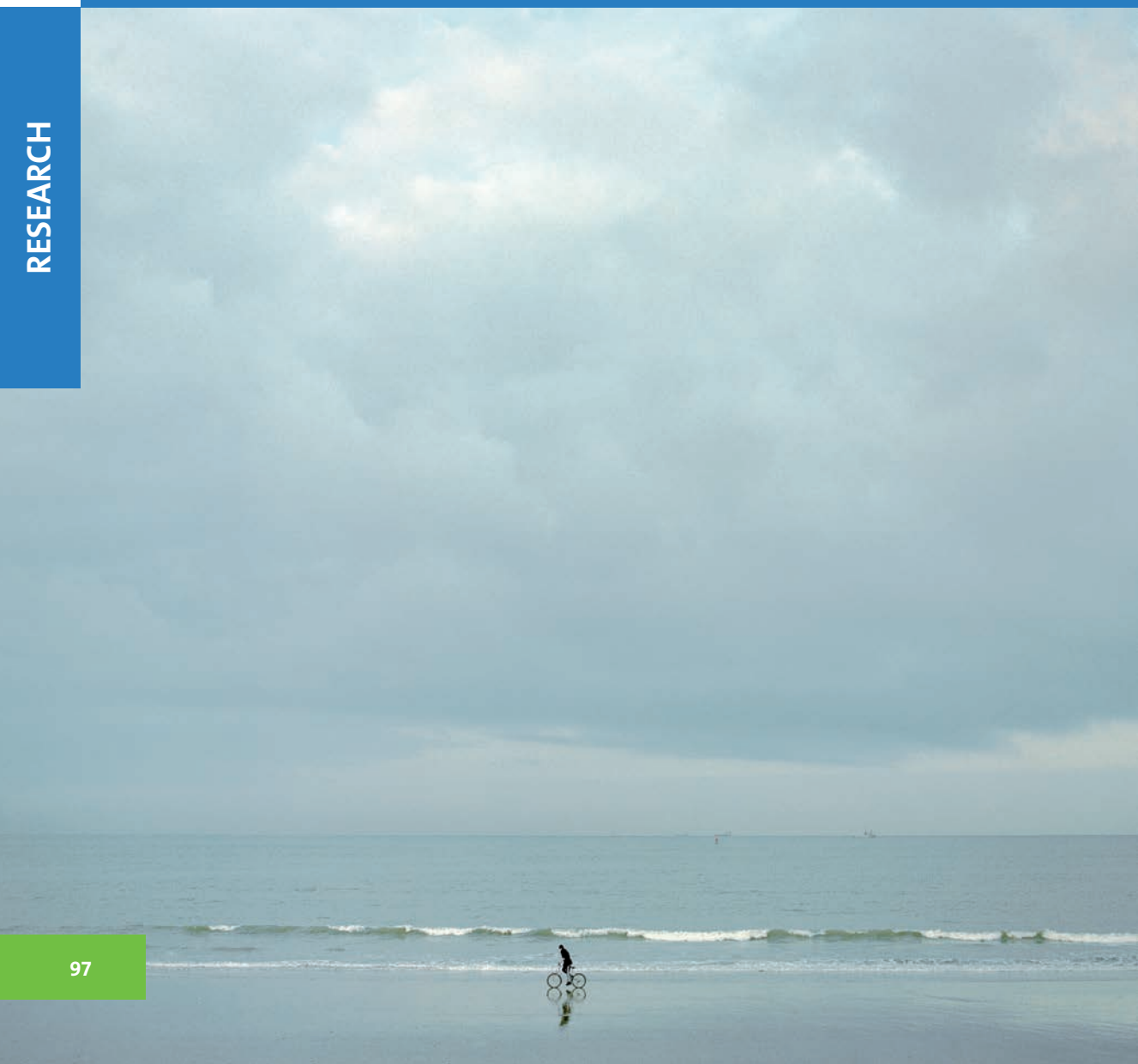
Jonna Perälä

Epidemiology of Psychotic Disorders



RESEARCH

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Jonna Perälä

Epidemiology of Psychotic Disorders

ACADEMIC DISSERTATION

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National Institute for Health and Welfare
Department of Mental Health and Substance Abuse Services
Helsinki, Finland

and

University of Helsinki
Department of Psychiatry
Helsinki, Finland

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Supervisors
Professor Jouko Lönnqvist MD, PhD
Department of Mental Health and Substance Abuse Services,
National Institute for Health and Welfare, Finland
and
Department of Psychiatry
University of Helsinki, Finland

Adjunct Professor Jaana Suvisaari MD, PhD
Department of Mental Health and Substance Abuse Services,
National Institute for Health and Welfare, Finland
and
Department of Social Psychiatry,
University of Tampere, Finland

Reviewers
Professor Jarmo Hietala MD, PhD
University of Turku
Department of Psychiatry

Adjunct Professor Olli Kampman MD, PhD
University of Tampere
Department of Psychiatry

Opponent
Professor Juha Veijola
University of Oulu
Department of Psychiatry
Finland

To my Family

Abstract

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Schizophrenia and other psychoses are among the most severe and impairing medical diseases. They often cause lifelong disability and the affected subjects have increased physical morbidity and shortened life expectancy. Only few general population studies of psychotic disorders have been conducted. These studies of psychotic disorders have been burdened with many methodological difficulties. Most epidemiological studies have focused on schizophrenia and bipolar I disorder, while data of many other specific psychotic disorders are scarce.

This thesis investigated the lifetime prevalence and epidemiological features of psychotic disorders in the Finnish general population. The data were derived from the Health 2000 Study, a comprehensive general population survey of Finnish adults aged 30 years and over (N=8028). In the Psychoses in Finland study, the Health 2000 Study sample was screened for psychotic disorders. Those selected by the screens were invited for a mental health interview. Final best-estimate DSM-IV diagnoses were based on systematic evaluation of the interview and the case note data.

The lifetime prevalence of any DSM-IV psychotic disorder was 3.5%. The most common psychotic disorder was schizophrenia. Non-affective psychoses were more common than affective psychoses. Substance-induced psychotic disorders were common among working aged men and psychotic disorder due to general medical condition among women aged 65 years or over. Psychotic disorders were generally associated with socioeconomic disadvantage like being unmarried, pensioned or unemployed; having low income or education level. Geographic distributions of psychotic disorders were assessed using university hospital regions and categorization of urban and rural areas for the place of birth and residence. The highest lifetime prevalence was found in northern and eastern, and lowest in south-western parts of Finland. The region of birth was a more important determinant of the risk of psychotic disorders than the region of residence or urban-rural categorization, and most marked in schizophrenia.

Clinical features of some specific psychotic disorders were studied in more detail. Alcohol-induced psychotic disorder was common among working age men. Low socioeconomic status, high comorbidity, high use of medical services and very high mortality were found among the affected subjects, even when compared to subjects with alcohol dependence but no psychosis. Delusional disorder was found to be a

different disorder from paranoid schizophrenia and was characterized by high age of onset, absence of other symptoms than delusions and relatively good outcome. Disorganized subtype of schizophrenia was associated with early onset, male preponderance, chronic course, long hospitalizations and poor outcome. Paranoid and undifferentiated schizophrenia resembled each other.

In conclusion, psychotic disorders are more common in the general population than has been estimated in most recent general population studies. The high prevalence of psychotic disorders challenges the old interpretation of evenly distributed prevalence of psychotic disorders worldwide. These results of high and unevenly distributed prevalence of psychotic disorders provide tools for developing the health care systems. Best possible individual treatment and rehabilitation should be provided to minimize any disadvantage related to psychotic disorders.

Keywords: Psychotic disorders, schizophrenia, alcohol-induced psychotic disorder, delusional disorder, lifetime prevalence, general population, geographic variation, epidemiology.

Tiivistelmä

Jonna Perälä. Epidemiology of Psychotic Disorders [Psykoottisten Häiriöiden Epidemiologia]. Terveyden ja hyvinvoinnin laitos (THL). Tutkimus 97/2013. 130 sivua. Helsinki, Finland 2013.
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Skitsofrenia ja muut psykoottiset häiriöt kuuluvat vaikeimpiin ihmiskuntaa kohtaavista sairauksista. Häiriöihin liittyy usein elinikäinen toimintakyvyn heikkeneminen, suuri fyysinen sairastavuus ja lyhentynyt elinikä. Psykoottisten häiriöiden esiintyvyydestä on tehty vain vähän väestötutkimuksia. Tutkimuksiin liittyy monia menetelmällisiä ongelmia. Useimmat epidemiologiset tutkimukset ovat keskittyneet skitsofrenian ja tyypin I kaksisuuntaiseen mielialahäiriöön. Monista muista psykoottisista häiriöistä on vain vähän väestötason tietoa.

Tässä väitöskirjassa selvitettiin psykoottisten häiriöiden elämänaikaista esiintyvyyttä ja esiintyvyyteen liittyviä piirteitä suomalaisessa aikuisväestössä. Tutkimusaineisto perustuu kattavaan Terveys 2000 väestötutkimukseen yli 30 -vuotiaiden suomalaisten terveydentilasta ja toimintakyvystä (N = 8028). Psykoosit Suomessa -jatkotutkimukseen seulottiin 746 osallistujaa käyttämällä tutkimusta varten kehitettyä psykoosiseulaa. Heidät kutsuttiin tarkempaan mielenterveyshaastatteluun. Mielenterveyshäiriöt diagnosoitiin DSM-IV -tautiluokituksen mukaisia diagnostisia kriteereitä käyttäen, hyödyntäen sekä haastattelu- että potilaskertomustietoja.

Kaikkien psykoottisten häiriöiden elämänaikainen esiintyvyys Suomessa oli 3.5 %. Yleisin psykoosi oli skitsofrenia. Ei-mielialaoireiset psykoosit olivat yleisempiä kuin mielialaoireiset psykoosit. Päihdepsykoosit olivat yleisiä työikäisillä miehillä ja yleissairauteen liittyvät psykoosit yli 65-vuotiailla naisilla. Psykoottiset häiriöt olivat yhteydessä matalaan sosioekonomiseen asemaan. Erityisesti ei-mielialaoireiseen psykoosiin sairastuneet olivat useammin naimattomia, työttömiä ja eläkeläisiä tai alhaisten peruskoulutuksen ja tulotason omaavia kuin yleisväestö. Psykoottisten häiriöiden alueellisia eroja tarkasteltiin viiden yliopistosairaala-alueen sekä kaupunki- että maaseutuympäristön välillä. Häiriöitä esiintyi eniten Pohjois- ja Itä-Suomessa ja vähiten Lounais-Suomessa. Syntymäpaikka oli asuinpaikkaa tai kaupunki- tai maaseutuympäristöä tärkeämpi psykoottisen häiriön ja erityisesti skitsofrenian riskiin vaikuttava tekijä.

Tässä tutkimuksessa kartoitettiin tarkemmin tiettyjen psykoottisten häiriöiden piirteitä. Alkoholiin liittyvä psykoottinen häiriö oli erityisen yleinen keski-ikäisillä miehillä. Matala sosioekonominen asema, runsas samanaikaissairastuvuus, runsas terveyspalvelujen käyttö ja korkea kuolleisuus olivat yleisempiä alkoholipsykoosin

sairastaneilla kuin muilla alkoholiriippuvaisilla. Harhaluuloisuushäiriö erosi skitsofrenian alatyypeistä. Sille oli ominaista myöhäinen sairastumisikä, vähäinen muiden oireiden kuin harhaluulojen esiintyvyys ja suhteellisen hyvä ennuste. Hajanaisoireiseen skitsofreniaan liittyi varhainen sairastumisikä, miessukupuoli, krooninen kulku, pitkät sairaalahoidot sekä huono ennuste. Paranoidinen ja erilaistumaton skitsofrenia sen sijaan muistuttivat toisiaan.

Tämän tutkimuksen perusteella psykoottiset häiriöt ovat yleisempiä kuin useissa viimeaikaisissa väestötutkimuksissa on arvioitu. Psykoottisten häiriöiden korkea esiintyvyys haastaa vanhan tulkinnan maailmanlaajuisesti tasaisesti jakautuneesta psykoottisten häiriöiden esiintyvyydestä. Tulokset psykoottisten häiriöiden esiintyvyyden alueellisesta vaihtelusta voidaan hyödyntää terveydenhuollon järjestelmiä kehitettäessä. Psykoottisiin häiriöihin liittyvät haitat tulisi minimoida tarjoamalla parasta mahdollista yksilöllistä hoitoa ja kuntoutusta.

Avainsanat: Psykoottiset häiriöt, skitsofrenia, alkoholipsykoosi, harhaluuloisuuhäiriö, esiintyvyys, väestötutkimus, alueelliset erot, epidemiologia.

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II Jonna Perälä, Samuli I Saarni, Aini Ostamo, Sami Pirkola, Jari Haukka, Tommi Härkänen, Seppo Koskinen, Jouko Lönnqvist, Jaana Suvisaari. Geographic variation and sociodemographic characteristics of psychotic disorders in Finland. Schizophrenia Research 2008, 106, 337-47.

III Jonna Perälä, Kimmo Kuoppasalmi, Sami Pirkola, Tommi Härkönen, Samuli I Saarni, Satu Viertiö, Annamari Tuulio-Henriksson, Antti Latvala, Seppo Koskinen, Jouko Lönnqvist, Jaana Suvisaari. Alcohol-induced psychotic disorders in the general population. British Journal of Psychiatry 2010, 197, 200-206.

IV Jaana Suvisaari, Jonna Perälä, Samuli I Saarni, Hannu Juvonen, Annamari Tuulio-Henriksson, Jouko Lönnqvist. The epidemiology and descriptive and predictive validity of DSM-IV delusional disorder and subtypes of schizophrenia. Clinical Schizophrenia & Related Psychoses 2009B, 289-297.

Abbreviations

AIPS	Alcohol-induced psychotic syndrome (includes alcohol-induced psychotic disorder and delirium)
AD	Alcohol dependence
AUD	Alcohol use disorders
BPI	Bipolar I disorder
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
DSM	Diagnostic and Statistical Manual for Mental Disorders
DSM-IV-TR	Diagnostic and Statistical Manual for Mental Disorders, 4th Edition, Text Revision
GMC	General medical condition
HR	Hazard ratio
ICD	International Classification of Diseases
LTP	Lifetime prevalence
M-CIDI	Munich Composite International Diagnostic Interview
MDD	Major depressive disorder
MSSS	Major Symptoms of Schizophrenia Scale
NOS	Not otherwise specified
OECD	Organization for Economic Co-operation and Development
OR	Odds ratio
PIF	Psychoses in Finland study
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SCID	Structured Clinical Interview for DSM-IV
WHO	World Health Organization

1 Introduction

Although schizophrenia and other psychoses are not very frequent disorders, they are among the most severe and impairing medical diseases (Insel, 2010). Active psychosis was ranked the most disabling condition after quadriplegia and dementia in a WHO multi-country study (Ustün et al., 1999). Psychotic disorders cause enormous suffering for patients and their family members. As the average age of onset for many psychotic disorders is at the most critical period of educational, occupational and social development, their consequences often lead to lifelong disability. These patients also have increased physical morbidity and mortality compared with population without a psychotic disorder (De Hert et al., 2011, Kiviniemi et al., 2010, Saha et al., 2007, Tiihonen et al., 2009, 2012). Economic costs to society consist of the expense of treatment and loss of productivity. The costs of psychotic disorders were estimated to be the third largest of brain diseases in Europe in 2010, after mood disorders and dementia (Gustavsson et al., 2011).

Schizophrenia and bipolar I disorder are the most common of psychotic disorders. Most studies of epidemiology have focused on them. However, other psychoses also cause long-term disabilities (Widerlöv et al., 1997), and the distinction between schizophrenia and other psychoses is still quite challenging (Dikeos et al., 2006). There are many studies investigating differences and similarities on genetics, brain structures, neuropharmacological mechanisms, neuropsychological functioning and environmental risk factors of psychotic disorders (Murray et al., 2004). Still, the pathogenesis of psychosis is far from fully understood. Thus, broader inclusion of psychotic disorders in epidemiological studies may be a useful agenda.

Few population-based studies on psychotic disorders have been conducted in the last decades (Kendler et al., 1996, Kessler et al., 2005, van Os et al., 2001), many of them focusing on non-affective and affective psychotic disorders as groups. Only one study has estimated the prevalence of specific psychotic disorders (Bogren et al., 2009). General population studies have faced increasing problems in case finding and ascertainment (Jablensky, 1995). Survey response rates have fallen, and people with psychotic disorders, especially schizophrenia, are less likely than others to participate in mental health surveys (de Graaf et al., 2000, Haapea et al., 2007, 2008). Studies that are not able to use information other than from interviews seem to produce lower estimates compared with studies having access to other sources of information (Saha et al., 2005). Regardless of the problems, general population data are needed. If studies on psychotic disorders were based on clinical samples, our knowledge of psychotic disorders would be biased towards the most severe and chronic types of psychotic disorders.

The Psychoses in Finland (PIF) study is based on the Health 2000 Study, a general population survey of adults aged 30 years and over living in mainland Finland. It is a comprehensive general population survey of the prevalence of psychotic disorders in terms of diagnostic assessment and diagnostic coverage. The aim of this study was to report for the first time the prevalences of all specific psychotic disorders separately in one study. Besides determining the prevalence, sociodemographic correlates, regional distribution and clinical features of psychotic disorders which are investigated in this thesis, the aim of the PIF project was to study neuropsychological functioning, somatic comorbidity and its causes, functional disability, and quality of life in psychotic disorders.

2 Review of the literature

2.1 Diagnostic classification of psychotic disorders

Psychotic disorders have been classified according to different systems during the last 150 years (Tandon et al., 2009). Current psychiatric diagnostic classifications are based on operational diagnostic criteria. The goal of the operational diagnostic criteria is to define and describe the disorders in terms of simple signs and symptoms, which are externally observable and often behavioural symptoms. This is necessary as knowledge of aetiology in psychiatric disorders is still limited.

Psychotic disorders according to the definition on the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000) are presented in Table 1. DSM-IV is currently the most often used diagnostic system in international research practice. Individual psychotic disorders are distinguished from each other based on the duration, dysfunction, type of delusions and hallucinations, presence of depression and mania, and associated substance use or medical condition.

Psychotic symptoms are conventionally characterized to be the central features of schizophrenia and other non-affective psychotic disorders, while affective psychoses and secondary psychoses are often regarded as disorders where psychotic symptoms are present as an associated feature. In different psychotic disorders, different aspects of psychosis are emphasized. In schizophrenia, schizoaffective disorder, schizophreniform disorder and brief psychotic disorder psychotic symptoms include delusions, prominent hallucinations, disorganized speech and disorganized or catatonic behaviour. In psychotic forms of mood disorder, e.g. bipolar I disorder and MDD, delusions and hallucinations are the only symptoms included in the diagnostic criteria. In psychotic disorder due to general medical condition or substance induced psychotic disorder, only delusions and hallucinations without insight are regarded as psychotic. Thus, even between the DSM-IV diagnoses, the definition of psychosis is varying. Modifications to these definitions have been suggested for the DSM-V criteria that will be published in 2013 (Tandon, 2012).

Table 1. Psychotic Disorders in the DSM-IV-TR (American Psychiatric Association, 2000)

Non-affective psychotic disorders	
	Schizophrenia
	Schizoaffective disorder
	Schizophreniform disorder
	Delusional disorder
	Brief psychotic disorder
	Shared psychotic disorder
	Psychotic disorder NOS
Affective psychotic disorders	
	Bipolar I disorder with psychotic features
	Major depressive disorder with psychotic features
Substance-induced psychotic disorder	
	Alcohol-induced psychotic disorder
	Other substance-induced psychotic disorder
Psychotic disorder due to a general medical condition	

As the aetiology and pathogenesis of psychiatric disorders are largely unknown, the diagnostic classification is based on symptoms and sets of symptoms. At the beginning of the history of psychiatric nosology, the different definitions of psychotic disorder were based on the "great professor principle" (Kendler, 1990, 2010). Most famous among these have been the descriptions by Kraepelin, Bleuler and Schneider, all of whom emphasized different aspects of the psychotic disorders. All of these authors have had their own impact on the subsequent psychiatric classifications, but the differentiation of the dementia praecox (later named as schizophrenia) and manic depression has formed the basis of the classification of psychoses over the last 100 years. The World Health Organization (WHO) first tried to develop a universal diagnostic system and the International Classification of Diseases (ICD-6) was published in 1948. The first version of the Diagnostic and Statistical Manual for Mental Disorders (DSM) was published in 1952. Soon after this, the first revisions ICD-8 and DSM-II were published (Tandon et al., 2009). However, the diagnostic practices were varying for decades. It was shown that in the 1960s and 1970s American psychiatrists diagnosed schizophrenia more often than

British psychiatrists, who were more likely to diagnose affective disorders (Kramer, 1969). The large variation in diagnostic practices promoted the development of the psychiatric nosology based on scientific knowledge (Kendler, 1990) and this research was very active in the 1980s and 1990s. The first operational diagnostic criteria such as Feighners Criteria (Feighner et al., 1972), the Research Diagnostic Criteria (Spizer et al., 1978), DSM-III (American Psychiatric Association, 1980) and DSM-III-Revised (American Psychiatric Association, 1987) were introduced earlier in the United States than in Europe (WHO, 1992). In fact, DSM-IV (American Psychiatric Association, 2000) and ICD-10 classifications of psychotic disorders are largely based on dividing endogenous psychoses into dementia praecox and manic depressive insanity proposed by Emil Kraepelin (1919). This dichotomy, currently called schizophrenia and bipolar disorder, is still today under continuous critical discussion. Already Kreapelin recognized that many patients present symptoms from both disorders, and this "in-between" concept was later named as schizoaffective disorder (Kasanin, 1933).

The diagnostic criteria of schizophrenia have been narrowed since the introduction of the DSM-III criteria (Andreasen et al., 1993, Andreasen, 1997). Concordance between diagnoses made using DSM-III and more recent criteria and those using more historical definitions are only modest (McGorry et al., 1992). At the same time the diagnostic criteria of affective disorders have been widened (Tohen and Angst, 2002). Manic depressive and depressive disorders were separated from each other already in the ICD-8, and the diagnostic criteria for recurrent depressive disorder were introduced in the DSM-III and ICD-10. Depressive disorder with psychotic features was described in the DSM-III.

The tenth edition of the International Classification of Diseases ICD-10 (WHO, 1992) is most often used in clinical practice. Although the definitions of psychotic disorders in the current DSM-IV and ICD-10 classifications overlap to a great extent, there are still some differences. For example, in the diagnostic criteria of schizophrenia, ICD-10 gives slightly more weight to the Schneider's first-rank symptoms: audible thoughts, voices arguing and/or discussing, commenting voices, somatic passivity experiences, thought withdrawal or broadcasting, delusional perception, made impulses, thoughts, or volitional acts (Carpenter et al., 1973), than the DSM-IV. The duration of illness is 6 months in the DSM-IV and 1 month in the ICD-10. The differentiation of schizophrenia, schizoaffective disorder and affective disorders also vary. The DSM-IV stresses poor outcome in schizophrenia, while this criteria is not included in the ICD-10. Both systems require exclusion of substance use and general medical condition. The concordance of the diagnostic systems seems to be higher in studies including subjects with long duration of illness (Pihlajamaa et al., 2008).

The aim the diagnostic classification is the diagnostic validity. Diagnostic validity is a complex construct, which First et al. (2004) listed as:

- Face validity: Whether the diagnostic criteria seem to accurately describe the disorder.
- Descriptive validity: Whether the diagnostic criteria specify a disorder uniquely relative to other disorders.
- Predictive validity: Whether the diagnosis is predictive of future clinical course and outcome.
- Construct validity: The extent to which the diagnosis correlates with external validators, such as neurobiological markers or genetic risk.

Psychiatric diagnoses often lack construct validity (Jablensky et al., 2006, Zachar et al., 2007). For example, the risk of many psychotic disorders is elevated in same families, suggesting that they partly share a common genetic cause (Lichtenstein et al., 2009). Neuropsychological deficits occur in many psychotic disorders, but they may be more severe in schizophrenia (Lewandowski et al., 2011, Tuulio-Henriksson et al., 2011). Multifactorial aetiology of disorders makes it difficult to determine the construct validity (Kendler et al., 1980). Psychiatric diagnoses should also be helpful in clinical practice, i.e. have clinical utility. The clinical utility guides the choice of effective interventions and the prediction of future clinical management needs, and provides information on prognosis (First et al., 2004, Kendell and Jablensky, 2003). Predictive and descriptive validity of psychiatric diagnoses are among the most decisive factors in clinical utility.

2.1.1 Description of specific psychotic disorders

Schizophrenia

Schizophrenia is one of the most common and severe psychotic disorders. In fact it is a cluster of disorders characterized by fundamental disturbances of thinking, perception and emotions. The onset of schizophrenia is often in young adulthood, and for those affected the disorder often causes many years of severe suffering. The course and symptoms in individual patients are highly variable, but for a smaller group the disorder causes lifelong disabilities with deterioration in functional capacity (Insel, 2010). A recent meta-analysis found a median proportion 13.5% (25%–75% quantiles 8.1%–20.0%) of recovery in schizophrenia (Jääskeläinen et al., 2012).

Diagnostic criteria of schizophrenia in the DSM-IV are presented in Table 2. Some signs of the disorder have to persist at least six months to permit the diagnosis. During this continuous period, at least two of the following symptoms should be

present for at least one month: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, or negative symptoms. Social and occupational dysfunction is an essential characteristic of schizophrenia (American Psychiatric Association, 2000).

The subtypes of schizophrenia in the DSM-IV are paranoid, disorganized, catatonic, undifferentiated and residual types. The subtype diagnoses are hierarchic. Catatonic type is assigned if prominent catatonic symptoms are present regardless of other symptoms. In the absence of catatonic type, the disorganized type is assigned if disorganized speech and behaviour, and flat or inappropriate affect are present. In the absence of catatonic and disorganized type, the paranoid type is diagnosed if the person has prominent delusions or hallucinations and no or only mild negative and disorganized symptoms. Finally, undifferentiated type is assigned if none of the above mentioned criteria are fulfilled, but the symptoms fulfilling the diagnostic criteria of schizophrenia are present. Residual type is diagnosed when active-phase symptoms are no longer present, but there is continuing evidence for the disturbance (American Psychiatric Association, 2000).

Schizophreniform disorder

Schizophreniform disorder is basically identical with schizophrenia except that the duration of the disorder is at least one month, but full recovery in 6 months is required. Another difference is that decline in functioning is not required in diagnostic criteria of schizophreniform disorder, while decline in social and occupational function is one criteria of schizophrenia. The diagnosis is often provisional; if symptoms persist beyond six months, the diagnosis is changed to schizophrenia (American Psychiatric Association, 2000).

Schizoaffective disorder

In schizoaffective disorder, the full criteria of both the active phase of schizophrenia and a mood episode (major depressive episode, manic or mixed episode) should be met. During the same period of illness, there must be at least a 2 week period of delusions or hallucinations without prominent mood symptoms. Symptoms that meet criteria for a mood episode should be present for a substantial proportion of the total duration of the active and residual periods of the illness (American Psychiatric Association, 2000).

Table 2. Diagnostic Criteria for Schizophrenia (DSM-IV-TR, American Psychiatric Association, 2000).

A. Characteristic symptoms: Two or more of the following symptoms should be present for a significant portion of time during a one-month period (or less if successfully treated):
(1) Delusions
(2) Hallucinations
(3) Disorganized speech
(4) Grossly disorganized or catatonic behavior
(5) Negative symptoms

Only one Criterion A symptom is required, if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B. Social / occupational dysfunction: For a significant proportion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or if the onset is in childhood or adolescence, failure to achieve the expected level of functioning).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms, or two or more symptoms listed in Criterion A in an attenuated form.

D. Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either 1) no major depressive, manic or mixed episodes have occurred concurrently with the active-phase symptoms; or 2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance / general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance or a general medical condition.

F. Relationship to a pervasive developmental disorder: If there is a history of Autistic disorder of another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Delusional disorder

Delusional disorder is characterized with one or more non-bizarre delusions persisting at least 1 month. Other prominent active-phase symptoms of schizophrenia should not be present, except that tactile and olfactory hallucinations may be present if they are related to the delusional theme. Apart from the impact of delusion or its ramifications, functioning is not markedly impaired and behaviour is not obviously odd or bizarre (American Psychiatric Association, 2000).

Brief psychotic disorder

Brief psychotic disorder is characterized by sudden onset of psychotic symptoms (delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour) which last at least one day or more, but no longer than one month. After this, a full remission and return to the premorbid level of functioning should be achieved (American Psychiatric Association, 2000).

Bipolar I disorder

Bipolar I disorder BPI is an affective type of psychosis, characterized with one or more manic or mixed episodes, usually accompanied with major depressive episodes. Psychotic symptoms, which have to be delusions or hallucinations, can occur during manic, mixed and severe depressive episodes. Typical mood-congruent psychotic symptoms during manic episoders include grandiosity and persecutory delusions linked to some special features of the person. Mood-incongruent psychotic symptoms include persecutory delusions without grandiose themes or delusions of thought insertion, thought broadcasting or being controlled.

Bipolar II disorder diagnosis means that person has had at least one hypomanic, but no manic or mixed episodes, and one major depressive episode. Bipolar II disorder may also include psychotic symptoms during the severe depressive episodes. Bipolar I disorder leads to hospitalizations, need for treatment, and decline in daily functioning more often compared with bipolar II disorder (American Psychiatric Association 2000).

Major depressive disorder with psychotic features

Major depressive disorder with psychotic features is diagnosed when the criteria for major depressive disorder episode are met and delusions or hallucinations occur within the episode. Mood-congruent delusions or hallucinations are consistent with the depressive themes (delusions of guilt, delusions of deserved punishment, nihilistic delusions etc.). Mood-incongruent delusions or hallucinations do not have any apparent relationship to depressive themes (persecutory delusions, delusions of thought insertion, delusions of control etc.) (American Psychiatric Association, 2000).

Substance-induced psychotic disorder

Substance-induced psychotic disorders are characterized by prominent hallucinations or delusions that are judged to be due to the direct physiological effects of a substance (drug of abuse, a medication, or a toxin exposure). Substance-induced psychotic disorders are distinguished from the substance-induced delirium (clear consciousness), from substance intoxication or withdrawal with perceptual disturbances (more persistent, clinically relevant symptoms, and the person has no insight) and from primary psychotic disorders. The onset of substance use typically precedes the onset of psychotic symptoms, and the symptoms should disappear within one month after the substance use has ceased.

Psychotic symptoms can occur during intoxication or withdrawal of the following classes of substances: alcohol, sedatives, hypnotics and anxiolytics, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, phencyclidine and related substances. Some medications can also evoke psychotic symptoms (for example antiparkinsonian medications, corticosteroids, anticholinergic agents, antimalarial medications and chemotherapeutic agents). The clinical picture of the psychotic disorder varies depending on the substance (American Psychiatric Association 2000).

Psychotic disorder due to a general medical condition

Psychotic disorder due to a general medical condition is a category with the essential feature of prominent hallucinations or delusions. These symptoms can be judged to be due to the direct physiological effects of a general medical condition, and they are not explained by any other mental disorder. Clear temporal association should be found between the general medical condition and the onset of psychotic disturbance. Additionally, there must be literature evidence on the particular medical condition causing psychotic symptoms. Examples of general medical conditions that can cause psychotic symptoms include temporal lobe epilepsy, brain lesions and tumours, central nervous system infections and any severe medical condition requiring treatment in intensive care unit (American Psychiatric Association, 2000).

Other psychotic disorders

Shared psychotic disorder is a rare condition where an individual develops a delusion in a close relationship with another person, who has an already established delusion. The content of the delusion is similar to that of the person who already has the established delusion (American Psychiatric Association, 2000).

Delirium is a condition characterized by disturbance of consciousness and cognition which may have psychotic symptoms as an associated feature (American Psychiatric Association 2000). The aetiology of delirium varies, including substance-induced delirium and delirium due to a general medical condition. Despite the aetiology, the

disturbance develops over a short period of time, usually hours to days, and tends to fluctuate during the course of the day.

Psychotic disorder NOS is a category, which is used when psychotic symptoms (delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour) occur, but a specific diagnosis of any psychotic disorder cannot be made. There may be inadequate information to make a specific diagnosis, the information is contradictory or symptoms do not meet full criteria for a specific psychotic disorder. The diagnosis is assigned for example if 1) a postpartum psychosis does not meet criteria for a specific psychotic disorder, 2) psychotic symptoms have lasted for less than 1 month but have not yet remitted, 3) persistent auditory hallucinations occur in the absence of any other psychotic feature, 4) persistent non-bizarre delusions occur with periods of overlapping mood episodes that have been present for a substantial portion of the delusional disturbance, 5) there is uncertainty about whether psychotic symptoms are primary or due to substance use or general medical condition (American Psychiatric Association, 2000).

2.1.2 Delusional disorder and subtypes of schizophrenia

Some inter-diagnostic boundary issues in DSM-IV have received little attention, although these were discussed more during earlier stages of the DSM classification development. Two such examples are the diagnostic classification of psychoses with paranoid symptoms, i.e. between delusional disorder and paranoid schizophrenia, and the diagnostic validity of subtypes of schizophrenia.

Paraphrenias were defined already by Kraepelin as an entity separate from the dichotomy of dementia praecox and manic depressive insanity. These paranoid disorders were characterized by delusions and hallucinations, no prominent disorders of emotion and volition, and well preserved mental activities (Kraepelin, 1919). The nosological history of subtypes of schizophrenia is also long (Bleuler, 1950, Kraepelin, 1919) for example, hebephrenia and catatonia are older concepts than schizophrenia itself (Bleuler, 1950).

The validity of different definitions of psychoses with paranoid symptoms and schizophrenia subtypes was investigated actively during the formulation of the diagnostic operationalisations of DSM-III and DSM-III-R (Fenton & McGlashan, 1991, Kendler et al., 1981, 1984, 1994, Kendler & Hays, 1981, Kendler & Tsuang, 1981, McGlashan & Fenton, 1991). The diagnosis of delusional disorder was introduced in the DSM-III-R as a result of throughout nosological work (Kendler, 1980, Kendler and Tsuang, 1981). The validity of the DSM-III-R delusional disorder criteria was investigated in the early 1990s (Fennig et al., 1996, Kendler and Walsh,

1995), but little attention has been paid to the validity of the revised DSM-IV criteria.

Concurrent with the introduction of the criteria for delusional disorder, the criteria set in the DSM-III for different schizophrenia subtypes were modified for the DSM-III-R. These criteria were refined further for the DSM-IV. Paranoid schizophrenia was narrower in the DSM-III-R compared with the DSM-IV. The DSM-III-R criteria required the presence of either systematized delusions or auditory hallucinations related to a single theme. The criteria of disorganized schizophrenia are, in contrast, narrower in the DSM-IV. This diagnosis requires that disorganized speech, disorganized behaviour, and flat or inappropriate affect should all be prominent (American Psychiatric Association, 1994), while only one of the two first mentioned symptoms were required in the DSM-III-R.

In DSM-IV, prominent delusions are the core feature of both delusional disorder and paranoid schizophrenia. These disorders are differentiated by requiring that persons with delusional disorder may not have bizarre delusions or prominent hallucinations, and that their functioning should not be markedly impaired and behaviour obviously odd or bizarre - apart from the impact of delusion or its ramifications (American Psychiatric Association, 2000). Paranoid schizophrenia is characterized by preoccupation with one or more delusions or frequent auditory hallucinations, and by the absence of prominent thought disorder, disorganized or catatonic behaviour, and flat or inappropriate affect (American Psychiatric Association, 2000). Symptoms of schizophrenia must be present for at least six months, whereas only one month duration is required in delusional disorder (American Psychiatric Association, 2000). In practice, both disorders tend to last for years.

Little attention has been paid to the validity of the current delusional disorder diagnosis and schizophrenia subtypes criteria, even though a small change in diagnostic criteria can have a large impact on the validity of the diagnosis (Kendler et al., 1994a, Kupfer et al., 2002). However, research has been active recently when DSM-V has been planned (Pillmann et al., 2012a,b, Wustmann et al., 2011, 2012). The prevalence and outcome of the disorders has varied according to the used criteria (Bogren et al., 2009, Kendler 1980, 1981, Kendler and Tsuang 1981, Leboyer et al., 1990). The age at onset of psychotic symptoms has been found to be higher and the outcome better in subjects affected with delusional disorder than with schizophrenia (Kendler 1980, 1982, Marneros et al., 2012), although contradictory results of the age of onset of delusional disorders come from some clinical samples (Hsiao et al., 1999, Maina et al., 2001, Opjordsmoen et al., 1991). However, diagnosis of delusional disorder may be inconsistent in the early phase of the illness (Fennig et al., 1996, Schwartz et al., 2000), but it seems to be stable during later phases (Marneros et al., 2012). Subjects with delusional disorder are less often

hospitalized, and for shorter periods compared with subjects with schizophrenia (Marneros et al., 2012). These findings support the need for longitudinally based diagnostic assessment, and need for more general population samples in addition to clinical studies.

Results on the validity of delusional disorder as a separate disease from schizophrenia have been contradictory. Family studies have suggested that delusional disorder might not be genetically linked to schizophrenia (Howard et al., 1997, Kendler et al., 1981, Kendler and Walsh 1995). However, patients with delusional disorder resemble patients with schizophrenia in many neurobiological features like having abnormalities in eye movements (Campana et al., 1998, Gambini et al., 1993), cognitive deficits (Evans et al., 1996, Hardoy et al., 2004) and brain structural abnormalities (Howard et al., 1994). Contrary with the original description of paranoia by Kraepelin (Kraepelin, 1919), marked depressive symptoms have been found to associate with delusional disorders in some studies based on clinical samples (Hsiao et al., 1999, Maina et al., 2001, Serretti et al., 1999). The aetiological relationship between delusional disorder and major depressive disorder has been suggested to be stronger than the connection between delusional disorder and schizophrenia (Howard et al., 1997). However, all studies have not found the association with depressive symptoms (Marneros et al., 2012).

Subtypes of schizophrenia have not been included in the recent general population studies, and the knowledge of their occurrence is scarce. In previous studies, there has been more males than females in each subtype (Kendler et al., 1994a), although the results are contradictory (Fenton and McGlashan, 1991). Studies comparing the course and outcome of schizophrenia subtypes suggest that each subtype has distinctive course and outcome (Fenton and McGlashan, 1991, Kendler et al., 1984, 1994, McGlashan and Fenton, 1991). The age at onset has been found to be youngest in disorganized subtype and oldest in paranoid subtype and outcome best in paranoid and worst in disorganized schizophrenia (Fenton and McGlashan, 1991, Kendler et al., 1984, 1994, McGlashan and Fenton, 1991). Course and outcome of undifferentiated schizophrenia has resembled disorganized schizophrenia more than paranoid schizophrenia in the studies using DSM-III and DSM-III-R criteria (Fenton and McGlashan 1991, Gruenberg et al., 1985, Kendler et al., 1984, 1994). No differences in the familial risk for schizophrenia between the subtypes have been found (Kendler et al., 1994b, Peralta and Cuesta, 2007).

2.2 Epidemiology of psychotic disorders

Epidemiology means the study of the distribution and determinants of disease in human populations. The distributions of diseases are often studied by age, gender, region, social class, marital status, ethnicity and occupational status (Woodward, 1999).

Different measures of frequency are used in different settings and for different purposes when estimating the number of people in a community who have the studied disease. Incidence is the number of new cases of the disease within a specified period of time. It is expressed as the rate per person years. Cumulative incidence is the proportion of all people who develop the disease during a defined period. The denominator includes all people at risk for getting the disease, for example all persons in a certain birth cohort. Prevalence is the number of persons in a determined population who have a particular health condition at a time point or period. A period prevalence uses the same denominator as the time point prevalence, but it expands the numerator to include all cases present during a selected time period, like one month, six months, one year or lifetime. Lifetime prevalence allows individuals with chronic psychiatric conditions and temporarily in remission, to be included in prevalence counts. Thus, the lifetime prevalence of psychotic disorders is determined as the total number of cases now alive, presently of previously actively psychotic, divided by the size of the population studied (Tsuang and Tohen, 2002, p. 6). The lifetime risk or lifetime morbid risk is a measure which reflects the risk of a disease up to certain age. It is the probability of having a disesase for a person who survives through the susceptibility period to manifest the disorder. The problem is that there does not seem to be an age after which the chance of developing the disease is 0, and the total lifetime risk is thus usually unknown (Thompson and Weissmen, 1981).

Lifetime prevalence can be assessed in cross-sectional general population studies. It is a useful measure for example in service planning. Incidence is a better measure when causes of the disease are being investigated. The prevalence depends on the incidence, but it also depends on the duration of the disease and number of entries and exits in the studied population (for example births, deaths and migration). (Tsuang and Tohen 2002, p. 6)

2.2.1 Population-based studies on psychotic disorders

Most of the epidemiological studies of psychotic disorders have focused on schizophrenia and bipolar disorder. History of general population studies on psychotic disorders started with studies that relied on clinical diagnoses obtained from key informants, medical records or case registries (Jarvis, 1971, Faris and Dunham, 1939). However, diagnostic practices were varying and record-based

diagnoses were not necessarily a reliable source of information at the time. After the introduction of the first modern nosologic systems, the first structured interviewing methods were also introduced. Studies focused mainly on treated patients, and their attention was on representative sampling, use of structured diagnostic interviews and focus on first-admission patients (Jablensky et al., 1992). The next step of epidemiologic studies on psychoses were studies that combined modern community sampling techniques with structured interview approaches to case identification. The first large scale study of this type was the Epidemiologic Catchment Area ECA Study (Robins and Regier, 1991), in which lay interviewers administered the Diagnostic Interview Schedule DIS. However, it was noted that the diagnosis of schizophrenia obtained with these structured interviews was not congruent with psychiatrists' classification (Helzer et al., 1985, Spengler and Wittchen, 1988). To provide more reliable and valid rate estimates of schizophrenia and other psychoses, two-stage procedures for case identification have since been used (Phillips et al., 2009). Clinical re-interviews by telephone have been conducted with subjects who were screened for psychotic disorders with a structured interview administered by a lay interviewer, for example in the National Comorbidity Survey NCS (Kendler et al., 1996), the Netherlands Mental Health Survey and Incidence Study NEMESIS (van Os et al., 2001) and National Comorbidity Survey-Replication NCS-R (Kessler et al., 2005).

Besides the modern two-stage procedures, general population studies have relied either on psychiatric hospital case notes or national registers. These studies produce estimates of the treated prevalence, which does not include the proportion of subjects without hospital treatment, estimated at up to 15%-25% of subjects with schizophrenia (Isohanni et al., 1997, Jörgensen et al., 2010, Scully et al., 2004, Youssef et al., 1999). Studies based on the national registers are dependent on the accuracy of the diagnoses and studies based on the case notes are dependent on the diagnostic quality. There are not many register- based studies which have been able to confirm register diagnoses of psychotic disorder with interviews and/or review of the case notes (Arajärvi et al., 2005, Bogren et al., 2009, Isohanni et al., 1997, Kieseppä et al., 2000, Pihlajamaa et al., 2008, Sellgren et al., 2011). However, in studies where hospital registers or case records have not been available, prevalence rates of psychotic disorders have tended to be lower (Kessler et al., 2005, Kendler et al., 1996, Van os et al., 2001), probably reflecting the multiple methodological challenges in case finding and ascertainment in the general population. National registers have notable strengths regarding e.g. statistical power and representativeness and they also enable studying rare disorders, in which the study samples otherwise have to be enormous in numbers. However, the validity of the registers, and careful examination of the possible sources of bias are of main importance when studying register information (Haukka et al., 2007, Haapea et al.,

2008). National registers have been available only in the Nordic countries (Tsuang et al., 2011, s. 117).

One problem inherent to identification of subjects with psychotic disorder in general population studies is that there is no established method for screening individuals with psychotic disorders in the general population. Methods that have been developed (Bebbington et al., 1995) are usually sensitive and specific, but their positive predictive value remains poor because of the the prevalence of psychosis is low in the general population (Bebbington et al., 1995). Structured interviews, such as Diagnostic Interview Schedule and different versions of Composite International Diagnostic Interview have been used for screening non-affective psychoses in previous large scale community surveys (Kessler and Ustün, 2004). The questions assessing psychotic symptoms in these interviews were designed to normalize reports about delusions and hallucinations in order to make the reporting of the symptoms easier. An undesired consequence was that such questions have produced many false positive cases due to misinterpretation of questions according to clinical re-interviews (Kendler et al., 1996, Kessler et al., 2005, Regeer et al., 2004). The number of false negatives, as well as the magnitude of non-response is extremely difficult to estimate in these studies (Jablensky, 2000, Kessler et al., 2005).

Diagnostic procedures in recent general population studies have largely relied on the information from interviews. However, using only a single source of information seems to lead to a significant risk of missing symptoms (Eaton et al., 2007, Fanous et al., 2012). Studies that have used case notes in addition to semi-structured interviews have found more subjects having psychotic disorders compared to studies using only self-reported information (Bogren et al., 2009, Isohanni et al., 2001, Kendler et al., 1993, Lehtinen et al., 1990, McNaught et al., 1997, Östling et al., 2002). Scandinavian studies have been pioneers in this approach (Larsson and Sjögren 1948, Lehtinen et al., 1990, Lehtinen et al., 1993). Altogether, the most reliable studies are studies that integrate information from different sources; national registers, semi-structured interviews, information from case records or other important sources (Bebbington et al., 2004, Bogren et al., 2009, Isohanni et al., 2001, Jenkins et al., 1997, Saha et al., 2006).
General population studies of bipolar I disorder have not usually used two-stage strategies (Merikangas et al., 2011) and the diagnoses have been based on CIDI interviews. Only a few studies have used multiple sources of information for diagnostic assessment (Bogren et al., 2009).

2.2.2 Prevalence of psychotic disorders

Schizophrenia and bipolar I disorder are the most common psychotic disorders, and most of the epidemiological studies of psychotic disorders have focused on these, especially on schizophrenia. General population studies of other specific psychotic disorders have been scarce. The usual practice has been to report non-affective and affective psychotic disorders as groups in general population studies (Kendler et al., 1996, Kessler et al., 2005, Kirkbride et al., 2006, Lehtinen et al., 1990, van Os et al., 2001). Sometimes the group "other psychoses" has been used, variably including substance-induced psychotic disorders (Kirkbride et al., 2006) and psychoses related to general medical conditions or not (Lehtinen et al., 1990, 1993). Psychotic-like symptoms have been found to be over ten times more common compared with psychotic disorders in general population (Nuevo et al., 2012, van Os et al., 2001).

In the recent general population studies of psychotic disorders using two-stage strategies, the lifetime prevalence (LTP) in non-affective disorders has varied from 0.5% to 1.6% (Kendler et al., 1996, Kessler et al., 2005, van Os 2001), in schizophrenia from 0.12% to 1.3% (Bijl et al., 1998, Bland et al., 1988, Canino et al., 1987, Chen et al., 1993, Scully et al., 2004, Wittchen et al., 1992, Robins et Regier 1991) and in affective psychoses from 0.4% to 1.14% (Lehtinen et al., 1990, van Os et al., 2001).

Only few general population studies have been able to use register and case note data and have taken into account all psychotic disorders, or assessed specific psychotic disorders in the same study. The recent Lundby study (Bogren et al., 2009) found a 50-year period prevalence of 4.2% and LTP 2.82% for all psychotic disorders. The 50-year period prevalence estimate included all subjects in the original study population cohort, also persons deceased before follow-up. This estimate is thus higher than the lifetime prevalence. The LTP represented cohort subjects alive at the 40-year follow-up. The 50-year period prevalence was 2.25% for non-affective psychotic disorders, 0.62% for affective psychoses (including BPI, bipolar II disorder and bipolar disorder NOS) and 1.35% for secondary psychoses or delirium. The LTPs were 1.38%, 0.42% and 1.02%, respectively (Bogren et al., 2009). In the previous Finnish general population survey (Mini-Finland Survey, 1978-1980), the lifetime prevalence for any psychotic disorder was found to be 2.2%, for schizophrenia 1.3%, for affective psychoses 0.4% and for other psychoses 0.5% (Lehtinen et al., 1990). Studies conducted among subjects in public treatment services have produced lower estimates (Jablensky 2000, Morgan et al., 2012).
The British incidence study AESOP also studied a wide category of psychotic disorders and found the distribution of the new onset cases being 67% for non-affective, 28% for affective and 5% for substance-induced psychoses (Kirkbride et

al., 2006). The magnitudes of the psychosis groups were similar in a meta-analysis of British incidence studies (Kirkbride et al., 2012).

Although the general assumption of the lifetime prevalence of schizophrenia has been 1% throughout the world (Hirschfeld, 2001, Mueser & McGurk, 2004) , the median lifetime prevalence was found to be considerably lower, only 0.4% (10%-90% quantiles 0.16-1.21) in a comprehensive systematic review of prevalence in schizophrenia (Saha et al., 2005). The systematic review included a large number of studies related to the prevalence of schizophrenia published between 1965–2002. Particularly the recent population-based surveys (Kessler et al., 2005, Van Os et al., 2001, Kendler et al., 1996) have found considerably lower prevalence of schizophrenia than many older studies (Torrey, 1987, Lehtinen et al., 1990). These unconvincingly low prevalence estimates may be a result of several reasons. These could include narrowing of the diagnostic criteria of schizophrenia after the introduction of the DSM-III criteria (Andreasen et al., 1993, Andreasen, 1997), a true decline in the prevalence, but potentially also increasing problems in case-finding and ascertainment (Jablensky, 1995). Survey response rates have declined steadily for the past decades (Kessler et al., 2005). At the same time people with psychotic disorders are less likely than others to participate in a mental health survey (Allgulander, 1989, Bland et al., 1988, Kessler et al., 1995, 2005, Haapea et al., 2008). If the only source of information have been from personal interviews, false negative cases may have been generated due to inadequate probing or denial of prior psychotic symptoms (Helzer et al., 1985, Kendler et al., 1996, Kessler et al., 2005, Spengler et al., 1988). Supporting this, studies that have used information from hospital discharge registers or case notes have found higher prevalences (Lehtinen et al., 1990, Östling et al., 2002, Isohanni et al., 2001) compared with studies that have relied only on information from the interviews. The quality of studies, defined by different methodological features such as case ascertainment methods and method of diagnostic assignment have been found to be parallel with the reported schizophrenia prevalence estimates (Saha et al., 2005).

The incidence of schizophrenia has been found to be higher in men compared with women (Aleman et al., 2003), with male/female ratio of 1.4 (10 and 90 percent quantiles 0.3-2.4) found in the recent systematic review (McGrath et al., 2004). Some studies including older subjects have found no gender differences (Bogren et al., 2009). However, the gender difference has not been reflected in prevalence studies of schizophrenia (Saha et al., 2005). Some of the discrepancy in the estimates could be explained by more severe negative (Salokangas et al., 2007) and disorganized symptoms (Sharma et al., 1999; DeLisi et al., 2001, Tang et al., 2007, Thorup el al., 2007), poorer outcome (Grossman et al., 2006, Lauronen et al., 2007), earlier onset (Häfner et al., 2003) and higher mortality (Heilä et al., 2005) in men. However, the reason for this paradox is not clear (McGrath et al., 2008).

Diagnosing schizoaffective disorder is complex, and it is rarely included in general population studies. In older studies, it has been often grouped together with schizophrenia (Hovatta et al., 1997, Lehtinen et al., 1990). The prevalence of schizoaffective disorder has conventionally been thought to be up to half of that of schizophrenia and higher in women compared with men (Bardenstein et al., 1990). However, in the few existing studies very low prevalence estimates around 0%-0.11% have been found (Bogren et al., 2009, Cho et al., 2007, Scully et al., 2004). In service-based studies, one-year prevalence of 0.07% among adult population (Widerlöv, 1997) and 0.14% among population over 60 years old (Meesters et al., 2012) have been found. Results of gender differences are contradictory, some finding no gender differences (Laursen et al., 2007, Meesters et al., 2012, Scully et al., 2004, Widerlöv, 1997) others suggesting that the disorder is more common in women than in men (Coryell et al., 1984).

Psychotic disorders with brief duration were rare in the Lundby study. LTP for schizophreniform and brief psychotic disorders were 0% and 0.11%, respectively (Bogren et al., 2009). In cross-sectional general population studies, LTP estimates vary from 0.02 to 0.2 for schizophreniform disorder (Bland et al., 1988, Canino et al., 1987, Chen et al., 1993, Cho et al., 2007, Hwu et al., 1989, Oakley-Browne et al., 1989, Robins et al., 1984, Robins and Regier, 1991) and 0.9% for brief psychotic disorder (Cho et al., 2007). The diagnosis of acute psychoses changes to mainly schizophrenia and related disorders or affective disorders in about 60% of the new cases during the following 3-6 years (Castagnini et al., 2008, Singh et al., 2004), while about one third of the affected subjects functioned well after 7 years without medication (Pillmann et al., 2005). Differences in diagnostic practices make it difficult to compare the results between countries (Nugent et al., 2011).

Delusional disorder has been rarely included in general population studies. The LTP estimate of 0.30% was found in the Lundby study (Bogren et al., 2009), while other studies have found estimates ranging from 0.02%-0.04% (Copeland et al., 1998, Kendler et al., 1982, Widerlöv, 1997). In two studies using CIDI as diagnostic instrument, the LTP has varied from 0% (Cho et al., 2007) to 0.67% (Hwu et al., 1989). Recent clinical samples have produced low estimates (Maina et al., 2001).

The data on epidemiology of bipolar I disorder has not been as extensive as on schizophrenia, but in the last decades the research has shown a welcome increase. In bipolar I disorder, like in schizophrenia, the lifetime prevalence used to be reported as approximately 1% (Merikangas et al., 2009). In a recent World Mental Health Survey of 11 different countries, a LTP of 0.6% (range 0.0-1.0%) was found (Merikangas et al., 2011). Other recent general population surveys have commonly found higher lifetime prevalence rates for BPI, but the range is wider from 0% to 3.3% (Alhasnawi et al., 2009, Angst et al., 1998, Grant et al., 2005, Gureje et al.,

2006, Jonas et al., 2003, Kessler et al., 1994, Merikangas et al., 2007, 2009, Pini et al., 2005, ten Have et al., 2002, Weissman et al., 1996) than in the World Mental Health Survey (Merikangas et al., 2011). As opposed to non-affective psychotic disorders, most recent studies have used fully structured interviews for diagnosing bipolar disorders (Ferrari et al., 2011). Studies using older versions of fully structured interviews have found LTPs of BPI twice as high as studies using other diagnostic instruments (Waraich et al., 2004), which may be due to false positive diagnoses produced by these interviews when compared with clinical diagnoses (Kessler et al., 1997, Regeer et al., 2004). Accordingly, comparably low LTP 0.34% for bipolar disorders was found in the recent Lundby study where multiple sources of lifetime information were used for diagnostic assessment (Bogren et al., 2009). In Ireland, LTP 0.26% was found (Scully et al., 2004). The most recent and advanced version of the CIDI, the WHO-CIDI 3.0, was used in the World Mental Health Survey. This instrument was found to be equally reliable at diagnosing bipolar disorders when compared with clinical interviews, such as the the Structured Clinical Interview for DSM (SCID) interview (Kessler et al., 2006, Merikangas et al., 2011). However, the reappraisal studies have been based on a small number of possible bipolar disorder cases, and evaluation of false negative cases is a major challenge. In addition to methodological issues hampering the interpretation of the results, the changes in diagnostic criteria (Angst et al., 2004, Regeer et al., 2004) may be one reason why many older studies have detected lower estimates for BPI (Angst et al., 1998, Lehtinen et al., 1990).

Psychotic states of bipolar I disorder have rarely been reported separately, but they have been found to vary from 20% to around 70% of subjects with BPI (Suominen et al., 2009). Psychotic symptoms in mood disorders have been associated with poorer functioning, more severe symptomology, and a worse outcome and psychosocial functioning compared with mood disorders without psychotic symptoms (Canuso et al., 2008, Coryell et al., 2001, Goes et al., 2007, Keller et al., 2007, Kempf et al., 2005, Matthews et al., 2009). In psychotic mood disorders delusions and hallucinations are the only symptoms included in the diagnostic criteria, while for example disorganized behaviour is not regarded psychotic (Hua et al., 2011). Men and women have similar prevalence of bipolar disorder (Grant et al., 2005, Jonas et al., 2002, Merikangas et al., 2007, ten Have et al., 2002, Waraich et al., 2004), but the results are contradictory (Merikangas et al., 2011). There may be gender differences in clinical features and course of bipolar disorder (Suominen et al., 2009). In clinical cohorts, men have preponderance in BPI (Mantere et al., 2004) and bipolar disorder seems to be better recognized in men (Mantere et al., 2008, Viguera et al., 2001).

MDD with psychotic features, like other characteristic specifiers of MDD, have rarely been included in general population studies of major depressive disorders.

The Lundby study found a lifetime prevalence of 0.28% for MDD with psychotic features (Bogren et al., 2009). In the Epidemiologic Catchment Area study, the lifetime prevalence was estimated at 0.6% (Johnson et al., 1991), and point prevalence estimate at 0.4% was found in a community survey conducted by telephone interview (Ohayon et al., 2002). Other studies have been conducted among psychiatric outpatients (Gaudiano et al., 2009) or in hospital samples (Coryell et al., 1984, Tohen et al., 2012) in which 5.3%-25% of patients with MDD have had delusions or hallucinations.

Relatively little research has been conducted related to other psychotic conditions in community samples, particularly substance-induced psychotic disorders and psychotic disorders due to general medical conditions (Bogren et al., 2009).

2.2.3 Occurrence of psychotic disorders in Finland

In Finland there is a long tradition of epidemiological studies on the most severe mental disorders (Alanen, 1966, Kaila, 1942, 1966). Previous studies have found a considerably higher prevalence of schizophrenia in Finland than the median prevalence in the review by Saha et al. (2005). In the pioneer Finnish general population survey (Mini-Finland Survey, 1978-1980), the lifetime prevalence of any psychotic disorder was found to be 2.2% (schizophrenia 1.3%, affective psychoses 0% and other psychoses 0.5%) in the age group of 30 years and over (Lehtinen et al., 1990). Register data and clinical examination were used for case ascertainment. Structured psychiatric interview (Present State Examination interview) and register information were used for diagnosing mental disorders. Case notes were included in the complicated cases (Lehtinen et al., 1991). In a more recent register-based study, the prevalence of schizophrenia, schizophreniform disorder and schizoaffective disorder together was 1.2% (Hovatta et al., 1997). In the Northern Finland 1966 Birth Cohort study the cumulative incidence of psychoses has been estimated (Isohanni et al., 2001, Moilanen et al., 2010). By the age of 34, 111 of approximately 10 000 subjects had been diagnosed with schizophrenia, 26 with other non-affective psychoses and 19 with affective psychoses. The lifetime prevalence of psychotic disorders including the psychosis related to dementia, was 2.9% in the UKKI (Uusikaupunki-Kemijärvi) study (Lehtinen et al., 1993).
The prevalence and incidence of bipolar I disorder in previous Finnish studies has been low (Kieseppä et al., 2004, Räsänen et al., 1998, Sorvaniemi and Salokangas, 2005, Veijola et al., 1996, Väisänen, 1975). The prevalence of affective psychoses in the Mini-Finland Survey was 0.4% (Lehtinen et al., 1991). Prevalence of psychotic depression has not been studied separately in Finland. In the Health 2000 Study, 3.4% of those with major depression were estimated to have had a severe episode with psychotic features according to the CIDI interview (Pirkola et al., 2005).

Altogether, previous research suggests that the prevalence of schizophrenia is high and bipolar disorder is rare in Finland compared with several other countries. If these are true differences, it means that the future potential to identify risk and protective factors of these disorders could be exceptionally good in Finland. However, there has been debate on whether the observed prevalence differences are merely caused by diagnostic inaccuracy (Taiminen et al., 2001).

2.2.4 Sociodemographic features in psychotic disorders

Over-representation of psychotic disorders among lower socioeconomic groups is well established (Lehtinen et al., 1991, Isohanni et al., 2001, Miettunen et al., 2007, Morgan et al., 2012). The association of lower social class and psychoses has been an interest since the early 20th century (Faris and Dunham, 1939). Also in recent general population studies, non-affective psychotic disorders have been found to associate with low socioeconomic status: low education, low income levels, unemployment and being unmarried; never married, separated, widowed, or divorced (Kendler et al., 1996, Kessler et al., 2005, Miettunen et al., 2007, Honkonen et al., 2007). Many older studies of bipolar disorder have suggested that bipolar disorder is more common in upper socioeconomic classes (Winokur, 1969). However, recent epidemiological studies have found that bipolar disorder is associated with lower income and education, and with being divorced or unemployed (Grant et al., 2005, Jonas et al., 2003, Kessler et al., 1997, Merikangas et al., 2007). Even though bipolar disorder has been found to associate with personal low income levels (Grant et al., 2005, Merikangas et al., 2007) it may not be associated to family income (Merikangas et al., 2007). Overall, the socioeconomic difficulties seem to be less pronounced in affective psychoses compared with non-affective group (Gureje et al., 2002, Waghorn et al., 2012). Presenting sociodemographic features of non-affective and other psychotic disorders from the same studies has been scarce.

The question whether lower social class is a cause (causation hypothesis) of consequence (selection hypothesis) of psychotic disorders has not been resolved (March et al., 2008). Low social class could result from psychotic disorder by selection or drift, usually folded into a common category of selection. Selection is an intergenerational process by which individuals are selected into lower social positions before and during the prodromal phase of the disorder. Drift is an intragenerational process by which already affected persons occupy lower social positions (March et al., 2008). One Finnish study suggested association with higher, but not with lower social position of the parents in subjects with schizophrenia (Mäkikyrö et al., 1997).

Both current and chronic social deprivation act in cumulative way in increasing the risk of psychosis (Cantor-Graae, 2007, Morgan et al., 2008). The individuals experiencing several aspects of social deprivation, e.g. being unemployed, living alone, being single, having poor education or having no close friends are at particular risk (Morgan et al., 2008). This may apply for both non-affective and affective psychoses (Morgan et al., 2008), even though the associations with affective psychosis are less marked, and some studies have also found contradictory results (Jones et al., 1993).

In most of the recent general population studies, populations have been selected from residential/household units. Persons living in institutions and homeless persons have not been included (Kendler et al., 1996). However, schizophrenia is well over-represented in homeless compared with non-homeless subjects (Folsom and Jeste 2002, Folsom et al., 2005, Foster et al., 2012, Teesson et al., 2004). In a systematic review the average prevalence of schizophrenia among the homeless was estimated at 11% (range 4%–16%, Folsom and Jeste, 2002). Even though institutionalization and homelessness are highly variable in different countries, also the prevalence, age, gender distribution and socioeconomic characteristics may have a larger than thought impact on the results (Ran et al., 2009).

2.2.5 Geographic variation in psychotic disorders

Geographic comparisons in the prevalence of schizophrenia have been of interest since the end of 19th century, with multiplied number of epidemiological studies since the 1950s. There is substantial variation in the incidence and prevalence of schizophrenia when considered worldwide (McGrath et al., 2004, 2008, Saha et al., 2005), although the claim of evenly distributed incidence and lifetime throughout the world still persists in some literature (Mueser and McGurk, 2004, Hirschfeld, 2001). In systematic reviews, the central 80% of the estimates of prevalence and incidence showed around 5-fold differences (McGrath et al., 2004, Saha et al., 2005), while some older reviews have found up to 13-fold differences (Eaton, 1985, Goldner et al., 2002, Torrey, 1987) in the prevalence. In comparison, there are six- to nine-fold differences between countries in the prevalence of heart diseases, which is another disease entity with multifactorial aetiology (Thom et al., 1985).

In addition to variation between countries, occurrence of schizophrenia varies within countries. Up to threefold differences in prevalence have been found between different parts of countries (Torrey and Bowler, 1990, Scully et al., 2004, Youssef et al., 1999). There are also population isolates with exceptionally low (Egeland and Hostetter, 1983, Chen et al., 1993, Nimgaonkar et al., 2000) and high prevalence of schizophrenia (Böök et al., 1978, DeLisi et al., 2001, Hovatta et al., 1997, Varilo and Peltonen, 2004).

Urban-rural differences in psychotic disorders

Faris and Dunham showed already in the 1930s that rates of first hospital admission for schizophrenia were higher in the centre of the city than in the periphery (Faris and Dunham, 1939). Recently, urban-rural differences in schizophrenia have been actively studied (Krabbendam, 2005, Lederbogen et al., 2011, van Os, 2010, Vassos et al., 2012). It has been clearly shown that in many countries the risk of schizophrenia is about two times higher in persons born or raised in urban areas compared with rural areas (Harrison et al., 2003, Lewis et al., 1992, Marcelis et al., 1998, Mortensen et al., 1999, Pedersen and Mortensen, 2001, Scully et al., 2004, Sundquist et al., 2004, Van Os et al., 2001, Vassos et al., 2012). Similar result have been found for other non-affective psychoses (Harrison et al., 2003, Kirkbride et al., 2006, Laursen et al., 2007). A dose-response relation has been found in many studies: the higher the population density in the area, the higher the risk of schizophrenia (Van Os et al., 2001, Pedersen and Mortensen, 2001, March et al., 2008). Residing in urban area around the onset of illness is also associated with higher risk for schizophrenia to some extent (Sundquist et al., 2004), but the urban place of birth (Marcelis et al., 1998) and being raised in urban areas (Pedersen and Mortensen, 2001) are even more relevant. The most significant associations of increased risk of schizophrenia related to urban environment have been found in large metropolitan areas among the western societies like Denmark, the Netherlands, Sweden, United Kingdom and USA (March et al., 2008, Kelly et al., 2010). Contrary to this, negative results have been found for example from Finland (Suvisaari et al., 1999), Italy (Thornicroft et al., 1993), China (Phillips et al., 2009) and Australia (Mcgrath et al., 2001). Although urban-rural differences in the occurrence of schizophrenia have been shown in incidence studies (McGrath et al., 2004, Vassos et al., 2010) the association is not as clear in prevalence studies (Saha et al., 2005).

It has been suggested that urban lifestyle itself does not increase the risk of psychotic disorders. Instead, it can be regarded as a proxy variable for factors that more directly contribute to risk for schizophrenia (Keshavan et al., 2011). These factors responsible for or mediating the risk are still unknown. Several aspects including both environmental and genetic factors have been hypothesized to be of importance. Family history of schizophrenia and other severe mental illness (Pedersen and Mortensen, 2001, Van Os et al., 2003, 2004) as well as different environmental risk factors affecting from prenatal stages of life (Freeman, 1994, Takei et al., al 1995, Cannon et al., 2001) have been studied. Toxic exposures, vitamin D deficiencey, nutrition, infections, stress, variety of sociocultural factors or artifacts of selective migration (Eaton et al., 2000, Freeman, 1994, Pedersen and Mortensen, 2006a,b, Selten et al., 2007) have been included among such factors. Obstetric complications or maternal education did not mediate the association between urban environment and psychosis in one study (Harrison et al., 2003).

Recent studies suggest that different area level determinants (Zammit et al., 2010) like social capital (Allardyce et al., 2005, Kirkbride el al., 2008) and social fragmentation (March et al., 2008) and deprivation are strongly linked to psychotic disorders within cities. Similar area related characteristics associate with admissions in schizophrenia also in rural areas (Losert et al., 2012).

Prominent geographic or urban-rural variation differences do not exist in affective psychoses, especially in bipolar I disorder (Eaton et al., 2000, Kirkbride et al., 2007a, Laursen et al., 2007, Lloyd et al., 2005, Marcelis et al., 1998, Mortensen et al., 2003, Laursen et al., 2007, Scully et al., 2004). However, in the recent World Mental Health Survey (Merikangas et al., 2011), the LPT of BPI varied from 0% to 1.0% between different countries, while comparison with earlier studies is difficult due to differences in diagnostic methods and definitions (Waraich et al., 2004). Information on urban-rural differences in the occurrence of other psychotic disorders has been scarce.

The classification of urbanization has varied across studies according to the study focus, for example higher population density can be linked to the higher risk for infections. However, the results have usually remained regardless of different definitions of the urban environment (Harrison et al., 2003). In Sweden and USA, in spite of a detected increased risk for schizophrenia and non-affective psychoses in urban areas compared with rural areas, the rates of non-affective psychoses have been highest in sparsely populated areas (Harrison et al., 2003, Torrey and Bowler, 1997). Sparsely populated areas do not exist in many countries where urban-rural differences have been studied.

One challenge in studying urban-rural differences is that these regions vary by natural, cultural and social characteristics even within Europe (Ballas et al., 2003). For example in the UK, people in rural areas have lower proportions of limiting long-term illnesses, have higher education and own their houses more often compared with people in the urban areas. The situation has been quite contradictory in Finland, where the rural parts of the country have been least developed (Palmgren et al., 1964, Vaarama et al., 2010). Thus, it is very likely that the risk attributable to "urban" environment varies significantly in different sociocultural settings. Consistently with this, possible mechanisms acting in different levels of the environmental structures and contributing to the risk of an individual have been studied (Zammit et al., 2010, March et al., 2008). Recent interest has particularly focused on social capital and social fragmentation (March et al., 2008).

Social capital involves characteristics at the community level, such as connectedness, participation and positive support between individuals. Social capital can be regarded as a relational resource, which determines the quality of life,

including our well-being and good health (Shan et al., 2012). High level of social capital has been found to be inversely related to the incidence of psychoses even after adjusting for individual-level characteristics and neighbourhood deprivation (Kirkbride et al., 2007b, Lofors and Sundquist, 2007). Social fragmentation involves disorganization and instability among communities, characterized by social isolation and poor communication among the inhabitants (Faris and Dunham, 1939, Brown, 2011). Social fragmentation is associated with urban life, particularly in inner cities, and it has been associated with an increased risk for schizophrenia (Allardyce et al., 2005). In a Swedish multilevel study (Zammit et al., 2010) almost all of the variance in the risk for non-affective psychosis was explained by individual-level variation rather than by variation in schools or neighbourhood. The association between urbanicity and psychosis seemed to be a reflection of increased social fragmentation present within cities. The findings suggest that certain characteristics that define individuals as being different from most other people in their local environment may increase the risk for psychosis (March et al., 2008, Zammit et al., 2010).

Geographic variation of psychotic disorders in Finland

In Finland, regional variation in the prevalence of schizophrenia has been different from many other countries; for decades it has been more common in rural areas and showed marked regional variation (Hovatta et al., 1997, Lehtinen et al.,, 1990, Korkeila et al., 1998, Salokangas et al., 1987, Suominen et al., 1975, Suvisaari et al., 1999). In the Mini Finland general population survey conducted in 1978-1980 (Lehtinen et al., 1990), schizophrenia was found to be most frequent in the West, the East and the North and least frequent in south-western and southern Finland. The lifetime prevalence of primary psychotic disorders in the SouthWest, the South, the West, the East and the North were 1.8%, 1.8%, 2.4%, 3.1% and 3.0%, respectively. A register-based study (Hovatta et al., 1997) found even larger regional differences in the prevalences. One recent study found some evidence that urban birth may be emerging as a risk factor in Finland in those born after the year 1960. However, the size of the studied age group was small and they were followed only until the age of 26 (Haukka et al., 2001).

Finland has been different from many other Europian countries in the social and economic structure (Haukka et al., 2001). The least developed areas in Finland have been rural (Palmgren et al., 1964). Urbanization occurred in Finland much later than in many other European countries (Korkiasaari and Söderling, 2003) and the change was exceptionally rapid. At the same time, after World War II, fast change in economic structure occurred. The high incidence and prevalence of psychotic disorders in rural areas has been suggested to be caused both by isolated, genetically homogeneous sub-populations in which genes predisposing to schizophrenia have been enriched (Hovatta et al., 1997) and clustering of environmental risk factors predisposing to psychotic disorders in these areas (Haukka et al., 2001).

2.3 Alcohol-induced psychotic disorders

Alcohol-induced psychotic disorders belong to the substance-induced psychotic disorders. Substance-induced psychotic disorders are an important group of psychotic disorders, but they are rarely included in epidemiological studies (Bogren et al., 2009, Kirkbride et al., 2006). Recent studies on substance-induced psychotic disorders have generally focused on psychoses induced by illicit drug use (Caton et al., 2005, Drake et al., 2011). However, alcohol has a central role in substance use disorders (Somers et al., 2004), as it is the most commonly used substance among persons with substance-induced psychotic disorder (Caton et al., 2005). Alcohol use disorders (AUDs) are common in all developed countries (WHO, 2004, 2011). Alcohol consumption is the world's third largest risk factor for disease and disability (Mannelli and Pae, 2007, Room et al., 2005). It is a causal factor in 60 types of diseases and injuries and a component cause in 200 others. Almost 4% of all deaths worldwide are attributed to alcohol (WHO, 2011).

In general population surveys, the lifetime prevalence for DSM-IV alcohol dependence has been around 5%-14% (Bijl et al., 1998, Hasin et al., 2007, Kessler et al., 1994, 2005, Pirkola et al., 2006) and lifetime prevalence of all alcohol use disorders up to 30.3% (Hasin et al., 2007). AUDs are more prevalent in men than women (Pirkola et al., 2005, Rehm et al., 2009). These disorders are associated with young age, being unmarried, low education, unemployment and low income (Hasin et al., 2007, Jacobi et al., 2004, Kessler et al., 2005, Pirkola et al., 2005). Comorbidity with other substance use disorders and with mood, anxiety and personality disorders is common (Hasin et al., 2007, Pirkola et al., 2005). Mean age of onset of alcohol dependence is about 22 years (Pirkola et al., 2006). Only a quarter of the subjects with alcohol dependence have sought help for these conditions, with higher proportions in women than in men (Hasin et al., 2007, Pirkola et al., 2006).

In Finland, the use of alcohol has tripled during the last three decades (THL, 2012, WHO, 2011). Also, the number of subjects with alcohol-induced psychoses tends to increase when the use of alcohol increases in the population (Cohen and Johnson, 1988). In Finland, the LTP of alcohol dependence is 7.9% (Pirkola et al., 2006) for those aged 30 years and over and 5.6% for young adults (Latvala et al., 2009). Alcohol use disorders are also the most common substance-related disorders in Finland (Aalto-Setälä et al., 2001, Latvala et al., 2009). Substance use in Finland has been characterized by high level of drinking to intoxication and fairly low level of use of substances other than alcohol (Mäkelä et al., 2012, WHO, 2011).

In general population studies, subjects with alcohol dependence have had an almost twofold risk for psychotic symptoms compared with those without dependence

independently of many other risk factors, including drug dependence (Degenhardt et al., 2001, Johns et al., 2004). There is no consensus about the possible aetiological role of alcohol in schizophrenia (Mueser et al., 1998, Glass, 1989a, Soyka, 1990,).

Psychotic symptoms can occur in several clinical conditions related to alcohol: intoxication, withdrawal, alcohol-induced psychotic disorder or delirium, Wernicke-Korsakoff syndrome and alcohol-induced persisting dementia (Greenberg and Lee, 2001). Alcohol-induced psychotic disorder is usually preceded by heavy and long-lasting alcohol consumption (Achte et al., 1969, Glass, 1989a, Lehtonen, 1996) indicating an alcohol use disorder. AUDs comprise alcohol dependence and alcohol abuse in the DSM-IV and of dependence or harmful use in the ICD-10. Alcohol dependence is not a necessary feature for diagnosing alcohol-induced psychotic disorder, but usually at least diagnosis of alcohol abuse can be assigned to an affected person (American Psychiatric Association, 2000).

In DSM-IV, alcohol-induced psychotic disorders are characterized by an acute onset of hallucinations and/or delusions that occur either during or after a period of heavy alcohol consumption. Psychotic symptoms should be in excess of those usually associated with intoxication or withdrawal syndrome with perceptual disturbances, and symptoms should not persist more than a month during a substance free period. Alcohol withdrawal with perceptual disturbances is diagnosed instead of alcohol-induced psychotic disorder if hallucinations occur with intact reality testing, which criterion has been criticized (Mathias et al., 2008). Alcohol-induced delirium is a disturbance of consciousness which may also present with psychotic symptoms as associated features (American Psychiatric Association, 2000).

2.3.1 Epidemiology of alcohol-induced psychotic disorders

Epidemiological studies on the prevalence of alcohol-induced psychotic disorder and delirium are scarce (Mattisson et al., 2011). Previous information on alcohol-induced psychotic disorder and delirium is based on hospital samples, such as first-episode psychotic patients in mental hospitals or on patients in alcohol treatment units (Achte et al., 1969, Lehtonen, 1996, Schuckit et al., 1995, Soyka, 2008a,b Tjuang et al., 1994, Victor and Adams, 1953). The annual prevalences of alcohol-induced psychotic disorders (Soyka, 2008a) and alcohol-induced delirium (Soyka, 2008b) have been 0.6%–0.7% and 4.9%–7.4%, respectively, in patients with alcohol dependence who were treated in psychiatric hospitals in Germany. In other clinical studies from substance abuse services, it has been estimated that 2%–7% of patients with alcohol dependence have had alcohol-induced psychotic disorders with hallucinations (Tsuang et al., 1994, Victor and Adams, 1953), 5%–11% have had delirium tremens (Eyer et al., 2011, Glass, 1989b, Greenberg and Lee, 2001, Hemmingsen et al., 1979, Schuckit et al., 1993, 1995) and one quarter have

experienced psychotic symptoms in their lifetime (Tsuang et al., 1994). Delirium is a life threatening condition which should be intensively treated. The mortality has been up to 15% in older studies (Mayo-Smith et al., 2004). Alcohol-induced psychotic disorder is acutely a milder form of alcohol withdrawal compared with delirium, but it is also related with increased long-term mortality (Glass, 1989b, Lehtonen, 1996).

In first-episode psychosis studies, 5%-8.4% of the patients have had a substance-related psychosis (Cantwell et al., 1999, Kirkbride et al., 2006, Singh et al., 2004), and 1.3% pure alcohol-related psychoses (Singh et al., 2004). Of the first-episode patients with substance induced psychotic disorder, 15% to 17 % have had an alcohol-related psychotic disorder (Caton et al., 2005, Singh et al., 2004), and further 40% have used two or more substances, with alcohol commonly being involved (Caton et al., 2005).

In clinical samples of patients with alcohol dependence, those with alcohol-induced psychosis have had more severe dependence, earlier onset age of alcohol problems, higher consumption of alcohol per occasion, more alcohol-related life problems, and more drug use than those without psychosis (Achte et al., 1969, Lehtonen 1996, Tsuang et al., 1994). Subjects with delirium tremens are more likely to be male, older, less educated and separated/widowed (Schuckit et al., 1995). Also binge drinking, several earlier withdrawal episodes, use of illicit sedative-hypnotics, and a greater number of medical problems and psychiatric symptoms have been associated with a history of psychoses and delirium (Schuckit et al., 1995). Moderate or severe brain injury may increase the risk of delayed psychotic disorders (Achte et al., 1969, Hesdorffer et al., 2009, Koponen et al., 2002).

The validity of substance-induced psychotic disorders has been challenged by the finding that half of the subjects with cannabis-induced psychosis later develop schizophrenia spectrum disorder (Arendt et al., 2005). Familial predisposition to psychiatric disorders and psychotic disorders contribute equally to the risk of developing schizophrenia or cannabis-induced psychosis (Arendt et al., 2008), but it has no effect on the later risk of schizophrenia spectrum disorder after developed cannabis-induced psychosis. Familial loading of schizophrenia is associated with developing psychosis also among methamphetamine users (Chen et al., 2005).

Alcohol use disorders are associated with increased mortality (Hiroeh et al., 2001, Markkula et al., 2012, Poikolainen et al., 2011, WHO, 2011). Alcohol-related psychotic disorder (Moos et al., 1994) and delirium tremens among alcohol use disorder patients admitted to psychiatric treatment (Lewis et al., 1995) have been associated with high mortality compared with other subjects with alcohol or substance use disorders at follow-up. This is supported by recent findings in a

general population sample (Mattisson et al., 2011). Mortality associated with delirium has been found to be especially high in older studies, while the outcome of alcohol-induced psychosis has been found to be better (Lindelius et al., 1974, Lindelius and Salum 1972). In a Finnish study, 44% mortality was found for both groups during a 10 to 15 year follow-up (Lehtonen, 1996).

3 Aims of the Study

The main objective of this study is to report the lifetime prevalences of specific/different psychotic disorders according to DSM-IV in the adult population of Finland. In addition, the purpose is to examine sociodemographic features and geographic variation in psychotic disorders in the general population and study clinical features of some psychotic disorders in more detail.

The specific aims of this study are:

- to obtain estimates of lifetime prevalence of all specific DSM-IV psychotic disorders in the general population by using multiple sources of information and to compare different screening methods for detecting psychotic disorders in general population studies (Study I).

- to explore sociodemographic correlates and geographic variation of psychotic disorders in the Finnish adult population. Geographic variation is investigated both in terms of urban-rural differences and large area variation according to place of birth and place of residence (Study II).

- to study epidemiology, clinical features, morbidity and mortality of alcohol-induced psychotic disorder and delirium in more detail (Study III).

- to provide epidemiological and clinical data (age at onset, symptoms, outcome and treatment) on delusional disorder and schizophrenia subtypes and to investigate the descriptive and predictive validity of delusional disorder and different subtypes of schizophrenia in the DSM-IV (Study IV).

4 Methods

4.1 The Study design and subjects

4.1.1 Health 2000 Survey

This study forms part of the Health 2000 Survey, a national health examination survey (Aromaa and Koskinen, 2004). The main aim of the Health 2000 Survey was to provide an up-to-date comprehensive picture of health and functional ability of working age adults aged 30 years or over in the Finnish population. The major responsibility for project planning and implementation was carried out by the National Public Health Institute (KTL; since January 1st 2009 the National Institute for Health and Welfare, THL). Other agencies involved were the Finnish Centre for Pensions, the Social Insurance Institution of Finland, the Local Government Pensions Institution, the National Research and Development Centre for Welfare and Health, the Finnish Dental Association and the Finnish Dental Society, Statistics Finland, the Finnish Institute of Occupational Health, the Finnish Work Environment Fund, the UKK Institute for Health Promotion Research and the Occupational Safety and Health Fund of the State sector (Heistaro, 2008).

The Health 2000 Survey population

The Health 2000 Survey was based on a nationally representative two-stage stratified cluster sample of 8028 persons. The sampling design was developed by Statistics Finland's experts and the research team in the National Public Health Institute (Heistaro, 2008). The sampling frame comprised adults aged 30 years and over living in mainland Finland and was regionally stratified according to the five university hospital regions. From each of them, 16 health care districts were sampled as clusters (altogether 80 health care districts in the whole country, including 160 municipalities). The 15 largest towns in the country were all selected in the sample and the remaining 65 areas were selected by systematic probability proportional to population size PPS sampling in each stratum. These 80 areas were the primary sampling units. The ultimate sampling units, i.e. target persons, were selected by systematic sampling from the areas. No exclusion criteria were used in the sampling, e.g. institutionalized and homeless persons were included. Subjects 80 years of age or over were oversampled (2:1) in relation to their proportion in the population within the clusters to ensure adequate coverage of the oldest participants. (Heistaro, 2008)

The field work was carried out between September 2000 and June 2001, and consisted of:

- an interview at home (duration: 70-90 minutes).
- a health examination in the local health care centre (duration: 3-4 hours).
- a condensed interview and a health examination at home (or institution) for those unable to attend in the health care centre.
- a telephone interview or a mail questionnaire for remaining subjects.

Altogether, a total of 7419 subjects (93% of the 7977 subjects who were alive on the day they were contacted for the first phase of the survey) attended at least one study phase (Aromaa and Koskinen, 2004). Register information was also gathered on the whole sample both to complement baseline information and for follow-up purposes. Details of the sampling design and selection processes, as well as data collection for the Health 2000 Survey are described elsewhere (Aromaa and Koskinen, 2004, Heistaro, 2008, Laiho and Nieminen, 2004).

Assessment of mental disorders in the Health 2000 Survey

In the health examination, the physician assessed whether the subject had a definite or probable psychotic disorder. Mental disorders were also assessed in several other questionnaires and primarily by the Finnish translation of the Munich version of the Composite International Diagnostic Interview M-CIDI (Wittchen et al., 1998). The M-CIDI is a computerized, fully structured interview. The Finnish version covered 12-month diagnoses of mood, anxiety, psychotic and substance use disorders, as well as lifetime diagnoses of alcohol and other substance dependence (Pirkola et al., 2005). However, diagnoses of psychoses and bipolar disorder obtained using the CIDI have a poor level of agreement with clinical diagnoses, i.e. poor validity (Kendler el al 1996, Kessler et al., 2005, Regeer et al., 2004). Therefore, a second phase study called Psychoses in Finland PIF was conducted. The ethics committees of the National Public Health Institute and the Hospital District of Helsinki and Uusimaa approved the Health 2000 Survey (407/E3/2000) and the PIF reassessment (644/E3/2001). Participants provided written informed consent.

4.1.2 The Psychoses in Finland Study

The design of the PIF Survey is briefly introduced in Figure 1. First, the Health 2000 sample was screened for possible psychotic disorders, and second a detailed face-to-face interview using the Structured Clinical Interview for DSM-IV, SCID-I (First et al., 2001) was conducted to those with a suspected psychotic disorder and to a random sample of controls. In addition to the interview, case notes from lifetime treatments for psychiatric problems were collected and also for those who did not participate in the interview. The final best-estimate diagnoses were based on systematic evaluation of the interview and the case note data.

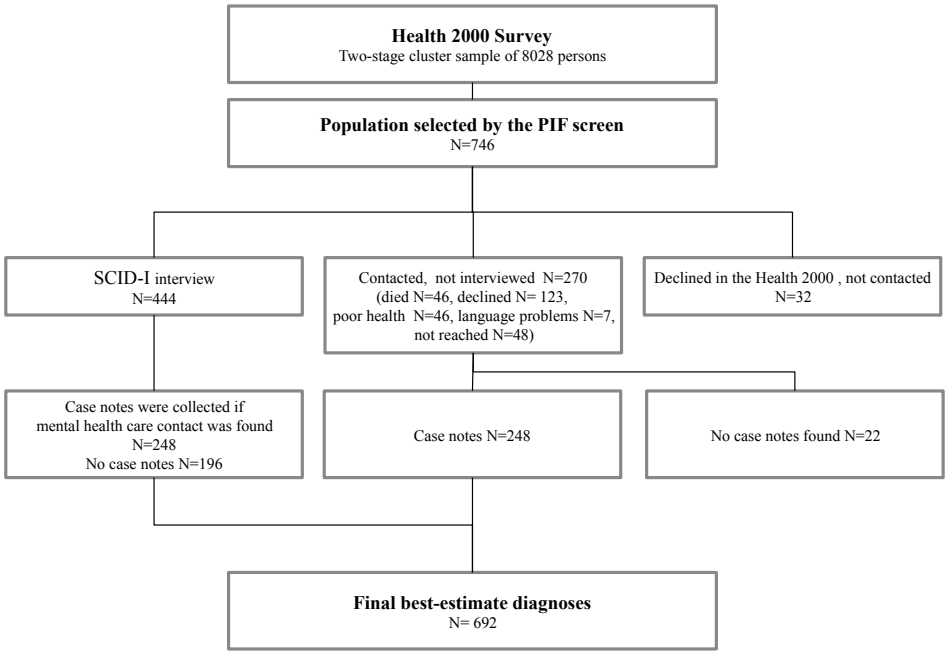

Figure 1. Design of the Psychoses in Finland Study.
Abbreviations: PIF, Psychoses in Finland; SCID-I, Structured Clinical Interview for DSM-IV.

4.1.3 Screening of psychotic disorders

Individuals were selected for the re-interview using a psychosis screen (PIF screen) specifically designed for this survey (Figure 2). Psychosis screen consisted of several screens constructed from elements of the Health 2000 health examination, including the CIDI interview and register data. If any individual screen (A-C below) was positive, the person was invited for the re-interview.

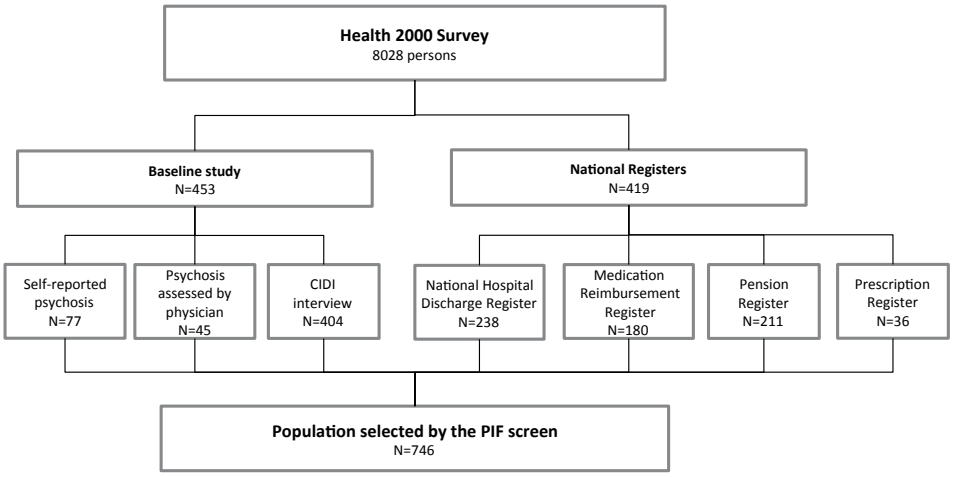

Figure 2. Number of Persons Selected by Specific Parts of the Psychosis Screen. One Person May be Selected by Several Screens.
Abbreviations: CIDI, Composite International Diagnostic Interview; PIF, Psychoses in Finland.

A. HEALTH 2000 –interview or the health examination:
(1) Self-reported psychotic disorder: Subject reported having been diagnosed with a psychotic disorder in the mental health treatment questions of the home interview, telephone interview or mail questionnaire (N=77).
(2) Psychotic disorder assessed by physician: Possible or definite psychotic disorder as assessed by the physician who conducted the health examination (possible N=17, definite N=28).

B. CIDI INTERVIEW:
In all sections of CIDI, subjects who reported that their symptoms had been caused by injury, physical illness, medication or substance abuse were also included.
(1) Section F screen for bipolar I disorder: A lifetime episode of elevated and/or irritable mood lasting at least four days was reported by 360 subjects. After this, there are 12 questions about manic symptoms in the CIDI. These questions cover the seven DSM-IV manic symptoms, but some symptoms are asked with two or three separate questions. If the subject answered yes to any three of these 12 CIDI questions, the mania screen was positive. Additionally, the index symptoms were not required to occur at the same time as the elevated/irritable mood in this study (N=124).
(2) Section G screen for lifetime positive psychotic symptoms: The symptom questions in the CIDI G section are presented in the Supplement 1. If any of these symptoms were scored positive (N=689), several questions concerning their clinical relevance, i.e. whether the symptom had interfered with normal life or whether the

person had talked about it with a health care professional, was asked. All subjects with any clinically relevant positive psychotic-like symptoms were considered screen-positives. In addition, all subjects reporting three or more psychotic-like symptoms regardless of clinical relevance were included (N=238).
(3) Section P screen for formal thought disorder, negative and catatonic symptoms: In the section P, the interviewer assessed the presence of symptoms of positive formal thought disorder, negative symptoms, behaviour suggesting that the person had either hallucinations or catatonic symptoms. The screen for these symptoms consisted of having any of these symptoms except for slowed speech, which was too common to be used as a screen (N=93).
(4) Remarks section of the CIDI interview, and the screen for odd behaviour: The interviewer noted remarks concerning the individual and the interview. If the subject was not selected by any of the other screens, but these remarks were indicative of psychotic disorder, the individual was selected for the re-interview (N=4).

C. REGISTERS:
(1) National Hospital Discharge Register: Hospital treatment with a diagnosis of any psychotic or bipolar disorder according to the National Hospital Discharge Register between 1969 and 2002 (N=238).
(2) Free Medication Register: Free medication for "Severe psychotic and other severe mental disorders" according to the Free Medication Register of the Finnish Social Insurance Institution (N=211).
(3) Pension Register: Disability pension (permanent or temporary) because of any psychotic disorder, bipolar disorder or major depressive disorder according to the Pension Register of the Finnish Centre for Pensions (N=180).
(4) The Finnish National Prescription Register: For screening bipolar I disorder the Finnish National Prescription Register of the National Insurance Institution was additionally used. All subjects not selected by any other screen who had used lithium, carbamazepine, oxcarbazepine, valproic acid, lamotrigine, gabapentin or topiramate between 1996-2002 without a self-reported or register diagnosis of epilepsy or any neurological or other somatic disorder which would account for the medication, were identified and selected for the re-interview (N=36).

Registers
The Finnish National Hospital Discharge Register has been computerized since 1968 and covers all public and private hospitals, inpatient wards of local health centres, military wards and prison hospitals. The Hospital Discharge Register contains personal identification numbers, hospital identification codes, admission and discharge dates for each inpatient and daypatient stay, primary diagnosis and up to three subsidiary diagnoses. The discharge diagnoses are made by the attending physician. The accuracy of the data in the Finnish National Hospital Discharge Register has been found to be excellent (Keskimäki and Aro, 1991, Pajunen et al.,

2005). The reliability of schizophrenia and schizophrenia spectrum disorders in the Finnish National Hospital Discharge Register has been assessed in several studies, and it has been found to be generally good (Arajärvi et al., 2005, Isohanni et al., 1997, Kampman et al., 2004, Mäkikyrö et al., 1998, Moilanen et al., 2003, Pihlajamaa et al., 2008, Taiminen et al., 2001). This means that when clinicians do diagnose schizophrenia, it is usually congruent with the research diagnoses. However, clinicians tend to underdiagnose schizophrenia (Isohanni et al., 1997) and up to 50% of cases with a research diagnosis of schizophrenia have a register diagnosis of other psychotic disorder (Isohanni et al., 1997, Moilanen et al., 2003). Validity of the Finnish register diagnoses of schizophrenia have improved after 1982 when the Finnish translation of the DSM-III was published (Pihlajamaa et al., 2008).

Bipolar I disorder is underdiagnosed in clinical practice, too (Mantere et al., 2008). The existing diagnoses in the Finnish National Hospital Discharge Register had 92% accuracy for both diagnoses of bipolar I disorder and the manic type of schizoaffective disorder compared with research diagnoses (Kieseppä et al., 2000). In a first-episode sample, the agreement of clinician and research diagnoses was lower, kappa value being of 0.64 for bipolar I disorder, and 0.49 for psychotic depression (Taiminen et al., 2001). Subjects, who have had both bipolar I disorder and schizophrenia diagnoses in the register have been found to be a heterogeneous group (Laursen et al., 2005, Munk-Jörgensen, 1992). Of subjects with both diagnoses in the register, 43% received schizophrenia or schizoaffective disorder diagnosis according to DSM-IV criteria (Pihlajamaa et al., 2008). Validity of other psychosis diagnoses in the hospital discharge register has not been studied as intensively.

The Pension register includes beginning and ending dates and the primary diagnoses for all permanent or disability pensions. The Free Medicine Register includes the diagnoses of persons entitled to free outpatient medication and the beginning dates. All persons residing permanently in Finland are entitled to medication reimbursement. Medications for severe and long-term diseases, including all psychotic and bipolar I disorders are fully reimbursed. The information in the Pension and Free Medicine Registers should be accurate as payments of the benefits are based on the registers.

The Finnish National Prescription Register covers all pharmacies in Finland and records all reimbursed purchases of drugs in Finland for which the Social Insurance Institution has paid any reimbursement. The reimbursement system covers all permanent residents in the country. At the time of the study, reimbursement used to be paid in Finland only if the total purchase price exceeded a certain sum (8.41 Euros in 2002) and thus low price medicines, like some older, generic medicines were not registered. Register contains information for example of the date of

purchase, the classification of medicines according to the Anatomic Therapeutic Chemical (ATC) classification system (WHO, 1994) and the dose of medicine stated as the international standard daily defined dose (DDD). The agreement between self-reported medication and medication data obtained from the prescription register has been found to be generally good (Haukka et al., 2007, Haapea et al., 2010), the agreement being best for lithium (Cohen's kappa 0.96) and antipsychotics (Cohen's kappa 0.77-0.87), and good also for other mood stabilizers (Cohen's kappa 0.84-0.74) (Haukka et al., 2007, Haapea et al., 2010).

Information on psychotic disorders was obtained from each register from 1969 up to December 2002, except from The Finnish National Prescription Register from 1st January 1996 to December 2002. The National Hospital Discharge Register records all five digits of diagnostic codes, allowing accurate identification of subjects with a diagnosis of psychotic disorder. In contrast, the Pension and the Free Medication registers recorded earlier only the first three digits, which means that MDD with and without psychotic disorders cannot be separated. It was decided to invite all subjects with a diagnosis of MDD from these two registers to ensure that all affective psychoses in these registers would be covered.

The diagnoses in the registers were coded according to the ICD-8 before the year 1987, from then until 1995, according to the ICD-9 using DSM-III-R criteria (Kuoppasalmi et al., 1989) and according to the ICD-10 since 1996. The five digits of the diagnostic codes in the National Hospital Discharge Register were included as presented in Table 3.

Subjects selected only by the Hospital Discharge Register screening were contacted through the person responsible for the treatment and the case notes were sought with the approval of Finnish Ministry of Social Affairs and Health, excluding the subjects who had actively declined to participate in the Health 2000 Survey. Subjects selected only by other registers were contacted through the institutions in question.

Table 3. The Diagnostic Codes Included from the National Hospital Discharge Register in Screening Psychotic Disorders

Diagnosis	Diagnostic classification	Years	Codes
Schizophrenia	ICD-10	1996-2002	F20
	ICD-8 and ICD-9	1969-1995	295.0-295.3, 295.5, 295.6, 295.8, 295.9
Schizoaffective disorder	ICD-10	1996-2002	F25
	ICD-8 and ICD-9	1969-1995	295.7
Other non-affective psychotic disorders	ICD-10	1996-2002	F22, F23, F24, F28, F29
	ICD-8 and ICD-9	1969-1995	295.4, 297, 298, 299
Bipolar disorder or manic episode	ICD-10	1996-2002	F30, F31
	ICD-9	1987-1995	2962-2967
	ICD-8	1969-1987	2961, 2963
Major depressive disorder with psychotic features	ICD-10	1996-2002	F32.3, F33.3
	ICD-9	1987-1995	2961E
Psychotic disorder due to to a general medical condition	ICD-10	1996-2002	F03.X1, F03.X2, F05, F06.0, F06.1, F06.2, F06.31
	ICD-9	1987-1995	293, 294
	ICD-8	1969-1987	292-294 (except 294.3)
Substance-induced psychotic disorders	ICD-10	1996-2002	F1X.4, F1X.5, F1X.7
	ICD-9	1987-1995	291.0, 291.3, 291.8, 292.1, 292.8
	ICD-8	1969-1987	291.0, 291.2, 291.3, 291.9, 294.3

4.1.4 Mental health assessment

The screen-positive subjects were invited to a re-interview which were conducted between the years 2002 and 2004 (Figure 1). Before the interview, all subjects signed informed consent after a detailed description of the study. The study protocol always began with a neuropsychological assessment. Thereafter, the same interviewer conducted the interview. After the interview, the subjects filled a questionnaire containing several scales (Table 4)

Table 4. The Mental Health Interview in the PIF study.

Neuropsychological tests:
Verbal learning strategies and declarative memory functions CVLT
(Delis et al., 1987).
Verbal and visual working memory (WMS-Span Tasks backward)
(Wechsler, 1987).
Mental tracking (WAIS-Digit Symbol) (Wechsler, 1981).
Executive function (Trails B) (Reitan, 1993).
Attention (WMS-Span Tasks forward; Trails A) (Wechsler, 1987, Reitan, 1993).
Primary capacity (WAIS-Vocabulary) (Wechsler, 1981).

Interview:
Information on social and occupational background, and treatment received for mental health problems.
SCID–I interview (First et al., 2001).
Questions assessing the lifetime occurrence of suicidal ideation and behaviour.
Questions assessing the family history of mental disorders.
Global Assessment of Functioning GAF and Social and Occupational Functioning Assessment Scale SOFAS

Questionnaire:
Health-related quality of life RAND-36 (Hays & Morales 2001),
Chapman Scales for Psychosis Proneness
(Chapman et al., 1976, 1978, Eckblad & Chapman, 1983, Eckblad et al., 1983).
Questions concerning social relationships and childhood experiences
Questions on seasonal variation of symptoms

Blood samples:
Three 10 ml tubes blood were drawn for genetic analyses

Experienced research nurses conducted the neuropsychological tests and the SCID-I interviews. The staff had prior experience of clinical work and they had previously been working in Finnish large scale genetic studies on schizophrenia and bipolar disorder (Ekelund et al., 2001, Paunio et al., 2001, Soronen et al., 2008, Tuulio-Henriksson et al., 2002) and had also been conducting interviews using SCID and administering neuropsychological tests full-time since 1998. All research staff participated in a one-month training period in March 2002 and they rated interviews simultaneously to ensure the inter-rater reliability. All SCID interviews were reviewed with a clinical supervisor (Jukka Hintikka, Jaana Suvisaari, Timo

Partonen, and Tuula Kieseppä), and final ratings and diagnoses were based on consensus between the interviewer and the clinical supervisor.

4.1.5 The final diagnostic assessment

For the final diagnostic assessment, all case notes from hospital and outpatient treatments for mental health problems were collected with the approval of the Finnish Ministry of Social Affairs and Health. Case notes were collected for both those who did and did not participate in the SCID-I interview. Case notes were collected first using information from the Hospital Discharge Register and self-reports of mental health care contacts from the interview. When case notes revealed other contacts, notes from these contacts were systematically collected, too. For those who did not participate in the interview and had no register diagnoses, case notes from primary care centres were collected and further records of treatment for mental health problems were collected based on this information. Case notes of subjects who did not report any mental health problems or health care contacts in the interview, and had no register information on mental health treatments were not collected. Case records of those who had declined from the Health 2000 baseline study were neither collected.

The final best-estimate diagnoses were made using the DSM-IV-TR criteria (American Psychiatric Association, 2000) by three clinicians Jaana Suvisaari, Jonna Perälä and Samuli Saarni. Diagnostic evaluation was based on all available, systematically evaluated longitudinal information from the subject and/or data provided by other professionals, e.g. the interview and/or case records. Definite evidence of psychotic symptoms was required for diagnosing a psychotic disorder. All symptoms at any phase of the illness were taken into account in diagnosing the entire episodes of illness.

The final diagnostic assessment was made for 692 study subjects and 140 controls. The first 20 cases were assessed together to ensure the consistency in ratings between rates. Thereafter, the reliability of diagnoses was tested by selecting 136 cases. These cases were selected mainly among study subjects with a diagnosis of any psychotic disorder or bipolar disorder according to the National Hospital Discharge Register (screening information) or according to the SCID interview. Selected cases were first rated separately by all three raters. In case of disagreement, a consensus diagnosis was made together. All problematic cases were reviewed together in meetings and consensus diagnoses were made for them together. The "probable" category was not used. If there was any uncertainty whether the symptoms were definitely psychotic or not, the axis I diagnosis was deferred. If the diagnostician was confident about the presence of psychosis, but there was not

enough information to assign a specific DSM-IV psychotic diagnosis, psychotic disorder NOS was diagnosed.

Cases with possible substance-induced psychotic disorders were also reviewed by Adjunct Professor Kimmo Kuoppasalmi, who is an expert in this area. In cases of disagreement, the final diagnosis was based on his review. It was not always possible to evaluate the diagnostic criteria whether the person had insight on psychotic symptoms being substance-induced or not. Therefore, if the person had specifically sought help for psychotic symptoms related to substance or alcohol use, the criteria that symptoms were in excess of the expected effects of intoxication and withdrawal was judged to be met. If a subject had had a definite secondary psychosis separately from primary psychotic disorder, e.g. substance induced psychosis prior to emerging "functional psychosis" or a psychotic disorder due to GMC after clear remission from functional psychosis, both lifetime diagnoses were assessed.

In some cases there was not enough information to assess the exact relationship between affective and psychotic symptoms and to differentiate whether bipolar I disorder with psychotic symptoms or schizoaffective disorder was the accurate diagnosis. For those cases both bipolar disorder NOS and psychotic disorder NOS was diagnosed. In difficult cases of possible bipolar disorder, Professor Erkki Isometsä was consulted.

Of all screen-positive subjects included in the final diagnostic assessment, 35.8% (248/692) had a lifetime diagnosis of a psychotic disorder. Diagnosis was deferred for 18 subjects, 8 of them having had psychotic symptoms. One hundred and forty-three did not receive any diagnosis: one of them had a coding error in Hospital Discharge Register, 18 were selected by the Prescription Register for using anticonvulsants, but they used the medication for somatic disease. Twenty-three persons came from the Free Medication Register or the Pension Register with a diagnosis of major depressive disorder or a specific diagnosis was not available. The rest, 101 with no diagnosis were selected by the CIDI screen. Of the subjects with the best-estimate DSM-IV diagnosis of any psychotic disorder, 51% (N=127) had attended the SCID interview. Of those attended, 60% could have been diagnosed accurately on the basis of the SCID interview alone, but in the remaining 40% with the interview the case notes were essential for accurate and specific diagnosis. Altogether, if case notes had not been included in the diagnostic procedure, 49% with the best-estimate diagnosis of a psychotic disorder, e.g. those without SCID interview, would have been missed, and further 21% (40% of those with SCID) would have obtained a less accurate diagnosis.

Kappa values between the three rates were 0.89-0.92 for schizophrenia, 0.91-0.96 for schizophrenia spectrum disorders, 0.74-0.91 for all non-affective psychotic disorders, 0.76-0.97 for affective psychotic disorders and 0.85-0.93 for general medical condition or substance-induced psychotic disorder and delirium. Kappa values for the Study IV were calculated separately for delusional disorder (range from 0.49 to 0.80) and for schizophrenia subtypes; paranoid schizophrenia (0.72 to 0.74), undifferentiated schizophrenia (0.24 to 0.76) and disorganized schizophrenia (1 between all raters). The kappa values were also similar for cases with both the SCID interview and case records available versus cases with case records only. Subtyping of schizophrenia was defined based on lifetime information of the characteristics of the disorder using the DSM-IV hierarchy for schizophrenia subtypes. Residual schizophrenia diagnosis was not routinely used.

4.1.6 Diagnostic categories

Subjects with the onset of symptoms of psychotic disorder before the end of 2001 were included in the prevalence analyses. Broad diagnostic category “non-affective psychoses” includes schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder and psychotic disorder not otherwise specified (NOS). “Other non-affective psychoses" includes all previously mentioned, except schizophrenia. “Affective psychoses” includes bipolar I disorder with/without psychotic features and major depressive disorder with psychotic features. “Substance-induced psychotic disorders” includes psychotic disorder due to alcohol or other substances. Psychotic disorders due to general medical condition (GMC) also include also vascular dementia with hallucinations or delusions. All psychoses comprised non-affective, affective, substance-induced psychotic disorders and psychotic disorders due to general medical condition. Alcohol-induced deliriums were included in the Study III.

4.1.7 Control subjects

To assess the validity of the PIF screen, but also for other research purposes, 174 controls were randomly selected for the re-interview from all subjects who had attended any phase of the Health 2000 Survey. Of the 174 selected controls, 24 were also selected by the PIF screen and were included in the screened population in these analyses. Of the remaining 150 subjects, 99 (66%) controls were successfully interviewed, 29 (19%) declined, 4 (3%) had died, 5 (3%) could not participate because of poor health, 7 (5%) had language problems and 6 (4%) were not reached. There was enough information from interview and/or case notes for diagnostic assessment for 140 (93%) of the 150 control subjects. One of the 150 screen-negative controls had a diagnosis of psychotic disorder due to dementia, but none of them had a primary psychosis.

4.1.8 Non-response group

Information from the registers was used to estimate the effect of non-response. Only 451 (5.4%) of the 8028 individuals had declined from the baseline Health 2000 Survey, including 32 screen-positive subjects. In addition, neither interview nor case notes from 22 subjects of the screened population were obtained. These subjects did not differ in age (mean age 54 and 55 years, p=0.25, respectively) or gender (47% and 48% males, p= 0.59, respectively) from subjects with best-estimate diagnoses. The effect of non-response on lifetime prevalence estimates was estimated by using a register diagnosis of non-affective psychotic disorder or affective psychotic disorder or any psychotic disorder in The National Hospital Discharge Register. In the Free Medication and Pension registers MDD diagnoses 296 in ICD-8 and ICD-9 and F32 or F33 in ICD-10 with three first digits were not included, as the psychotic form of the disorders could not be identified (N=10). Thus, altogether 34 of the 44 non-responders with a register diagnosis were included. Register diagnoses of these subjects were recorded to data and corrected prevalence rates were calculated separately.

4.2 Other Measures

4.2.1 Information collected during the diagnostic evaluation

In addition to assigning diagnoses, the three diagnosticians filled in the Major Symptoms of Schizophrenia Scale (MSSS, Supplement 2) (Fanous et al., 2004, Kendler et al., 1993, 1998) based on lifetime occurrence and severity of symptoms. Eleven key symptomatic variables also reported by Kendler et al. (1993, 1998), were used: delusions (any), bizarreness of delusions, hallucinations, positive thought disorder, e.g. loosening of associations, catatonic symptoms, affective deterioration, e.g. restricted or blunted affect, negative thought disorder, depressive symptoms and manic symptoms, chronicity of course (from single episode with recovery to chronic course with continuous psychotic symptoms) and the level of outcome (from full recovery to very poor outcome). Chronicity of course was rated to all those with any psychotic or affective disorder and outcome for those with any psychotic disorder. The ratings reflected clinical judgement and included the severity and duration of the symptom, and its relative prominence over the entire course of the illness (Kendler et al., 1995). All of these variables were coded on a five-point scale, with the exception of outcome which was coded on a four-point scale. The symptomatic variables were coded as follows: 1=clearly not present, 2=possibly present but subthreshold, 3=clearly present but moderate, 4=clearly present and prominent, 5=clearly present and severe. The course of disorders was coded as follows: 1=single episode, 2=multiple episodes, full recovery between episodes, 3=multiple episodes, partial recovery, 4=chronic course with exacerbations and 5=chronic course without exacerbations. Outcome was rated as follows: 1=recovery, 2=mild

deterioration, 3=moderate deterioration and 4=marked deterioration. The ratings of the course and outcome were done only if information from interview and/or medical records were detailed enough and extended until the year 2001. The MSSS has been used earlier, e.g. in Roscommon Family Study (Kendler et al., 1995), Helsinki High-Risk Study (Niemi et al., 2004), and Irish Study of High-Density Schizophrenia Families (Kendler et al., 2000). This study also assessed the Global Rating of Bizarre Behaviour item from the Scale for the Assessment of Positive Symptoms SAPS (Andreasen, 1984), and the Global Rating of Avolition-Apathy and of Anhedonia-Asociality items from the Scale for the Assessment of Negative Symptoms SANS (Andreasen, 1982). These ratings were made on a six-point scale, ranging from 0=not at all to 5=severe.

Information on treatment contacts for mental health and addiction problems during lifetime, age at the first treatment, lifetime and current antipsychotic medication and age at onset of psychotic symptoms were also collected based on all available information. Hospitalizations and involuntary treatments were assessed based on the Hospital Discharge Register information since the year 1969 and from case records before the time the register was established. Persons entitled to costfree outpatient medication were identified from the Medication Reimbursement Register of the Social Insurance Institution. Using global impression on current symptoms and functional capacity, subjects without current treatment were grouped into those who a) no longer needed treatment (sustained remission), b) had declined or dropped out from treatment and c) would have needed treatment but did not have it available either because they had never been diagnosed as having a mental disorder, or because treatment contact had been terminated by the health care system.

4.2.2 Sociodemographic variables

The Finnish Population Information System was used to obtain information on age, gender, and place of birth and residence, which are coded for each Finnish citizen. Household income was obtained from the registers on taxes and welfare benefits. It was adjusted for household size using the OECD equivalence scale, where the first adult of a household is weighted as 1.0, other adults as 0.7, and children less than 18 years old as 0.5 (OECD, 1982). The study sample was grouped into tertiles according to household income. Self-reported information on marital status, level of education and employment status was collected during the health interview of the Health 2000 Survey.

4.2.3 Geographic variables

There is no standard method for defining urbanization (Harrison et al., 2003). In this study, the place of residence was categorized into urban and rural (including semi-urban and rural) areas according to the official classification by Statistics Finland

(2001). Municipalities are classified according to the proportion of the population living in population centres and by the population of the largest population centre. According to this classification in the year 2000, 61% of the Finnish population lived in urban areas. The municipalities at the time of birth were categorized as urban or rural based on the 1960 census. According to this, 25% of the Finnish population lived in municipalities classified as urban. To compare different classifications of urban-rural environment, different classifications of urbanization of the place of residence were also used such as a) according to the number of inhabitants in the municipality (city >50 000, other town 10 000-49 999, rural < 10 000 inhabitants, Statistics Finland, 2001), b) the population density per km2 of land divided in quintiles, and c) capital area (city), other towns (at least 90% of the inhabitants reside in the population centre, or the population of the biggest centre is over 15 000, Statistics Finland, 2001), and rural areas.

For the regional analysis, Finland was divided into five university hospital regions. These are the same areas as used in the stratification during the Health 2000 sample selection: South, SouthWest, West, East and Northern Finland (Figure 1 in the original Study II). Of the subjects in the Health 2000 population living in urban areas, 44.4% resided in the South, 12.5% in the SouthWest, 23.3% in the West, 10.0% in the East and 10.0% in the North.

4.2.4 Alcohol-related variables

Lifetime diagnoses of alcohol dependence were based on the CIDI interview in the health interview of the Health 2000 Survey. The total number of CIDI mental health interviews was 6005, amounting to 75% of the original sample. If the criteria of alcohol dependence (AD) had not been fulfilled within the past 12 months, the subject was determined as being currently in remission from AD (Pirkola et al., 2006). The subjects were asked in the CIDI when they drank their first drink of alcohol and the age at onset of any of the symptoms of AD. As a part of the baseline survey, standardized questions about current alcohol consumption were asked in a questionnaire. This information was used in calculation of weekly consumption of alcohol. Parental alcohol use and mental health problems at the time when the subject was 16 years or younger, were asked in the same questionnaire.

Of the subjects with final diagnosis of alcohol-induced psychotic disorder or delirium, 74.4% had attended the CIDI interview even though many of them had not reported about the psychotic symptoms. Those who did not attend differed not in terms of age, gender, number of hospital treatments, or age at first hospital treatment from those who attended the interview.

Hospital treatments for alcohol-related disorders and traumas were collected from the Finnish Hospital Discharge Register (from 1969 to December 2002). The total number of hospital treatments and age at the first hospital treatment for alcohol-related disorders and traumas were collected. The diagnostic codes included are presented in the original Study III, Table DS1. Information on deaths was obtained from the Census data of the Social Insurance Institution of Finland (until 01.03.2008). The causes of deaths were available for the deaths that had occurred before the end of the year 2006 from the Causes of Death Register of Statistics Finland. They were classified into natural and unnatural deaths, including suicides. Alcohol-related deaths comprised all deaths where either the underlying cause or one of the contributory causes was attributed to alcohol, such as alcohol intoxications (including ICD-10 diagnoses E244, E52, F10, G312, G621, G721, 1426, K292, K70, K860, O354, P043, T51, X45, Z502, Z714, Z724, Mäkelä et al., 1999).

4.3 Statistical analysis

All analyses were conducted using SAS-callable SUDAAN Release 9.0 (Research Triangle Institute, 2004), which is able to take into account the two-stage cluster sampling design. The SAS 8.02 (SAS Institute Inc., 1999) was used in the Studies I-III and version 9.1.3 (SAS Institute Inc., 2002) in the Study IV. Sampling design was included in all statistical analyses to obtain figures representing the Finnish general population. Post-stratification weights were used to adjust for the oversampling of individuals aged 80 years and over. Whenever the data were obtained from the Health 2000 baseline survey, another set of weights were used to correct the effect of non-response in the Health 2000 Survey. The weights were calibrated by Statistics Finland (Lehtonen and Pahkinen, 2004).

4.3.1 Statistical analysis in the Study I

Lifetime prevalences were estimated by calculating proportions for dichotomous variables and asymmetric 95% confidence intervals for percentages were calculated using the logit transformation (Research Triangle Institute, 2004 pp. 243-244). Prevalences in different age groups and among women and men were compared using the chi-square statistics within the survey design. Values of $p<0.05$ were considered statistically significant. To estimate the effect of non-response, the prevalences were recalculated, by using register diagnoses for those non-respondents who had a register diagnosis of psychotic disorders. Inter-rater reliability in the final diagnoses of psychotic disorders was evaluated using unweighted kappa statistic (K). Concordances between the screens and the DSM-IV research diagnoses were evaluated by calculating simple K (Fleiss, 1981), sensitivity, specificity, and positive and negative predictive values (Akobeng, 2006). In each screen, the total number of subjects who participated in that particular phase of the baseline study was included.

4.3.2 Statistical analysis in the Study II

In the Study II, the non-response group was included in the analysis. The highest possible number of subjects for whom the data were available were included in the analysis. Schizophrenia, other non-affective psychotic disorders, affective psychoses and any psychotic disorders, also including substance-induced and psychotic disorders due to general medical condition, were modelled separately as groups. Proportions of subjects with different diagnoses in different sociodemographic groups were calculated. Also percentages of subjects being born or resident in urban and rural areas and different geographic areas were calculated. The differences were tested using the chi-square statistics within the survey design. Lifetime prevalence of psychotic disorders in different regions was estimated as predicted margins to obtain estimates adjusted for age and gender (Research Triangle Institute, 2004). Logistic regression models were used to determine whether some regional variables were independently associated with different psychotic disorders.

4.3.3 Statistical analysis in the Study III

In the Study III, subjects with alcohol-induced psychotic syndrome, alcohol dependence without alcohol-induced psychotic syndrome and general population without alcohol dependence were compared. Comparisons were made also between subjects with alcohol-induced psychotic disorder and delirium. Different analyses included always the largest possible number of participants in that particular phase of the study for whom the data were available. Proportions of subjects in different categorical groups were calculated, and the differences were tested using the chi-square statistics. Predicted margins were applied to adjust means and prevalences for age and gender (Heistaro, 2008 p. 191, Lee, 1981). Logistic regression was used to calculate odds ratios for categorical variables and linear regression was used in the cases of continuous variables. All the models were always adjusted for age and gender.

Cox proportional hazards models were used to examine the effect of alcohol-induced psychotic syndrome on mortality, when controlling for age and gender. The analysis of mortality and also of alcohol-related medical comorbidity, were restricted to population under 70 years. Only one subject with alcohol-induced psychotic disorder or delirium was found to be older than 70 years at the baseline. Hazard ratios (HR) and 95% confidence intervals were calculated for mortality among subjects with alcohol-induced psychotic disorder and delirium, alcohol dependence, and the rest of the sample. As the sample size was small, scaled score residuals were used for measuring the influence of individual observations (Therneau et al., 2000, Thompson et al., 2003). Scale score residuals measure the influence of one observation on the maximum partial likelihood estimate of a coefficient when deleting each observation in turn. The magnitudes of the scaled

score residuals were quite similar and near zero. That indicates that none of the observations were too influential individually.

4.3.4 Statistical analysis in the Study IV

Comparisons were made between subjects with delusional disorder, and with subtypes of schizophrenia. Paranoid, undifferentiated and disorganized schizophrenia were included. Catatonic subtype (N=3) was too rare to be analysed separately. Differences in age and mean age at onset between the groups were tested using analysis of variance, and post hoc differences between the groups were compared with Tukey's honestly significant difference. Differences in ordinal variables (MSSS, SANS and SAPS ratings) between the groups were tested using Kruskal-Wallis test, and differences in categorical variables with the the chi-square statistics test. The number of hospital treatment days was a highly skewed variable, and Kruskal-Wallis test was used to analyze between-group differences.

5 Results

5.1 The screening of psychotic disorders (STUDY I)

The psychosis screen found 248 subjects with lifetime diagnosis of psychotic disorder. One subject with psychosis due to GMC was found among the control sample. The number and the proportions of subjects within the same diagnostic category found by specific screens are presented in Table 5 in original Study I. The National Hospital Discharge Register alone captured 76%-81% of subjects with non-affective or affective psychotic disorders, while it was not as effective in finding substance-induduced psychoses or psychoses related to GMC. The CIDI psychotic symptoms screen was able to capture at best less than third of the non-affective psychotic disorders and substance-induced psychotic disorders. Altogether, if the only screen had been the Hospital Discharge Register, CIDI section G or self-reported psychotic disorder 75%, 27% and 25% of the cases with any psychotic disorder would have been found, respectively. Excluding the registers, other screens found 52.4% of the subjects with psychotic disorders. The CIDI manic symptom screen alone detected only 25% of the subjects with BPI.

The Prescription register is not included in these estimates. The register was used to complement the screening of bipolar I disorder. All Health 2000 subjects not selected by other screens were further assessed according to anticonvulsants or lithium use. Of the 36 subjects found, one had psychosis due to GMC and three had substance-induced psychoses. None of the four subjects selected by the CIDI remarks section had psychotic disorder as the final diagnosis.

Table 5 presents the concordance between different parts of the screen and the best-estimate diagnoses of any psychotic disorders as a group. The total number of subjects for each screen included all participants in that phase of the study and the subjects in the non-response group were excluded. The lifetime prevalence of psychotic disorders in the case that different parts of the screens would have been used is presented in the Figure 3.

Table 5. Concordance Between the Different Parts of the Screen and the Best-Estimate DSM-IV Diagnoses of Any Psychotic Disorders

Screen		Kappa	(95% CI)	Sensitivity	Specificity	PPV	NPV
National registers	All registers*	0.72	(0.68-0.76)	86.1	98.3	63.8	99.5
	Psychotic disorder in Hospital Disharge Register	0.80	(0.76-0.84)	75.3	99.7	88.4	99.2
	Psychotic disorder in Other Registers**	0.58	(0.52-0.63)	60.9	98.5	58.2	98.7
CIDI	CIDI all sections	0.25	(0.19-0.30)	43.5	95.1	19.7	98.4
	CIDIG psychotic symptoms	0.32	(0.25-0.38)	41.5	97.1	28.5	98.4
	CIDIF manic symptoms	0.12	(0.06-0.17)	12.1	98.3	16.0	97.6
	CIDIP other symptoms related to psychosis	0.27	(0.20-0.35)	22.4	99.1	40.0	97.9
Health 2000	Psychosis assessed by physician	0.37	(0.29-0.45)	24.5	99.9	91.0	98.0
	Self-reported psychoses	0.38	(0.31-0.44)	26.7	99.9	81.8	97.6

Abbreviations: CIDI, Composite International Diagnostic Interview; PPV, positive predictive value; NPV, negative predictive value

* Includes Hospital disharge register, the Medication Reimbursement register and the Pension register

** Includes the Medication Reimbursement register and the Pension register

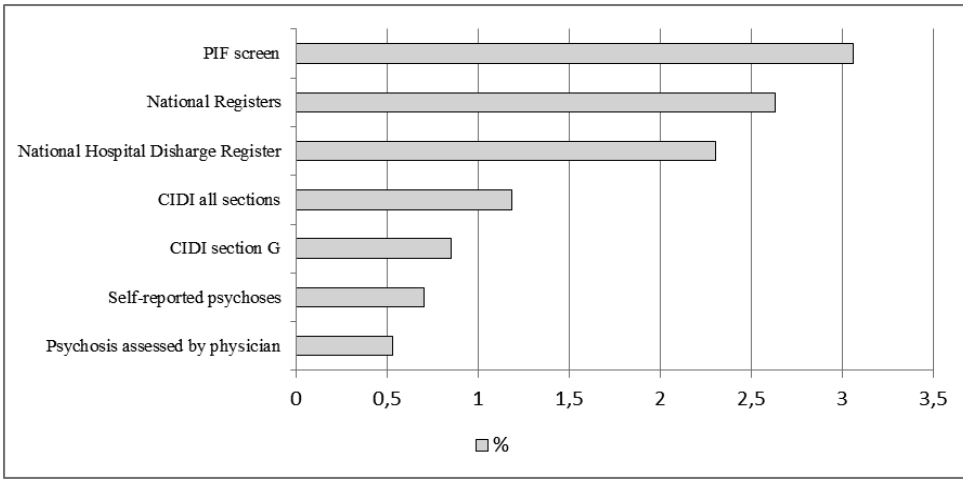

Figure 3. Lifetime Prevalence of All Psychotic Disorders if Different Screens Would Have Been Used.
Abbreviations: PIF, Psychoses in Finland; CIDI, Composite International Diagnostic Interview

5.2 Lifetime prevalences of psychotic disorders (STUDY I)

LTP estimates of psychotic and bipolar I disorders and their 95% confidence intervals are presented in Table 6. The most prevalent specific psychotic disorders were schizophrenia 0.87%, psychotic disorder NOS 0.45% and alcohol induced psychotic disorder 0.41%.

Register diagnoses of specific psychotic disorders were found in 34 subjects of the non-response group (N=55) of the PIF study. When these diagnoses were included, LTP in any psychotic disorder increased to 3.48%, in non-affective psychotic disorder to 2.29%, in schizophrenia to 1.00%, and in affective psychoses to 0.62%.

Table 6. Lifetime Prevalence Estimates and 95% Confidence Intervals of DSM-IV Psychotic and Bipolar I Disorders

	Total		Total, including non-respondents	
	%	(95% CI)	%	(95% CI)
Non-affective psychotic disorders	1.94	(1.63-2.29)	2.29	(1.95-2.69)
Schizophrenia	0.87	(0.68-1.11)	1.00	(0.79-1.25)
Schizoaffective disorder	0.32	(0.21-0.46)		
Schizophreniform disorder	0.07	(0.03-0.16)		
Delusional disorder	0.18	(0.11-0.30)		
Brief psychotic disorder	0.05	(0.02-0.14)		
Psychotic disorder NOS	0.45	(0.33-0.62)		
Affective psychotic disorders	0.59	(0.45-0.77)	0.62	(0.47-0.80)
Bipolar I disorder	0.24	(0.16-0.37)		
with psychotic features	0.12	(0.06-0.23)		
without psychotic features	0.12	(0.07-0.23)		
MDD, with psychotic features	0.35	(0.24-0.51)		
Substance-induced psychotic disorders	0.42*	(0.30-0.59)	0.43	(0.31-0.60)
Alcohol-induced	0.41	(0.29-0.57)		
Other substance-induced	0.03	(0.01-0.11)		
Psychotic disorders due to a GMC	0.21	(0.14-0.32)	0.22	(0.15-0.34)
Any psychotic disorders	3.06*	(2.66-3.51)	3.48	(3.06-3.96)

* In the estimated prevalence, each individual has only been counted once

If all subjects with bipolar disorder NOS because of insufficient information would have BPI, its prevalence increased to 0.39%. If also register diagnoses of BPI in non-responders were included, the LTP would be 0.42%.

Gender differences were found only in schizoaffective disorder, GMC induced psychotic disorders and substance-induced psychotic disorders (Table 3 in original Study I). Women had more schizoaffective disorders and GMC induced psychoses compared with men. Substance-induced psychotic disorders were more common in men and most common in the age group 30-54 years (Table 4 in original Study I). The LTP of GMC induced psychotic disorders increased markedly from 0.74% in the age group 65 years and older to 1.71% among subjects 80 years and older. Most

(92.9%) subjects in this group had dementia. Delusional disorder was found only in the age group 45 years and older.

Sociodemographic characteristic of psychotic disorders (STUDY II)
Sociodemographic characteristics of subjects with schizophrenia, other non-affective psychotic disorders, affective psychotic disorder and any psychotic disorders were assessed (Table 2 in original Study I). When adjusted for age and gender, the odds of having any psychosis were high among not married, pensioned and unemployed persons and among those having low income, or basic education. Being pensioned was common among subjects with non-affective psychotic disorders: 70% of them pensioned. One third of subjects with non-affective psychotic disorder had reached the pension age (63 years) and 87.0% of the pensioned below that age reported having disability pension. Only 20% of subjects with non-affective psychotic disorders, and 7% of subjects with schizophrenia were employed compared to 57% of the rest of the population.
In schizophrenia, a high OR was found among those who were unmarried, pensioned or unemployed and among those having low income. The odds of having other non-affective psychotic disorder was high in widowed, never married, pensioned, unemployed and persons having low income. In contrast, the odds of affective psychoses were high in those divorced or separated and low in the group of secondary level education.

5.3 Geographic differences in lifetime prevalence of psychotic disorders in Finland (STUDY II)

Lifetime prevalence of psychotic disorders in five university hospital regions of Finland is presented in Figure 4.

In separate logistic regression models, after adjusting for age and gender, any psychotic disorder was associated with birth in rural areas compared with urban birth (OR 0.73, 95% CI 0.54-0.98), and birth in the South (OR 2.18, 95% CI 1.16-4.09), the West (OR 2.46, 95% CI 1.33-4.54), the East (OR 3.13, 95% CI 1.76-5.55) or the North (OR 3.52, 95% CI 1.97-6.31) compared with the SouthWest. Associations were also found with residence in the South (OR 1.68, 95% CI 1.02-2.77), the East (OR 1.87, 95% CI 1.09-3.24) or the North (OR 2.15, 95% CI 1.26-3.68). In schizophrenia, a high OR was found among those being born in the East (OR 3.99, 95% CI 1.22-13.11) or the North (OR 7.72, 95% CI 2.48-24.04) and residing in the North (OR 3.00, 95% CI 1.37-6.55). The odds of having other non-

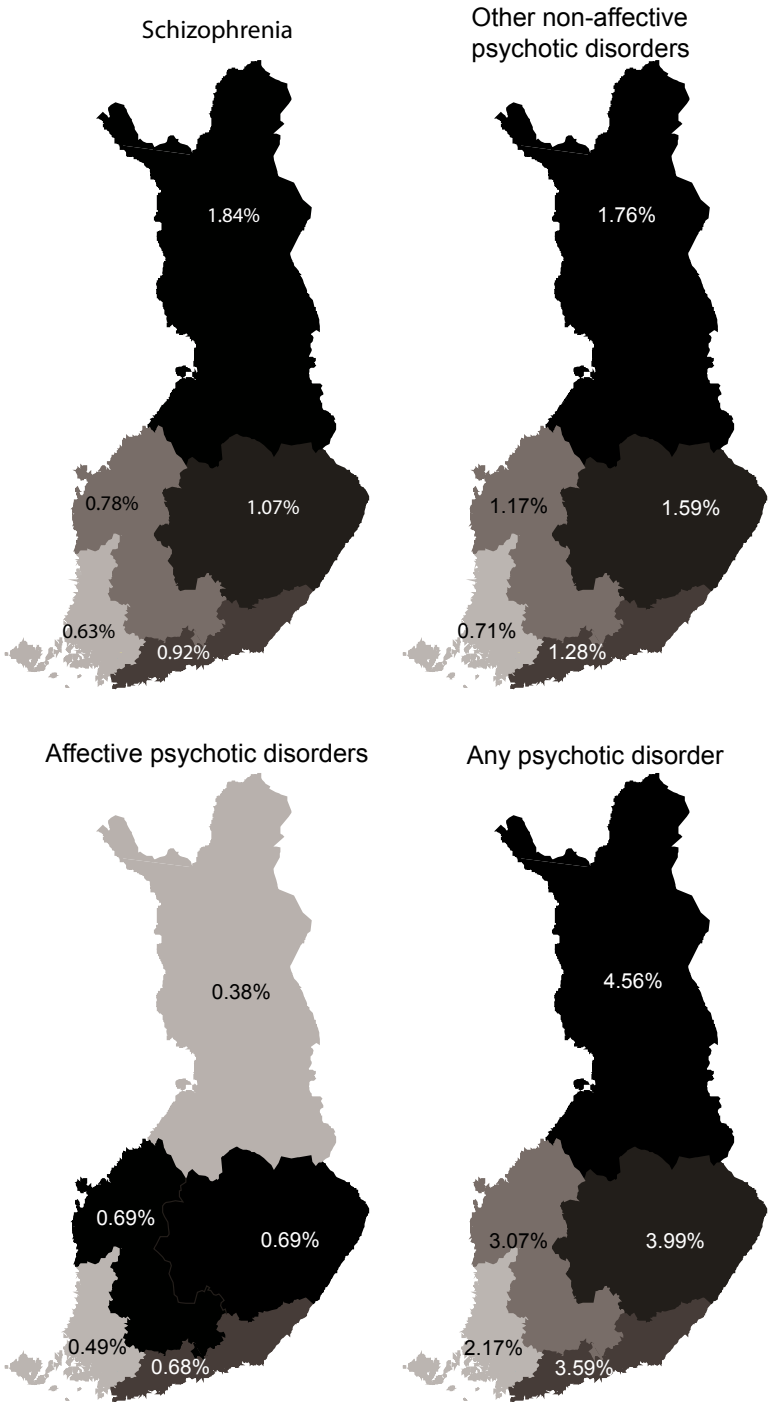

Figure 4. Lifetime Prevalence of Psychotic Disorders in Five University Hospital Regions of Finland. Age and Gender Adjusted.

affective psychotic disorders were high among those being born or residing in the East or the North (Table 2 in original Study II).

When all geographic variables were included in logistic regression model concerning any psychotic disorders, the association with region of birth remained statistically significant (p=0.02), while associations with region of residence and with having birth in rural region attenuated (Table 7). The adjusted results were similar for other psychosis groups. The odds ratios for schizophrenia, other non-affective psychoses and affective psychoses in different regions of birth, adjusting for urbanicity, are presented in the Figure 5.

No differences were found in internal migration between persons with any lifetime psychotic disorder and non-affected population. 65.1% and 67.8% (p=0.37) still lived in the region of birth, respectively. The odds of any psychotic disorders (OR 1.13, 95% CI 0.87-1.47), schizophrenia (OR 0.89, 95% CI 0.55-1.44), other non-affective disorders (OR 1.30, 95% CI 0.84-2.00) and affective psychoses (OR 1.43, 95% CI 0.81-2.53) was similar in subjects who had migrated to other regions of the country as in subjects who had stayed in the area of birth.

Table 7. The Associations of Any Psychotic Disorders with Urbanicity and Regions of Birth and Residence. Age and Gender Adjusted.

	Any psychotic disorder	
	OR	**(95% CI)**
Place of birth		
Rural	1	
Urban	0.79	(0.57-1.09)
Region of birth		
SouthWest	1	
South	2.09	(0.98-4.42)
West	2.49	(1.23-5.02)*
East	2.97	(1.42-6.20)*
North	3.30	(1.54-7.09)*
Place of residence		
Rural	1	
Urban	1.03	(0.76-1.40)
Region of residence		
SouthWest	1	
South	1.13	(0.56-2.26)
West	0.94	(0.45-1.94)
East	1.00	(0.46-2.18)
North	1.07	(0.48-2.34)

* Significant at the 0.05 level.

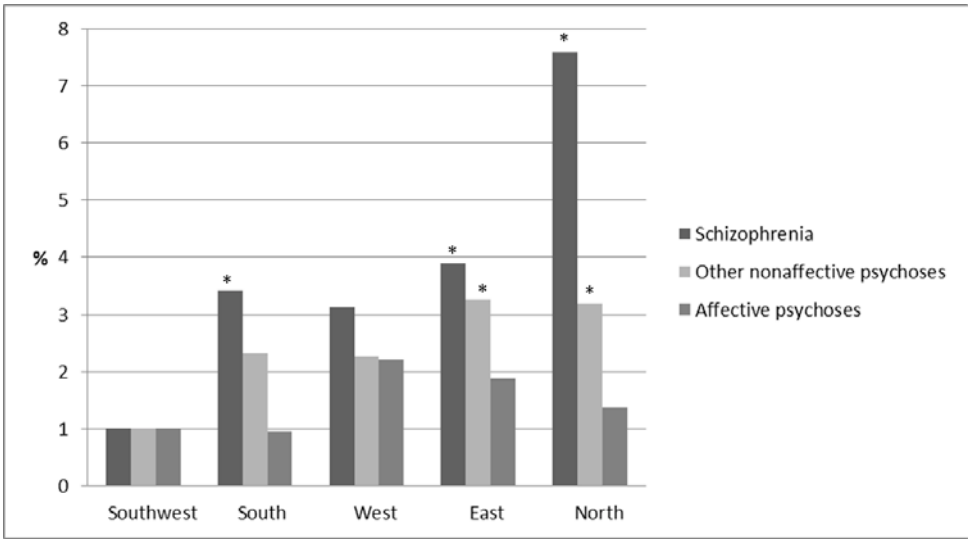

Figure 5. The Odds Ratios for Schizophrenia, Other Non-Affective Psychotic Disorders and Affective Psychotic Disorders for birth in Five Main Regions of Finland. Age, Gender and Urbanicity adjusted.
* Significant at the 0.05 level.

5.4 Alcohol-induced psychotic syndrome in the general population (STUDY III)

The lifetime prevalence of alcohol-induced psychotic disorder was estimated at 0.41% (95% CI 0.29–0.57, N=31) and delirium at 0.18% (95% CI 0.11–0.32, N=14). Six subjects had had both diagnoses. When each individual was counted once, the LTP for the total alcohol-induced psychotic syndrome was 0.51% (95% CI 0.38-0.70, N=39). The majority of subjects with AIPS were men, among whom the highest LTP 1.77% (95% CI 1.06-2.94) was found in the age group 45–54 years (Figure 6).

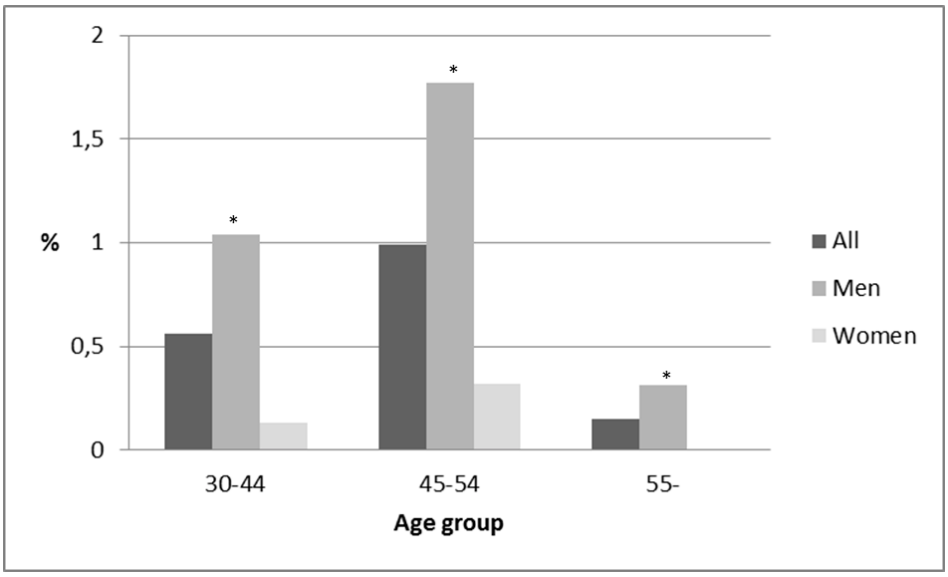

Figure 6. Lifetime Prevalence of Alcohol-Induced Psychotic Disorder and Delirium by Age Group and Gender.
* Difference between men and women significant at the 0.05 level.

In subjects with alcohol-induced psychotic disorder, the subtype "with hallucinations" was common (N=30, 97%), and 53% of them had had delusions in addition to hallucinations. Most subjects (87%) had had multiple episodes of alcohol-induced psychosis with full recovery between the psychotic episodes.

Comorbid mental health disorders were found in 64% of the subjects with AIPS, subjects with alcohol-induced psychotic disorder having higher rates (76%) than subjects with delirium (43%). The most common comorbid disorders were affective disorders, followed by personality, other substance use disorders and anxiety disorders. Other substance use disorders (N=10, 26%) included six cases with sedative dependence or abuse, two cases with polysubstance dependence, one case with sedative and polysubstance dependence, and one case with opioid, cannabis and polysubstance dependence. During the episodes of the alcohol-related psychosis, there was no evidence found of the concurrent substance use.

Five subjects (12.8%) developed some other primary psychotic disorder 5 to 10 years after the alcohol-induced psychotic episode. One subject with alcohol-induced psychotic disorder developed schizophrenia, one schizophreniform disorder and one psychotic disorder NOS. One subject with delirium developed bipolar disorder with psychotic features and one had a later episode of brief psychotic disorder.

All subjects with AIPS had had some mental health or alcohol treatment unit contact. 82% had had psychiatric hospital treatment during their lifetime, but only 59% had sometimes been treated in psychiatric hospital with a diagnosis of any psychotic disorder. The first treatment unit for alcohol-induced psychosis was psychiatric hospital in 46%, primary health care centre in 28%, alcohol treatment settings 8%, general hospital 3% and psychiatric outpatient care 3%. 13% had received no treatment for the first episode.

Long and heavy use of alcohol was a usual finding among the subjects with AIPS. The mean age at the time of the first ever drink was 15.5 years (95% CI 14.4-16.7), onset age for alcohol use disorder was 24.6 years (95% CI 22.2-27.1) and for psychotic symptoms 34.3 years (95% CI 31.3-37.2) in the subjects with AIPS. The mean duration of alcohol use ranged from 14 to 50 years (mean 29.5 years, 95% CI 26.8 -32.2). Time from the first drink to the onset of psychotic symptoms was 18.4 years (95% CI 15.4-21.4, range 6-34 years), and from the onset at alcohol use disorder to psychotic symptoms 10.4 years (95% CI 7.8-12.7, range 1-28 years). The time from the onset of alcohol use disorder to the first treatment contact for alcohol problems was 6.8 years (95% CI 4.5-9.1) and to the first treatment for psychosis 10.4 years (95% CI 7.9-12.9). No differences were found in current remission rates or alcohol consumption between subjects with alcohol dependence with or without psychosis.

The LTP for AIPS among subjects having alcohol dependence was 4.8% (95% CI 3.23–7.17), and for alcohol-induced psychotic disorder 4.0% (95% CI 2.6–6.1) and for delirium 1.9% (95% CI 1.0–3.6). There was no difference in the mean ages (45.0 and 46.8 years) between those with and without psychosis. The odds of having had AIPS were higher in subjects having low income, being never married, unemployed, and belonging to the age group 45–54 (Supplement table DS2 in original Study III) compared with subjects with alcohol dependence only. Subjects with AIPS reported more parental and specifically paternal alcohol problems, and more paternal mental health problems than subjects with alcohol dependence only. The results were similar when subjects who later developed primary psychotic disorder were excluded.

Alcohol-related hospital treatments in subjects with AIPS, alcohol dependence only and the rest of the study population are presented in Table 4 in original Study III. Hospital treatments for any alcohol-related causes were found from the National Hospital Discharge Register for 91% of the subjects with AIPS, 16% with alcohol dependence and 3% of the rest of the sample. Subjects with AIPS had younger age (mean 32.9, 95% CI 30.2- 35.6) at first treatment and higher number of treatments (mean 6.5 95% CI 2.8-10.2) compared with those with alcohol dependence (39.8 years, 95% CI 37.6-42.1, mean 2.8, 95% CI 1.9-3.7) or without this (40.9 years,

95% CI 38.9-42.9, mean 2.5, 95% CI 1.8-3.3, respectively). The OR of having had hospital treatments for any intoxications, other substance use, alcohol-related liver disorders, gastritis, fractures, and head injuries were higher in subjects with history of AIPS compared with subjects with alcohol dependence only and the study population without alcohol dependence. Pancreatitis in subjects with AIPS was more common than in subjects without alcohol dependence, but no difference was found in comparison with subjects with alcohol dependence.

During follow-up from 2000 to 2008, 37% of subjects with AIPS had died (Table 8). No differences were found in mortality between subjects with alcohol-induced psychotic disorder (40.0%) and delirium (30.8%) (HR 1.38, 95% CI 0.43-4.48). The risk of death was substantially higher among subjects with AIPS compared to subjects with alcohol dependence (HR 12.33, 95% CI 6.28-24.21). The underlying cause of death was available for 10/14 participants with AIPS: 4 of the deaths were natural, 2 were suicides and 4 were other unnatural deaths. Six of these deaths were alcohol-related according the register data.

Table 8. Deaths and Hazard Ratios for Death among Persons with Alcohol-Induced Psychotic Syndrome or Alcohol Dependence, Compared with the Rest of the Sample

	Deaths 2000-2008			
	N	% (95% CI)	HR	(95% CI)
No alcohol dependence (N=5891)	242	4.11 (3.57-4.72)	1	
Alcohol dependence without alcohol-induced psychotic syndrome (N=443)	29	6.54 (4.51-9.41)	1.61	(1.05-2.45)
Alcohol-induced psychotic syndrome (N=38)	14	36.84 (22.13-54.50)	19.91	(11.48-34.53)

Individuals over 70 years were excluded. Age and gender adjusted.

5.5 Delusional disorder and schizophrenia subtypes

The lifetime prevalence of delusional disorder was 0.18% (95% CI 0.11-0.30). The lifetime prevalence of schizophrenia subtypes were: paranoid schizophrenia 0.24% (95% CI 0.15-0.37), undifferentiated schizophrenia 0.42% (95% CI 0.30-0.59), and disorganized schizophrenia 0.16 % (95% CI 0.09-0.27).

Differences between men and women were not found in delusional disorder, paranoid schizophrenia, or undifferentiated schizophrenia. On the contrary, there were more men than women in the disorganized schizophrenia group compared with the other groups. The mean age at onset of psychotic symptoms was oldest in delusional disorder and youngest in disorganized schizophrenia, while paranoid and undifferentiated schizophrenia did not differ from each other (Table 2 in original Study IV).

The severity of delusions did not differ between any of the groups, but there were differences in all other symptom dimensions (Table 2 in original Study IV). Paranoid schizophrenia and delusional disorder resembled each other in having milder negative thought disorder, catatonic symptoms, and anhedonia/asociality. However, compared with any of the schizophrenia subtypes, persons with delusional disorder had milder hallucinations, bizarre delusions, positive thought disorder, affective deterioration, manic symptoms, bizarre behaviour, and avolition. Persons with paranoid schizophrenia had less severe formal thought disorder, affective deterioration, avolition, and catatonic symptoms than persons with undifferentiated schizophrenia. Persons with disorganized schizophrenia had had more severe positive and negative thought disorder, affective deterioration, bizarre behaviour and avolition than subjects in all other groups

Based on the longitudinal information, the course of delusional disorder was less chronic than in undifferentiated and disorganized schizophrenia, and the course of paranoid schizophrenia less chronic than in disorganized schizophrenia. Outcome was better in delusional disorder than in any of the schizophrenia subtypes, and worse in disorganized schizophrenia compared with paranoid and undifferentiated schizophrenia (Table 3 in original Study IV).

All persons with schizophrenia had had contact with psychiatric treatment and all but one had used antipsychotic medication. Of the persons with different schizophrenia subtypes, 70%-92% also had current treatment contact and 65%-92% had current antipsychotic medication. Although 81% of persons with delusional disorder had also had psychiatric treatment contact during lifetime and 63% of them had used antipsychotic medication, the current situation was different from the schizophrenia subtypes; only 21% subjects with delusional disorder had current

treatment contact, and 14% were currently using antipsychotic medication. Of persons with delusional disorder not having current treatment contact, 18% did not need treatment anymore (sustained remission), 27% had declined from treatment, and 54% needed treatment, but did not have it available. Of persons with schizophrenia without current treatment contact 14% no longer needed treatment, 57% had declined from treatment, and 21% did not have treatment available.

Lifetime psychiatric hospitalizations were less common in persons with delusional disorder (50%) than in persons with any schizophrenia subtype (84%-100%), as were involuntary hospital treatments (13% and 61%-92%, respectively). The most notable difference between the groups was in the lifetime duration of hospitalizations. At the extreme ends were persons with disorganized schizophrenia, who had spent on average almost 10 years in inpatient treatment, and persons with delusional disorder, whose average duration of hospitalizations was only 21 days during their lifetime. Persons with delusional disorder who had had a psychiatric hospital treatment tended to have more severe symptoms and course of illness than those without hospital treatments. Their mean age at onset was also lower (46.2 years) compared with persons with delusional disorder without hospitalizations (57.2 years). However, none of these differences were statistically significant.

6 Discussion

The present thesis investigated psychotic disorders and their correlates in the Finnish adult population sample. The thesis was based on the Health 2000 Survey and especially on the Psychoses in Finland (PIF) study. The aims of this thesis were to estimate the lifetime prevalence of different psychotic disorders as accurately as possible, to evaluate sociodemographic and geographic factors associated with the disorders, and to study in more detail the epidemiology and clinical features of alcohol-induced psychotic disorders, delusional disorder and subtypes of schizophrenia.

6.1 Summary of the main findings

Psychotic disorders were found to be common in the Finnish adult population. Approximately 3.5% of persons aged 30 years or over had met the criteria for any psychotic disorder during their lifetime. Non-affective psychoses (2.29%) were more common than affective psychoses (0.62%), while substance-induced psychotic disorders were common in working age men and psychoses related to general medical condition in the oldest age groups.

Detecting psychotic disorders from the general population reliably and diagnosing them accurately required collecting information systematically from several sources. National registers, especially the National Hospital Discharge Register were the most reliable and effective in screening psychotic disorders from the general population. Composite Structured Diagnostic Interview (CIDI) alone was not sufficient in screening psychotic disorders.

As expected, psychotic disorders were generally associated with socioeconomic disadvantage like being unmarried, pensioned or unemployed; having low income level or basic education. Affective psychoses were associated with higher level of education and income compared with other psychotic disorders. Highest prevalence of psychotic disorders was found in northern and eastern, and lowest in south-western parts of Finland. The area of birth was a more important determinant of the risk of psychosis than the area of residence.

Alcohol-induced psychotic disorder or delirium were common (LTP 1.8%) among men aged 45-54. Subjects with AIPS had on average a long history of heavy alcohol use before the onset of psychotic disorders, they had often had both hallucinations and delusions during the psychotic episodes. Most (64%) of them had other comorbid mental disorders. Subjects with AIPS belonged to lower socioeconomic

group, they had been treated in hospital for alcohol-related causes more often and at younger age compared with subjects with alcohol dependence. The mortality risk during eight years follow-up was 20 times higher in subjects with AIPS compared with general population, and 12 times higher compared with alcohol dependent subjects.

Delusional disorder was found to be a different disorder from paranoid schizophrenia and from other schizophrenia subtypes. It was characterized by high age of onset, absence of other symptoms than delusions and relatively good outcome. Disorganized subtype of schizophrenia also showed good validity. It was associated with early onset, male preponderance, chronic course, long hospitalizations and poor outcome. Paranoid and undifferentiated schizophrenia showed no marked clinical differences. All subjects with schizophrenia had had some treatment contact and 70% also had current treatment. Almost all subjects with delusional disorder also had an earlier treatment contact, but only 21% had current treatment, even though in most cases this would have been necessary.

6.2 Lifetime prevalence of psychotic disorders (STUDY I)

The lifetime prevalence (3.5%) of psychotic disorders was higher than in most previous general population surveys using two-stage strategies (Kendler et al., 1996, Kessler et al., 2005, van Os et al., 2001). One study, based on the CIDI interview, has obtained higher prevalence estimate (4.5%), of all psychoses (Jacobi et al., 2004).

The results of this study are surprisingly similar with the recent Lundby study (Bogren et al., 2009) where a 50-year period prevalence was found to be 4.2% and LTP 2.82%. The 50-year period prevalence estimate is higher than the lifetime prevalence because it includes all subjects in the original study population cohort, also persons deceased before the 50-year follow up. The slightly lower LTP represents cohort subjects alive at the 50-year follow up. Although the results are not directly comparable, the proportions of non-affective, affective and other psychoses, are highly concordant in the Lundby study (53%, 15% and 32%, respectively) and PIF (64%, 18% and 18%, respectively, Figure 7). Higher proportion of psychoses due to GMC in the Lundby study partly explains the lower proportion of other psychoses compared with PIF. The results were also in keeping with the British incidence study AESOP, where the distribution of the new onset cases was suprisingly similar (67% non-affective, 28 affective, 5% substance induced psychoses, Kirkbride et al., 2006). The magnitudes of the psychosis groups were also supported by a meta-analysis of British incidence studies (Kirkbride et al., 2012).

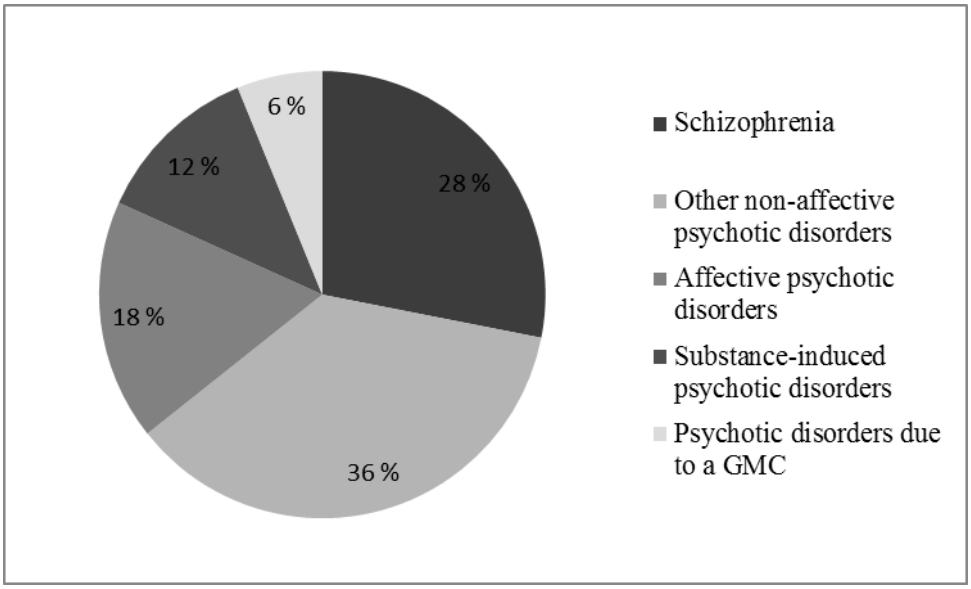

Figure 7. Proportions of psychotic disorders in the PIF study

The Finnish pioneer of general population surveys, the Mini-Finland Survey obtained very similar results 25 years ago, with LTP for functional psychoses 2.2%, schizophrenia 1.3% (broad definition) and other psychoses 0.9% (Lehtinen et al., 1990). The study setting in the Mini-Finland Survey was also a two-stage procedure: health examination and register data were used for case ascertainment, and information from psychiatric hospital treatments, register diagnoses, as well as a semi-structured interview (Present State Examination/CATEGO computer program) were the basis for the final clinical diagnostic decision (Lehtinen et al., 1991). Different diagnostic classification between studies makes the direct comparison of the results difficult. The same concerns other older studies (Astrup, 1989, Torrey, 1987).

Further support for the high prevalence of psychotic disorders, especially schizophrenia, comes from the Northern Finland 1966 Birth Cohort, where the cumulative incidence of affective psychoses is even lower than in our study (Moilanen et al., 2010). By the age of 34, 111 of approximately 10 000 subjects had been diagnosed with schizophrenia, 26 with other non-affective psychoses and 19 with affective psychoses. The lifetime prevalence of psychotic disorders, including psychosis related to dementia, was 2.9% in the UKKI study (Lehtinen et al., 1993).

Other modern general population studies on the whole category of psychotic disorders using multiple sources of information and best-estimate diagnoses on lifetime basis are lacking. Altogether, all these results indicate that psychotic disorders are common, and non-affective psychotic disorders the most common group in Finland.

The lifetime prevalence of schizophrenia in the Finnish general population was 0.87%. When register diagnoses in the non-response group were included, the prevalence increased to 1.00%. These estimates are considerably higher than the median lifetime prevalence 0.4% (0.18-1.16) found in the recent systematic review (Saha et al., 2005). Older studies have obtained even higher estimates (Torrey, 1987) but comparisons are again difficult due to changes in diagnostic criteria (McGorry et al., 1992, Pihlajamaa et al., 2008). In contrast, it is likely that the prevalence of schizophrenia in many recent population surveys would have been considerably higher if information in healthcare registers and case notes would have also been used. Supporting this, the estimates of schizophrenia from the Lundby study are concurrent with our results with 50-year period prevalence 1.43% and LTP 0.84% (Bogren et al., 2009). Results are also in line with other Finnish general population studies (Isohanni et al., 2001, Lehtinen et al., 1990, Moilanen et al., 2010) as well as with Finnish register-based studies (Hovatta et al., 1997, Suvisaari et al., 1999), and this fact suggests that the prevalence of schizophrenia is relatively high in Finland.

We found no gender difference in the prevalence of schizophrenia in accordance with prevalence studies (Bogren et al., 2009, Lehtinen et al., 1990, Saha et al., 2005). However, incidence (McGrath et al., 2004) and morbid risk (Aleman et al., 2003) of schizophrenia are higher in males. This discrepancy is a subject for further studies. Earlier age of onset in males (Eranti et al., 2012), the preponderance of women in later-onset cases (Meesters et al., 2012, Thorup et al., 2007) and differences in mortality (Brown 1997, Brown et al., 2010, Heilä et al., 2005, Joukamaa et al., 2001, Kiviniemi et al., 2010) may be among the issues that could explain this discrepancy (Eranti et al., 2012). However, as the the number of cases is small, differences approximately two-fold and over could have been detected in this study.

A higher LTP of schizoaffective disorder was found compared with the few recent studies where the estimates have varied between 0% and 0.11% (Bogren et al., 2009, Scully et al., 2004, Widerlöv, 1997). In a service-based study of individuals over 60 years, one-year prevalence of 0.14% was found (Meesters et al., 2012). Comparison of the estimates is difficult, as the diagnostic thresholds of schizoaffective disorder may vary between studies (Jäger et al., 2011). Another question is the diagnostic instability, which often occurs during the variable course of the disorder (Laursen et al., 2005, 2007, Salvatore et al., 2009, Schwartz et al., 2000, Tohen et al., 2012). In

this study, the diagnosis of schizoaffective disorder was based on the lifetime assessment of symptoms, and the duration of mood episodes had to be over half of the total duration of the illness. Thus, the diagnostic procedure accords with the suggested revisions for the DSM-V criteria (Tandon, 2012). The findings of this study support the older established interpretation that the prevalence of schizoaffective disorder is up to half of schizophrenia (Tsuang et al., 2003) and the disorder is more common in women compared with men (Malhi et al., 2008).

The lifetime prevalence of delusional disorder was 0.18%. This estimate was higher than in previous clinical (Kendler, 1982) and general population (Hwu et al., 1989) samples, but slightly lower compared with the Lundby study (Bogren et al., 2009). The higher estimate compared with hospital samples (Kendler et al., 1982) was predictable, since only half of the affected subjects had been treated in hospitals. The prevalence reported here is probably an underestimation due to lack of insight associated with the disorder, and relatively well preserved functional capacity, which makes involuntary treatments less likely. As delusions are non-bizarre in this disorder, it is extremely difficult to assess the genuineness of delusions in one interview, if no other source of information is available. There were several subjects in the diagnosis deferred category for whom a delusional disorder was suspected but this could not be confirmed. However, with the longitudinal information, persons who turned out to have dementia after a year or two after the onset of delusions, could be adequately diagnosed as having a psychotic disorder caused by a general medical condition rather than delusional disorder (Korner et al., 2009).

Schizophreniform disorder and brief psychotic disorder were rare. When these were combined, our results showed equal numbers with Lundby study (Bogren et al., 2009), but lower than estimates from another study (Cho et al., 2007). The low estimate accords with 3-to 6-year follow-up studies of subjects with ICD-10 acute and transient psychoses, in which the diagnosis had remained unchanged in only 34%-40% of the subjects (Castagnini et al., 2008, Singh et al., 2004). Psychotic disorder NOS was diagnosed when there was not enough data to assess a specific diagnosis. There may be some subjects who would have had the diagnosis of brief psychotic disorder if there had been more information available. Nevertheless, these results suggest that schizophreniform and brief psychotic disorder are rare disorders in the general population.

The lifetime prevalence of psychotic disorder NOS was 0.46%. This means that the study failed to assign a specific diagnosis for part of the subjects. In this study, the cases given a diagnosis of specific psychotic disorder were easy to diagnose according to typical description of the DSM-IV. However, there were several cases in which it was not possible to assign any specific psychosis diagnosis according to the criteria. Most problems were associated to the lifetime duration and relation of

the psychotic and affective symptoms, or the impossibility to differentiate primary and psychotic disorder induced by substance use or general medical condition. Also other comorbid psychiatric disorders often blurred the "typical" clinical picture. While it is somewhat misleading to categorize all these subjects into non-affective psychoses, using the NOS category is a common practice (Kirkbride et al., 2006).

Prevalence of affective psychotic disorders

The lifetime prevalence of affective psychoses in the Finnish general population was 0.59%. The result is again very similar with the Lundby study (Bogren et al., 2009), where the 50-year prevalence 0.62% was found. The prevalence of 0.4% affective psychoses in the Mini-Finland survey was also very similar (Lehtinen et al., 1991).
The lifetime prevalence of BPI was 0.24% and 0.12% of subtype with psychotic features. Although the prevalence 1% of BPI has been usually presented in the literature, in recent World Mental Health Survey, a LTP of 0.6% (range 0.0%-1.0%) was found (Merikangas et al., 2011). The variation of estimates has been larger in earlier studies (Ferrari et al., 2011, Grant et al., 2005). The result presented here cannot be directly compared with the World Mental Health Survey, where the WHO CIDI version 3.0 was used. Instead, a very similar result was obtained in the Lundby study (Bogren et al., 2009) with methods close to this study. Their slightly higher estimate, 0.34%, included also bipolar II and NOS types. The low prevalence of bipolar I disorder in this study is not likely to be a consequence of inadequate screening, because of the multiple sources of information used. However, there may be subjects with bipolar I disorder among the eleven subjects who received a diagnosis of bipolar disorder NOS because of inadequate information to assign a more specific diagnosis. If all these subjects had bipolar I disorder, the prevalence would increase up to 0.39%.

The prevalence and incidence of bipolar I disorder in previous Finnish studies (Kieseppä et al., 2004, Räsänen et al., 1998, Sorvaniemi and Salokangas, 2005, Veijola et al., 1996, Väisänen, 1975) have been even lower compared with these results. Higher LTP 0.53 % for Bipolar I disorder was reported among the young adults in the same Health 2000 Survey (Suvisaari et al., 2009). However, the estimate also included those who developed the disorder later than the baseline Health 2000 Survey, which increased the prevalence. Altogether, it seems that the lifetime prevalence of bipolar I disorder in Finland is being towards the lower end, but still within the reported range worldwide.

The LTP (0.35%) of MDD with psychotic features was lower than in the few older studies (Johnson et al., 1991, Ohayon et al., 2002) but close to the Lundby study (Bogren et al., 2009). Diagnosing psychotic depression is challenging in clinical settings (Maj et al., 2007), and especially in general population studies. If the

diagnosis of psychotic depression is not assessed and symptoms carefully recorded during treatment, it is extremely difficult to evaluate later, whether thoughts, for example mood congruent thoughts of guilt are of delusional intensity or not. Thus, this study's estimate is probably conservative. Suprisingly, no statistically significant differences were found between genders, even though the LTP of MDD is almost twice as common in women compared with men (Pirkola et al., 2006).

The substance-induced psychotic disorders were frequent in the Finnish general population, and more prevalent in men compared with women, as could be expected. Most of these disorders were alcohol-induced with LTP 0.41%, while LTP for other substance-induced psychotic disorders was lower, 0.03%. In young adults (Suokas et al., 2010), the proportion of other substances in psychotic disorders was higher. Prevalence of substance-induced psychotic disorders are not included in the most recent general population studies of psychoses, but comparable 50-year prevalence 0.59% was found in the Lundby study (Bogren et al., 2009). Almost 10% of first-admission patients submitted to hospitals have been found to have substance-related psychoses, caused mainly by substance other than alcohol (Cantwell et al., 1999, Kirkbride et al., 2006). This proportion still underestimates the disorders, as many subjects with substance-induced psychotic disorders are not treated in hospitals. Concordant with this, the case ascertainment was challenging: half of the subjects with substance-induced psychotic disorders were found by the diagnosis of a psychotic disorder diagnosis in the hospital discharge register and one third by the screen of CIDI positive psychotic symptoms. Case notes were the most important source of information in diagnosing substance-induced psychotic disorders.

The lifetime prevalence of psychotic disorders due to GMC was 0.21%, in the age group 65 years and over 0.75% and aged 80 and over 1.71%. The prevalence of psychosis due to GMC was higher in the Lundby study compared with this study's results. This is not suprising, as in a prospective setting with multiple sources of information many more affected subjects could be found. These often elderly subjects may not recall their symptoms in one interview and psychosis diagnoses may not be recorded during treatment. High prevalence of any psychotic disorder in the elderly has been also found in previous studies including individuals over 65 or over 80 years old (Alanen et al., 2008, Ritchie et al., 2004, Östling et al., 2009). The age range in the previous general population sample studies of psychotic disorders has been of lower age (Kendler et al., 1996, Kessler et al., 2005, van Os et al., 2001). The majority of subjects (92%) having psychotic disorder due to GMC and over half (57.6%) of the subjects with any lifetime psychotic disorder had been diagnosed with dementia in the age group of 80 years and over. Lifetime prevalence of psychotic disorders due to GMC is clearly an underestimate here, since many somatic diseases are associated with psychotic symptoms, which are though rarely diagnosed separately and reported in case notes. However, with the information

from the case notes, this study was able to identify many subjects with a new onset psychosis, subsequently diagnosed with dementia and thus diagnosed with GMC related psychotic disorder (Korner et al., 2009).

Sociodemographic features of psychotic disorders (Study II)
Sociodemographic correlates of non-affective psychotic disorders in the PIF study were generally similar to other general population studies (Isohanni et al., 2001, Kendler et al., 1996, Kessler et al., 2005, Lehtinen et al., 1991, Miettunen et al., 2007, Morgan et al., 2012). Being retired was common (70%) among subjects with non-affective psychotic disorders, most of them being below the pension age and reported having disability pension. One third of subjects with non-affective psychotic disorder had reached the pension age (63 years) and 87.0% of those retired below that age reported having disability pension.

Being divorced was more common in subjects with affective psychoses than in the general population, which fits with earlier studies on bipolar disorders (Kessler et al., 1997, Mitchell et al., 2004). Many studies of affective psychoses have found an association with low income and education (Grant et al., 2005, Jonas et al., 2003, Kessler et al., 1997, Merikangas et al., 2007). The overall picture is similar compared with other studies finding socioeconomic difficulties to be less pronounced in affective psychosis group compared with non-affective group (Gureje et al., 2002, Waghorn et al., 2012).

6.3 Geographic variation of psychotic disorders (STUDY II)

All psychotic disorders were more common in subjects born in rural areas compared with those born in urban areas. Other urban-rural differences in the prevalence of psychotic disorders were not found. Instead, prominent regional variation was found in the LTP of schizophrenia, other non-affective psychotic disorders, and for any psychotic disorders, consistent with previous Finnish studies (Haukka et al., 2001, Hovatta et al., 1997 Lehtinen et al., 1990, Suominen, 1975). Over two-fold differences were detected between the lowest and the highest prevalences. The LTP of schizophrenia in Northern Finland (1.8%) was substantially higher than the 90% percentile of LTP 1.16% in the review of Saha et al. (2005).

These results may be related to using prevalence data: urban–rural difference in the prevalence of schizophrenia is not clear (Saha et al., 2005) even though the incidence is higher in urban areas (McGrath et al., 2004). It has to be noted that urban-rural differences have mainly been detected in developed western countries, mainly in Europe and in USA (Kelly et al., 2010, March et al., 2008). However, there are also other western countries, such as Australia, Ireland and Sweden, where being born in sparsely populated areas may increase the risk of schizophrenia

(Harrison et al., 2003), or rural high prevalence areas have been found (McGrath et al., 2001, Torrey et al., 1984, Scully et al., 2004).

The larger regional differences in prevalence according to place of birth than according to place of residence in this study agree with earlier findings and support the view that area-related environmental factors influence the risk of psychoses early during the lifespan (Marcelis et al., 1998, Pedersen and Mortensen, 2001, Scully et al., 2004). The highest impact of place of birth was found on schizophrenia: the OR 7.72 was found for those born in the North compared with those born in the SouthWest.

Affective psychoses differed from non-affective psychoses in showing no regional variation. The results were consistent with previous studies (Kirkbride et al., 2007b, Pedersen and Mortensen, 2006b, Scully et al., 2004). The findings may support higher vulnerability to early environmental risk factors in schizophrenia compared with bipolar disorder (Murray et al., 2004, 2005). However, the small number of cases with affective psychosis in the current study may contribute to the negative finding.

The results of this study support the earlier conclusions that the possible risk factors for psychotic disorders affecting in the urban environment in many other western countries have been, and may still be, more prevalent in the mostly rural Eastern and Northern regions of Finland (Haukka et al., 2001). For example at the beginning of the 1960s, Eastern and Northern Finland used to be the least developed regions with higher infant mortality, shorter duration of pregnancies, and newborns significantly more often underweight than in South and West Finland (Palmgren, 1964). These regions are still today characterized by high migration rates, high unemployment, and lower level of education. Thus, many early environmental risk factors (Cannon et al., 2001) for psychoses have existed in these high prevalence areas.

There are also many other factors that might explain the different geographic variation of psychotic disorders in Finland compared with many other European countries. Differences in sociocultural settings, existence of sparsely populated areas and lack of large metropolitan cities may affect the distribution. High latitude (Saha et al., 2006) could be one factor affecting the high prevalence of schizophrenia in the North. Another possible explanation for regional differences is clustering of genes predisposing to psychotic disorders in the East and the North (Hannelius et al., 2008). Different genetic background of the illness could result from genetic drift related to small number of founder families in genetic isolate found from NorthEast Finland (Hovatta et al., 1997, Varilo et al., 2000). Diverse populations have also been found to differ in the associated risk alleles of schizophrenia in addition to the differences in the prevalence (Paunio et al., 2009).

No evidence of marked selective migration of subjects with psychotic disorders was found. The risk of psychotic disorders was equal in those born in the same area, regardless of whether they had later migrated to other regions of the country or not. As both good and poor mental health may provoke higher rate of mobility than the average, though for different reasons in different places, migration is a difficult issue to examine in relation to psychiatric morbidity (Freeman, 1994, Salokangas et al., 2001, Pedersen and Mortensen, 2006a). The bias due to regionally variating availability and use of services was minimized by including those without psychiatric hospital admission and also obtaining information on mental health treatments in primary care.

These results support the view that urban life in itself does not increase the risk of psychotic disorders (Zammit et al., 2010). Instead, it can be seen as proxy variable for a factor or factors that more directly contribute to the risk of schizophrenia (Tandon et al., 2008). These factors responsible for, or mediating the association, are largely unknown although several different aspects including environmental and genetic factors have been hypothesized. Wide diversity of potential candidates including for example air pollution, cannabis and social exclusion has been studied (Kelly et al., 2010). There may be a synergistic effect between the exposure to urban environment and genetic vulnerability to schizophrenia (Van Os et al., 2004) The words of Tandon (2008) well describe the situation: "Although it appears that our understanding of the causation of schizophrenia has substantially increased over the past two decades, what we can confidentially assert is essentially the same - both genetic and environmental factors are important, but exactly which specific exposures and exactly how they cause schizophrenia is still unclear".

When investigating determinants of urban-rural variation in schizophrenia, it may be important to study both individual and different area level determinants (March et al., 2008, Zammit et al., 2010) like social capital (Allardyce et al., 2005, Kirkbride el al 2008) and social fragmentation (March et al., 2008), and generally signs of deprivation (Losert et al., 2012, Wicks et al., 2010). Moreover, it is likely that the risk attributable to 'urban' varies significantly in different sociocultural settings in different times.

6.4 Alcohol-induced psychotic disorders (STUDY III)

This study found LTP of 0.51% of alcohol-induced psychotic syndromes in the Finnish population aged 30 and over, 0.96% for men and 0.12 for women. A notably high LTP (1.8%), which was higher than schizophrenia, was found in working age men. The results are comparable with cumulative incidence of substance-induced psychotic disorders in a Swedish (Bogren et al., 2009), as well as with a Norwegian study (Astrup, 1989). Higher prevalence of AIPS in men was expected, as alcohol

dependence is much more common in men (Pirkola et al., 2006). Consistent with previous findings (Tsuang et al., 1994, Schuckit et al., 1995), disadvantaged socioeconomic position among people with alcohol-induced psychotic disorders was pronounced even when compared with subjects with alcohol dependence without psychosis.

A higher LTP of alcohol-induced psychotic disorders than delirium was found contrary to earlier hospital samples (Soyka, 2008a,b). As the study sample included a random sample of individuals aged 30 and over, many of the subjects with delirium could have died already before the sample selection (Lindelius et al., 1974, Lindelius and Salum, 1972). Hospital samples (Soyka, 2008a,b) may also produce higher estimates of delirium, as the syndrome usually leads to intensive hospital care everywhere, but alcohol-induced psychotic disorder may not. The variability between the treatment systems in alcohol and drug treatment (Babor et al., 2008) affects the accessibility of hospital treatment in subjects with alcohol dependence in different countries. High variability between the treatment units for alcohol-induced psychotic disorders was also notable in this study.

Assessing the subtype of the disorder according to whether the person had had hallucinations or delusions as the most prominent symptoms was challenging. Although 98% were diagnosed as having the subtype with hallucinations as prominent symptoms, over half of them had also had delusions. This finding is consistent with previous results (Achte et al., 1969, Lehtonen, 1996), suggesting that diagnostic validity of subtypes in the psychotic disorders related to specific substances should be further studied (Matthias et al., 2008).

Supporting earlier results two thirds of subjects with AIPS had comorbid psychiatric disorders (Jordaan et al., 2009, Lehtonen, 1996, Tsuang et al., 1995, Schuckit et al., 1995). The high frequency of comorbidity of different mental disorders with alcohol abuse reflects the overlapping environmental, genetic and neurobiological factors that negatively influence both types of disorders (Kendler et al., 2003). One view to explain this complex issue has been the chronic stress model which suggests how the substance abuse of some susceptible patients increases their risk of mental disorders and the other way around (Bardy et al., 2005). Sedative or hypnotic misuse, which has been associated with more severe alcohol withdrawal episodes (Schuckit et al., 1995), was also common in AIPS.

The group of subjects with AIPS had in most cases had a long history of heavy alcohol use, as expected (Eyer et al., 2011, Jordaan et al., 2010, Soyka et al., 2008a). All subjects had sought some treatment for alcohol problems, although not necessarily for psychotic symptoms. In comparison, only 25% of subjects with

active alcohol dependence had used some services for alcohol or mental health problems during 12 months (Pirkola et al., 2006).

AIPS was also associated with high medical comorbidity (Moos et al., 1994) and high use of health services. Subjects with AIPS compared with subjects with alcohol dependence had had more hospital treatments (91% and 16%, respectively) and among the hospital treated, higher number of treatment episodes (mean 6.5 and 2.8, respectively). Twin studies have suggested organ-specific vulnerabilities of alcohol damage (Kendler, 1985, Hrubec and Omen, 1981). No evidence was found for this. On the contrary, the affected subjects had a wide range of medical consequences due to alcohol use. Subjects with alcohol-induced psychosis had more comorbid mental disorders compared with subjects with alcohol-induced delirium. Unexpectedly there were no differences found in medical comorbidity between these groups (Glass, 1989b, Fiellin et al., 2002). These results support the hypotheses that the two conditions could be different manifestations of the same process (Glass, 1989a). However, the small number of subjects in this study did not allow the detection of small differences.

Thirteen percent of subjects with alcohol-induced psychotic syndrome developed another psychosis 5 to 10 years later, including 3% who developed schizophrenia. Half of the subjects with cannabis-induced psychosis have been found to later develop a schizophrenia spectrum disorder, challenging the validity of substance-induced psychotic disorders (Arendt et al., 2005). The effect of psychotic disorders in parents on the risk of developing alcohol-induced psychotic syndrome in patients could not be assessed (Arendt et al., 2008, Chen et al., 2005), but paternal alcohol problems and paternal mental health problems were associated with developing alcohol-induced psychosis or delirium in subjects with alcohol dependence. This result is in agreement with earlier studies finding an association between alcohol disorders in parents and offspring (Merikangas et al., 1998, Pirkola et al., 2005). Specifically the paternal problems could suggest that elevated risk might be related to the family environment instead of genetic predisposition only (Jaffee, 2003). The complex mechanism of family-related genetic and environmental factors in developing psychosis related to alcohol and other substances is a subject for future studies.

The mortality of subjects with lifetime AIPS was high: 37% of subjects had died during the eight years of follow-up. The age and gender adjusted HR was 20 compared with the rest of the sample and 12 compared with alcohol dependent subjects without psychosis. This accords with the Swedish Lundby study which also found that AIPS was a risk factor for high mortality among subjects with alcohol use disorders (Mattisson et al., 2011). There were no differences in mortality between subjects with history of alcohol-induced psychosis or delirium. These results accord

with a Finnish study which found 44% mortality for both groups during a 10 to 15 year follow-up (Lehtonen, 1996). These high figures inform about the substantially elevated mortality risk of subjects with prior history of AIPS compared with the general population.

6.5 Comparison of delusional disorder and subtypes of schizophrenia (STUDY IV)

Delusional disorder compared with subtypes of schizophrenia
Delusional disorder showed typical features different from paranoid schizophrenia and the other schizophrenia subtypes, suggesting good validity of the diagnosis. The mean age of onset of delusional disorder was higher and outcome was better compared with persons with schizophrenia, consistently with previous research (Kendler et al., 1980, 1982). Symptom severity, as assessed by the Major Symptoms of Schizophrenia Scale, was very similar to that found by Kendler and Walsh (1995) in the Roscommon Family Study sample. The subjects had prominent delusions, but low levels of other symptoms.

Compared with the results of this study, some clinical samples have found lower age of onset and high levels of depressive symptoms (Hsiao et al., 1999, Maina et al., 2001, Serretti et al., 1999). It is possible that persons with high level of mood symptoms had turned out to have another disorder during their lifetime and persons finally diagnosed with delusional disorder represented a group close to the original description of paranoia by Kraepelin (Kendler and Tsuang, 1981). Delusional disorder and paranoid schizophrenia were different in clinical features, prognosis and treatment, as in another recent study (Marneros et al., 2012).

The severity of delusions did not differ between groups, but there were differences in almost all other symptom dimensions. Subjects with paranoid schizophrenia had more severe hallucinations, bizarre delusions, affective deterioration, depressive symptoms, bizarre behaviour and avolition, but also more often chronic course and poorer outcome of illness than subjects with delusional disorder. Many of the differences are expected by the diagnostic criteria, like differences in hallucinations, bizarre behaviour and negative symptoms. Mental hospital admissions, and also involuntary admissions, were less frequent in subjects with delusional disorder compared with subjects with any schizophrenia subtype. Only half of subjects with delusional disorder had ever received inpatient treatment. Thus, hospital samples may provide a biased picture of delusional disorder. The largest differences were seen in the status of current treatment: only 21% of subjects with delusional disorder had current treatment contact and 14% used antipsychotic medication, whereas the majority of subjects with schizophrenia had both of these. However, over 80% of subjects with delusional disorder and without current treatment were rated as in the

need for it. Thus, more attention should be paid to the continuity of treatment in delusional disorder. Even though the outcome of delusional disorder is better compared with paranoid schizophrenia (Marneros et al., 2012), their subjective quality of life was second lowest among the psychotic disorders (Saarni et al., 2010).

Subtypes of schizophrenia

The lifetime prevalences of schizophrenia subtypes in DSM-IV were 0.24% for paranoid schizophrenia, 0.42% for undifferentiated schizophrenia and 0.16 % for disorganized schizophrenia. Disorganized schizophrenia was more common in males than females. No gender differences were found for paranoid or undifferentiated subtypes, contrary to older studies (Fenton and McGlashan, 1991, Kendler, 1984). The observed gender distributions could be explained by the cross-sectional sample representing relatively old population and not including earlier deceased subjects from the same birth cohorts. Suicide mortality is higher in subjects with paranoid schizophrenia than in the other subtypes (Fenton and McGlashan, 1991), and higher in males than females (Gruenberg et al., 1985).

Disorganized schizophrenia differed notably from the other schizophrenia subtypes, contrary to studies using DSM-III and DSM-III-R that found undifferentiated schizophrenia resembling disorganized schizophrenia (Fenton and McGlashan, 1991 Gruenberg et al., 1985, Kendler et al., 1984, 1994, Korver-Nieberg et al., 2011). Subjects with disorganized schizophrenia had a 13-15 years earlier age at onset, more severe thought disorder, catatonic symptoms, bizarre behaviour, and negative symptoms and worse outcome than subjects with paranoid and undifferentiated schizophrenia. None of them were rated as recovered, while a recent meta-analysis of recovery in schizophrenia found a median proportion 13.5% (25%–75% quantiles 8.1%–20.0%) of recovery in schizophrenia (Jääskeläinen et al., 2012). They had spent almost ten years in inpatient treatment. This study's results support the validity of DSM-IV disorganized schizophrenia as a schizophrenia subtype. It has good descriptive and predictive validity delineating a group of patients with schizophrenia with poor outcome.

There were relatively small differences between subjects with paranoid and undifferentiated schizophrenia. There were only minor differences in formal thought disorder and some negative symptoms between the subtypes and no significant differences in age at onset, course and outcome between paranoid and undifferentiated schizophrenia. These results suggest that paranoid and undifferentiated schizophrenia are more similar in the DSM-IV than in previous definitions of the subtypes.

All subjects with schizophrenia had had mental health treatment contact, but subjects with disorganized schizophrenia had more often been treated in mental

hospitals and more often had current treatment contact. Most subjects with schizophrenia were also using antipsychotic medication at the time of the survey (64%-92%). Similar results have been found in the Northern Finland 1966 birth cohort study, in which 77% of subjects with schizophrenia had a treatment contact and 71% were using antipsychotic medication after median 11 years since the onset of psychotic disorder (Lauronen et al., 2007).

Altogether, paranoid and undifferentiated schizophrenia as defined by the DSM-IV were quite similar disorders. This could reflect the overlapping of the constructs of the subtypes and support the subtypes being left out from the DSM-V (Keller et al., 2011, Tandon, 2012). However, disorganized schizophrenia was a diagnosis with a good validity and clinical utility as delineating a group of patients with schizophrenia with poor outcome. Instead of subtyping, use of a severity scale is proposed for the DSM-V psychotic disorders. It closely resembles the MSSS (see Supplement 2). However, the symptom scale in the DSM-V is proposed to describe the symptom dimensions during last month while MSSS assessed average severity of the symptoms over the entire course of illness. The criterion of a bizarre delusion or a Schneiderian first-rank symptom hallucination as a single symptom to judge a diagnosis of schizophrenia, has been proposed to be omitted from the DSM-V. At the same time bizarre delusions would not exclude delusional disorder (Tandon, 2012). Thus the results of this study cannot be directly generalized to the proposed DSM-V.

6.6 Methodological considerations

This study was a nationally representative general population study of different psychotic disorders. The major strength was the use of multiple sources of information for screening and diagnostic assessment, making possible to assess specific psychosis diagnoses. The diagnoses were based on careful evaluation of the lifetime information from the case notes and the SCID-I interview.

The agreement between register diagnoses in the National Hospital Discharge Register and the best-estimate diagnoses was excellent, with all registers together good, but only modest or poor with other screens. Registers were the most sensitive screens, while self-reported psychosis and psychosis assessed by the physisian in were specific, but sensitivity was poor. Registers were the most important source of information also in the Mini-Finland Survey (Lehtinen et al., 1990). The kappa value 0.80 for the National Hospital Discharge Register was similar to findings in the Northern Finland Birth Cohort study (Isohanni et al., 1997, Moilanen et al., 2003). In this study, registers were most reliable in ascertaining non-affective and affective psychoses, whereas in substance-induced and GMC related psychotic disorders the collection of information from several sources was even more

essential. Thus, hospital register information is good, but not excellent, for case ascertainment of psychotic disorders alone. The lower concordance of other registers could be expected, as only three first digits of the ICD diagnoses were recorded earlier and therefore all subjects with MDD were also included for screening. It has also to be noted that the good agreement of research and register diagnoses concerned the group of all psychotic disorders and conclusions on specific diagnoses on the basis of this information cannot be made.

Different availability and use of services in different areas is a potential source of bias especially in register-based studies (Kelly et al., 2011). However, individuals without history of psychiatric hospital admission were included in this study, and information from primary care was also obtained. The highest prevalence of psychotic disorders was found in the northern, rural parts of the country with long distances to nearest hospitals. Thus the bias due to mental health organizational differences (Korkeila, 1998, Jörgensen et al., 2009, Salokangas et al., 2001, 2011) was minimalized. Mortality in schizophrenia has been highest in the East and the North for decades (Jousilahti et al., 1998), but it does not explain regional differences in prevalence in this study. However, mortality varies even in small regions and may affect the prevalence (Kiviniemi et al., 2010, Rantanen et al., 2009). As all subjects with schizophrenia had had some treatment contact during their lifetime, a great improvement on the coverage of the registers is that information from outpatient treatment, both secondary and primary services is also possible to be gathered from the beginning of the year 2011 (Rautiainen and Saukkonen, 2012). A major problem is that similar high quality register information is available only in other Nordic countries (Tsuang et al., 2011 p. 117). This could also account for at least part of the high prevalences found in the high latitudes (Saha et al., 2006). However, these findings emphasize that several sources of information are essential to achieve the best possible coverage of the subjects with psychoses in the general population

CIDI alone was not a reliable method of screening psychotic disorders. The high proportion of false positive in the psychotic symptoms section was in accordance with earlier results (Kendler et al., 1996, Kessler et al., 2005, vanOs et al., 2001), but the proportion of false negatives was found to be higher than previously thought (Kessler et al., 2005). Less than third of all subjects with psychotic disorders would have been found if the only screen would have been the CIDI section G. The section F assessing mania symptoms in the CIDI was found to be equally unreliable, finding only 25% of the subjects with bipolar I disorder. The results support the view that re-interviews and extensive collection of information is of equal importance in affective and non-affective psychoses (Kessler et al., 1997, Mitchell et al., 2012, Regeer et al., 2004), although the new version CIDI 3.0 seems to be more reliable than older CIDI-versions (Kessler and Ustün, 2004, Kessler et al., 2006). To also

find earlier unrecognized subjects with affective psychosis, all subjects with temporary or permanent pension and medication reimbursement with the diagnosis of MDD were included. All subjects treated with lithium or anticonvulsants were also included, if they were not selected already by any other screens. Altogether, these screens should have found at least those with the most severe course and outcome of BPI and psychotic depression. However, in affective psychoses, sociodemographic features, social functioning, quality of life or medical comorbidity (Partti et al., 2010, Saarni et al., 2010, Viertiö et al., 2012) did not as markedly differ from the general population as in non-affective psychoses, suggesting that there may not be a bias toward the most severely affected cases. Self-reported or phycisian assessed psychotic disorder produced only few false positive cases, e.g. the specificity was excellent, supporting previous results (Jablensky et al., 2001). However, the sensitivities of these screens were poor.

Also the effect of diagnostic methods was of major importance. Obtaining case notes and assessing the best-estimate diagnoses on the basis of all available information made possible the estimation of prevalences across all of psychotic disorders. Even in semi-structured SCID interview, all subjects were not able nor willing to describe their psychotic and affective symptoms or the precise course of them accurately enough for a specific diagnosis. This supports earlier findings showing that interviews concerning the lifetime presence of mental health disorders have a significant risk of missing information (Fanous et al., 2012). General population studies, as well as incidence and family studies of psychoses using case notes in addition to semi-structured interviews have found more subjects having psychotic disorders compared to studies using only self-reported information (Bogren et al., 2009, Isohanni et al., 1997, Kendler et al., 1993, King et al., 1994, McNaught et al., 1997, Östling et al., 2002)

The oldest subjects might not have remembered psychotic and affective symptoms, if these have occurred decades ago. This recall bias was partially overcome by using register data, and case note data collected on a lifetime basis also from primary care if needed. However, the recall bias may have affected more the estimates of disorders with intermittent course like BPI. If all subjects diagnosed with bipolar disorder NOS because of insufficient information had BPI, the prevalence would rise to 0.39%.

The diagnoses of this study were based on the lifetime duration of the disorder. Many subjects had received different psychoses diagnoses during their lifetime. Differential diagnosis between different psychotic disorders is difficult especially during the acute phases and during the early course of the disorder (Laursen et al., 2005, Castagnini et al., 2008, Singh et al., 2004, Tohen et al., 2012), as these disorders share a number of symptoms (Rosen et al., 2012). Challenges in diagnostic

assessment may be reflected as the high prevalence of psychotic disorder NOS found also in this study.

Although this study was based on a survey of more than 8000 individuals, the number of cases in different disorder categories was still relatively small, leading to wide confidence intervals. The response rate of the Health 2000 Survey was excellent (93%). In spite of this the effect of nonresponse on prevalence estimates was even higher than previously thought (Kessler et al., 2005). Including also subjects having a specific register diagnosis of psychosis in the nonresponse group still increased the prevalence of all psychotic disorders from 3.06% to 3.48%. This study included also homeless and institutionalized persons, population segments that might have a high prevalence of psychoses (Fazel et al., 2008, Goldner et al., 2002, Kessler et al., 2005, Teesson et al., 2004). However, these findings cannot be directly generalized to other studies because the rates of institutionalization and homelessness are highly variable between countries.

The lifetime prevalence found here can be regarded as conservative estimates, as subjects with a lifetime psychotic disorder not having prior hospital treatment or other mental health care contact exist, and may have declined from the Health 2000 Survey. Especially, LTP of psychotic disorder due to GMC is underestimated. Most of the affected subjects are elderly and majority of them are not treated in psychiatric field and they are impossible to find for this kind of study, which was also supported by one case with psychotic disorders due to GMC in the control group. The same concerns substance-induced psychoses, even though the LTP was unexpectedly high.

Major limitation in the current study is the exclusion of young adults under 30 years. Among young adults, the incidence of schizophrenia is high (Suvisaari et al., 1999), but the lifetime prevalence may be lower compared to middle-aged groups. In overall prevalence, the exclusion of this age group was probably compensated by the higher mortality of subjects with psychotic disorders. However, the exclusion of young adults may have lowered the prevalence of bipolar I disorder (Suvisaari et al., 2009) and substance-induced psychotic disorders (Suokas et al., 2010). The minor differences in results between genders in this study could be explained by the age group inclusion: young men, among whom the incidence of schizophrenia is high, were not included. The oldest age groups were included in this study, compared to more usual 54-64 year upper limit. This increased the lifetime prevalence of especially delusional disorder and psychoses related to GMC. Exclusion of young adults may have also lowered the risk related to urban birth (Haukka et al., 2001). The psychotic or psychotic-like symptoms (van Os et al., 2001) in young adults especially are a subject for further studies.

The LTP figures of AIPS are underestimates, as subjects with alcohol dependence are over-represented in the non-response group (Mäkelä et al., 2010). Symptoms of the subjects may not be systematically described in alcohol related treatment services. Further, diagnoses may neither be coded within these services. There was not always enough information on the diagnostic criteria requiring the lack of insight related to psychotic symptoms during the psychotic episode. Thus, those who specifically sought help for psychotic symptoms were included. This may limit the comparison with clinical studies. Other substance-induced psychoses were not included in this study, as they were extremely rare in this age group. In young adult population the use of of illicit drugs and other substance induced psychoses was more common: 91% of the substance-induced psychotic disorders were induced by other substance than alcohol among young adults below 30 years (Suokas et al., 2010) compared with 6% in this age group.

Variability in service systems (Babor et al., 2008) may have had an effect on the estimates of AIPS in earlier hospital samples (Soyka, 2008a,b) as well. In some countries, psychiatric sector plays a large role in alcohol and drug treatment, while in Finland the social service sector has played a major role in treatment. Delirium usually contributes to intensive hospital care everywhere, but the variability of the treatment systems affects the accessibility of psychiatric hospital treatment in other patients with alcohol dependence. Accordingly, only a third of study subjects with a first episode of alcohol-induced psychosis were treated in a psychiatric hospital, whereas the corresponding figure was over 70% for subjects with delirium.
Subtypes of schizophrenia have not been included in previous general population studies. This study sample is older compared with many clinical studies, thus including potentially more late-onset cases, but also those with better outcome, as mortality in schizophrenia is high already at young age (Heilä et al., 2005). The reliability of the diagnoses in subtypes of schizophrenia was best for disorganized schizophrenia, but poor between two raters for the undifferentiated type. However, there were only a few cases of individual schizophrenia subtypes, and thus small disagreements had a large effect on kappa values (Spitznagel et al., 1985). If undifferentiated schizophrenia cannot be diagnosed reliably even in research settings, its reliability in clinical practice is questionable. On the other hand, the overall reliability of schizophrenia diagnosis was excellent between all raters. Diagnostic assessment based on longitudinal information improved diagnostic reliability, compared with cross-sectional studies, and the diagnostic challenges caused by instability of the diagnoses in the early phases of the illness (Fenton and McGlashan, 1991, Fennig et al., 1996) was avoided. Catatonic subtype (Fink et al., 2009) was too rare to be investigated.

6.7 Conclusions

PIF was the first general population survey reporting the lifetime prevalence of specific psychotic disorders in DSM-IV. The results are congruent with a recent study from Sweden with comparable methods, as well as with other Finnish studies. Schizophrenia, in accordance with earlier Finnish studies, was found to be in the highest range of the findings from many countries. In contrast, bipolar I disorder was found to be more common than in previous Finnish studies, but still in the lower range of international findings. However, schizophrenia and bipolar I disorder represent together only less than half of psychotic disorders occurring in the general population. In the elderly, delusional disorder and psychoses related to general medical condition are common conditions causing suffering and need of care. Further studies including also young adults are needed. As psychotic disorders are among the most severe and impairing conditions, with a lifetime prevalence exceeding 3%, these disorders are a major public health concern.

National registers, especially National Hospital Disharge Register, were most reliable in screening non-affective and affective psychotic disorders. The validity of register diagnoses of different specific psychosis diagnoses is a subject for further studies. The use of multiple sources of information in detecting and diagnosing psychotic disorders in future epidemiological studies improves obtaining reliable estimates.

Psychotic disorders occur unevenly in different areas. As opposed to many countries with high density populations and metropolitan areas, the psychotic disorders are not more common in urban areas in Finland. In Finland, the North and the East are high prevalence areas of psychotic disorders, particularly of schizophrenia. This should be taken into account when resources are allocated to health care. Longitudinal studies are needed to investigate the reasons for the regional differences in prevalences. Although selective migration was not found in this study, studying association of the time lived in the area of birth with psychoses may be also fruitful in future studies. Affective psychoses showed no geographic variation, but were also associated with different socioeconomic factors than non-affective psychoses. Schizophrenia and other non-affective psychoses were associated with considerable socioeconomic disadvantage.

Alcohol-induced psychotic disorder and delirium have not been included in recent general population studies. However, these syndromes have severe consequences when they do appear. The disorders are associated with high number of hospital treatments and with high mortality. The important role of alcohol in psychosis should be noted in future studies and interventions for those at risk should be presented. Clinical picture of delusional disorder was different from other forms of

traditional paranoid psychoses, especially paranoid schizophrenia. All schizophrenia subtypes did not show distinctive features proposing diagnostic validity. This supports the proposition that the subtypes are being left out from the DSM-V. However, disorganized schizophrenia was associated with earlier age of onset and more severe symptoms contributing to far longer hospital care. Even if the subtypes of schizophrenia may be removed from the next diagnostic classifications, the symptoms associated with severe course of illness should be recognized during treatment. Attention should be paid to the recognition and treatment continuity in delusional disorder.

The studies comprising this thesis represent basic epidemiological studies assessing different psychotic disorders, also with the purpose of providing tools for future aetiological studies. Including other comorbid psychiatric disorders in addition to the whole dimension of psychosis in the future epidemiological studies may also help to understand better this complex phenomenon. The high prevalence of psychotic disorders found here challenges the old interpretation of evenly distributed prevalence of psychotic disorders worldwide. The knowledge and recognition of different psychotic disorders and psychotic symptoms should be improved. The high and unevenly distributed prevalence of psychotic disorders should also be taken into account when resources are allocated to health care. Possibility to work and to have an active and meaningful life should also be provided for those affected by a severe mental disorder. Health care systems should be developed to provide the best possible individual and flexible treatment and active rehabilitation for individuals affected by different psychotic disorders.

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8 Supplements

Supplement 1. The questions assessing psychotic symptoms in the M-CIDI section G (Wittchen et al 1998).

CG1	Have you ever believed people were spying on you?
CG2	Was there ever a time when you believed people were following you?
CG2B	Have you been convinced that people you saw talking to each other were talking about you or laughing at you?
CG3	Have you ever believed that you were being secretly tested or experimented on?
CG4	Have you ever believed that someone was plotting against you or trying to hurt you or poison you?
CG5	Have you ever been convinced that someone you had not met was in love with you?
CG6	Have you ever been unreasonably convinced that your spouse or partner was being unfaithful, although ^AS1^ told you that was not true?
CG7	Have you ever believed that someone was reading your mind?
CG8	Have you ever been convinced you could actually hear what another person was thinking, even though he or she was not speaking?
CG9	Have you ever been convinced that others could hear your thoughts?
CG10	Have you ever been convinced that you were under the control of some power or force, so that your actions and thoughts were not your own?
CG11	Have you ever been convinced that strange thoughts, or thoughts that were not your own, were being put directly into your mind?
CG12	Have you ever been convinced that someone or something could take or steal your thoughts out of your mind?
CG13	Have you ever been convinced that you were being sent special messages through television or the radio, or that a program had been arranged just for you alone?
CG13B	Have you felt that a book, or newspaper, or song was meant only for you and no one else?
CG14	Have you ever felt strange forces working on you, as if you were being hypnotised or magic was being performed on you, or you were being hit by x-rays or laser beams?
CG17	Have you ever seen something or someone that others who were present could not see - that is, had a vision or hallucination when you were completely awake?
CG18	Have you more than once heard things other people couldn't hear, for example sounds or something like a voice?

CG20	Have you ever been bothered by strange smells around you that nobody else seemed to be able to smell, perhaps even unusual odours coming from your own body?
CG20C	Have you ever had strange tastes in your mouth that could not be explained by anything you had eaten or put in your mouth?
CG21	Have you ever had unusual feelings on your skin or inside your body - like being touched when nothing was there or feeling something moving inside your body?
CG22	Have you ever had a time when you were unable to move at all when it wasn't due to a physical or other medical reason?
CG22A	Have you ever had a time when you moved constantly and couldn't stop when it wasn't due to a physical or other medical reason?

Supplement 2. MAJOR SYMPTOMS OF SCHIZOPHRENIA SCALE
(MSSS, Kendler et al 1984, Printed by permission from Kenneth S. Kendler)

1. Hallucinations

1 – Absent	No evidence of hallucinations.
2 – Mild	Hallucinations either suspected or if present subject is aware that it is his imagination and is usually able to ignore the hallucinations.
3 – Moderate	Hallucinations definitely present, and patient generally believes in the reality of the hallucinations but the hallucinations have little, if any, influence on his behavior. Hallucinations are usually not very frequent.
4 – Severe	Hallucinations are usually frequent, and they have a significant effect on patient's actions, e.g., he locks doors to keep pursuers, whom he hears, away from him.
5 - Extremely severe	Hallucinations are usually very frequent and patient's actions based on them have a major impact on him or others, e.g., converses with voices so much that he is unable to work.

2. Delusions

1 – Absent	No evidence of delusions.
2 – Mild	Delusions either suspected or definitely present, but patient frequently questions the veracity of his beliefs.
3 – Moderate	Generally has conviction in his false belief, but delusion has little, if any, influence on his behavior.
4 – Severe	Delusion has significant effect on patient's actions, e.g. takes apart light fixture looking for "bugs". Patient usually somewhat preoccupied with delusion(s).
5 - Extremely severe	Actions based on delusion have major impact on him and others, e.g., stops eating because of belief that food is poisoned, boards up apartment and refuses to go out because of "mob" waiting to kill him. Patient is usually completely preoccupied with delusion(s).

3. Bizarreness of delusions

This item attempts to measure in the delusion the amount of departure from culturally determined consensual reality.

1 - Plausible -Example- The FBI is out to get me because I called up a radio talk show and told them I believed in Communism.

2 – Possible -Example- May next door neighbors have been putting drugs in my coffee so that they can knock me out and have sex with me.

3 – Unlikely -Example- They're trying to confuse me so they may change the stories around in my newspaper and come in and change the numbers in my telephone book.

4 – Bizarre -Example- I know what you're doing here. I hear the screams at night. Don't think I don't know that you kill people downstairs and then feed them to us.

5 – Extremely bizarre

-Example- They've got this machine all right. It causes mybrains to spin around at nighet and turns them inside out, causing me great pain.

4. Positive thought disorder

1 – Absent May be difficult to understand due to unnecessary details, little education, rambling or other nonpathological impediments to clear communication or simple flight of ideas which is completely understandable.

2 - Mild Occasional instances of though disorder which are of doubtful clinical significance and / or produce little impairment in understandability

3 – Moderate Thought disorder definitely present and severe enough to produce some impairment in understandability

4 – Severe Frequent instances of thought disorder which produce definite impairment in understandability

5 – Extremely severe

Thought disorder is so severe that most of speech is difficult or impossible to understand

5. Catatonic behavior

1 – Absent No evidence of catatonic behavior

2 – Mild Possibly present, but not clinically striking, e.g., possible brief posturing, some stereotyped gestures, occasional grimacing

3 – Moderate Definitely present, but only "mild" catatonic symptoms present, e.g., stereotyped gestures and gait, frequent grimacing, short episodes of posturing

4 – Severe Definitely present, "full" catatonic symptoms present, including catalepsy, negativism, mutism, prolonged posturing or episodes of excitement

5 – Extremely severe

Patient either persistently cataleptic, stuporous, negativistic and mute and has to be fed and bathed and / or has episodes of marked catatonic excitement (prolonged presence of purposeless, disorganized, highly excited behavior) requiring seclusion and usually restraints.

6. Affective deterioration

1 – Absent	No evidence of affective deterioration
2 – Mild	Only subtle evidence of mild blunting or inappropriateness of affect
3 – Moderate	Flattening and/or inappropriateness of affect definitely present, but not striking. Mild evidence of poor self-grooming or other socially inappropriate behavior may be present.
4 – Severe	Flattening and/or inappropriateness of affect is quite evidence usually with evidence of poor self-grooming or other socially inappropriate behavior
5 – Extremely severe	Patient's flattening of affect and / or affective inappropriateness are striking. Poor self-grooming and gross violations of public "mores" are frequent (i.e. masturbating in public, urinating on floor)

7. Negative though disorder

Poverty of speech and poverty of content of speech

1 –Absent	
2 – Mild	
3 – Moderate	Somewhat difficult to communicate with
4 – Severe	Rather difficult to communicate with
5 – Extremely severe	Effectively mute

8. Depressive symptoms

Include symptoms of mood, psychomotor activity, cognition and associate neurovegetative symptoms.

1– Absent
2 – Mild
3 – Moderate
4 – Severe
5 – Extremely severe

9. Manic symptoms

Include symptoms of mood, psychomotor activity, cognition and associate neurovegetative symptoms.

1 – Absent
2 – Mild
3 – Moderate
4 – Severe
5 – Extremely severe

10. Course

1 - Single episode
2 - Multiple episodes - full recovery between episodes
3 - Multiple episodes - partial recovery
4 - Chronic course with exacerbations - no true recovery
5 - Chronic course without exacerbations - no true recovery

11. Outcome

1 – Recovery
2 – Mild deterioration
3 – Moderate deterioration
4 – Marked deterioration

12. Precipitating factors

1 – Absent
2 – Possible
3 – Probable
4 – Definite

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