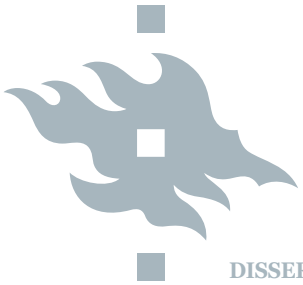

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METABOLIC CHANGES, INFLAMMATION AND MORTALITY IN PSYCHOTIC DISORDERS

Jaakko Keinänen

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To my family

ABSTRACT

People with psychotic disorders have an increased risk of obesity, cardiovascular disease and diabetes. There is also a pro-inflammatory activation associated with psychotic disorders which may increase cardiovascular risk. The mortality of people with psychotic disorders is increased, reducing the average lifespan by 15-20 years. However, people with first-episode psychosis (FEP) are generally physically healthy at the onset of the first psychotic episode, and the longitudinal development of low-grade inflammation in psychosis is largely unknown.

This study aimed to examine anthropometric (weight, waist circumference) and metabolic parameters in people with FEP at treatment onset and during a one-year follow-up. Predictors of weight gain and increase of waist circumference were investigated in FEP. The relationship between changes in anthropometric measures and low-grade inflammation was analysed. Weight, waist circumference and laboratory parameters, including a high-sensitivity assay of the inflammatory marker C-reactive protein (hs-CRP), glucose and lipid levels, were measured at study baseline, and at two and 12 months. At baseline, patients with FEP were compared to healthy, age, gender and region of residence matched controls. The longitudinal changes in anthropometric and laboratory parameters were examined within the group with FEP.

Another aim of the study was to investigate mortality and factors associated with mortality risk in psychotic disorders in Finland. The mortality in the Health 2000 population sample of 5642 Finns aged 30-70 years, including 106 patients with non-affective psychosis (NAP), was analysed with information on mortality and causes of death during a 13-year follow-up period.

People with FEP and healthy controls had similar body mass index, waist circumference, hs-CRP and fasting glucose at study baseline. However, people with FEP had higher total and low-density lipoprotein (LDL) cholesterol, triglyceride, insulin and insulin resistance levels at baseline. The median weight gain in FEP patients at the 12-month assessment was 9.6kg and increase of waist circumference 6.0cm. Insulin resistance and olanzapine medication at baseline predicted more weight gain during the 12-month follow-up in FEP. In addition, baseline insulin resistance predicted increase in waist circumference. A significant, over 2.5-fold increase was observed in hs-CRP during the follow-up in FEP. The hs-CRP levels were predicted by waist circumference and female gender in mixed-effects regression analysis.

The all-cause mortality hazard ratio (HR) adjusted for age and gender in NAP was 2.99, and the HR for mortality from natural causes 2.81. The all-cause mortality HR was reduced to 2.11 and natural cause HR to 1.98 when adjusted for socioeconomic factors, smoking, body mass index, chronic

physical disease and inflammation. Antipsychotic medication use was associated with lower natural cause mortality risk, and smoking with increased natural cause mortality risk in people with NAP.

In this study, people with FEP had a significant increase in body weight, waist circumference and low-grade inflammation during the first year of treatment of the psychotic disorder. Insulin resistance early in the treatment of FEP may be a marker for vulnerability for weight gain and abdominal obesity. The low-grade inflammation was strongly related to the increase in abdominal adiposity, suggesting that hs-CRP is primarily a marker of metabolic risk in FEP. Olanzapine was the most commonly prescribed antipsychotic in FEP despite the high risk for the associated weight gain. Antipsychotics with less weight gain potential should be considered as first-line treatment in FEP. Smoking cessation should be promoted in people with psychotic disorders to reduce excess mortality. The excess mortality in NAP was not completely explained by socioeconomic or lifestyle factors nor by chronic physical disease. There may be factors associated with quality of treatment of physical disease in NAP explaining part of the premature mortality in this population.

TIIVISTELMÄ

Psykoottisiin häiriöihin liittyy kohonnut lihavuuden, sydän- ja verisuonisairauksien ja diabeteksen riski. Lisäksi psykoottisiin häiriöihin on todettu liittyvän matala-asteinen tulehdus, joka nostaa sydän- ja verisuonisairauksien riskiä. Psykoosisairauksia sairastavien riski ennenaikaiseen kuolleisuuteen on muuta väestöä suurempi, ja heidän keskimääräinen elinikänsä on 15-20 vuotta muuta väestöä lyhyempi. Ensimmäistä kertaa psykoosiin sairastuneet ovat kuitenkin yleensä fyysisesti terveitä, eikä matala-asteisen tulehduksen kehittymistä ensipsykoosin yhteydessä ole juurikaan tutkittu pitkittäisasetelmissa.

Tämän tutkimuksen tavoitteena oli tutkia ensimmäistä kertaa psykoosiin sairastuneiden painoa, vyötärönympärystä sekä rasva- ja sokeriaineenvaihduntaa psykoosin hoidon alkaessa ja ensimmäisen hoitovuoden aikana. Tutkimuksessa selvitettiin painonnousun ja vyötärönympäryksen muutoksen ennustajia. Lisäksi tutkittiin painon ja vyötärönympäryksen yhteyttä matala-asteisen tulehduksen kehittymiseen. Paino, vyötärönympärys ja laboratoriomittaukset, kuten matala-asteisesta tulehduksesta kertova herkkä C-reaktiivisen proteiinin määritys (CRP), veren glukoosi ja rasva-arvot, mitattiin tutkimuksen alkaessa sekä lisäksi kahden ja kahdentoista kuukauden kohdalla. Tutkimuksen alkaessa ensimmäistä kertaa psykoosiin sairastuneita verrattiin terveisiin, iän, sukupuolen ja asuinalueen mukaan kaltaistettuihin verrokkihenkilöihin. Lisäksi tutkittiin seuranta-aikana ensipsykoosiryhmässä havaittuja muutoksia painossa, vyötärönympäryksessä ja laboratorioarvoissa.

Tutkimuksen toinen tavoite oli selvittää psykoottisiin häiriöihin liittyvää kuolleisuutta ja siihen liittyviä tekijöitä Suomessa. Kuolleisuutta ja kuolinsyitä tutkittiin Terveys 2000 -aineiston 5642 30-70-vuotiaan suomalaisen ja otokseen sisältyvän 106:n ei-affektiivista psykoottista häiriötä sairastavan joukossa 13 vuoden aikana.

Tutkimuksen alkaessa ensipsykoosiryhmän ja verrokkihenkilöiden välillä ei ollut eroja painoindeksissä, vyötärönympäryksessä, herkässä CRP-määrityksessä tai paastoglukoosissa. Ensipsykoosiryhmässä todettiin tutkimuksen alussa korkeampi kokonais- ja LDL-kolesteroli-, triglyseridi- ja insuliinipitoisuus sekä insuliiniresistenssi. Ensipsykoosiryhmässä painonnousu 12 kuukauden seurannan aikana oli 9,6 kg (mediaani) ja vyötärönympäryksen kasvu 6,0 cm. Insuliiniresistenssi ja olantsapiinilääkitys tutkimuksen alkaessa ennustivat suurempaa painonnousua 12 kuukauden aikana. Insuliiniresistenssi ennusti lisäksi vyötärönympäryksen kasvua. Herkässä CRP:ssä havaittiin seurannan aikana 2,5-kertainen nousu ensipsykoosiryhmässä. Vyötärönympärys ja naissukupuoli ennustivat herkän CRP:n pitoisuutta.

Kuolleisuus oli ei-affektiivisissa psykoottisissa häiriöissä selvästi korkeampi kuin tutkimusväestössä keskimäärin; kokonaiskuolleisuuden riskisuhde ikä ja sukupuoli vakioituna oli 2,99. Luonnollisten kuolinsyiden osalta riskisuhde oli 2,81. Kun otettiin huomioon sosioekonomiset tekijät, tupakointi, painoindeksi, krooniset fyysiset sairaudet ja tulehdus, kokonaiskuolleisuuden riskisuhde oli 2,11 ja tautikuolleisuuden osalta 1,98. Psykoosilääkityksen käyttö oli yhteydessä matalampaan tautikuolleisuuteen, tupakointi puolestaan lisäsi riskiä.

Tutkimuksessa todettiin, että ensimmäistä kertaa psykoosiin sairastuneiden paino nousee ja vyötärönympärys kasvaa merkittävästi ensimmäisen psykoosin hoitovuoden aikana ja että tähän liittyy matala-asteisen tulehduksen kehittyminen. Ensipsykoosin hoidon alussa todettu insuliiniresistenssi voi olla painonnousun ja vyötärölihavuuden kehittymisen riskitekijä. Matala-asteinen tulehdus oli vahvasti yhteydessä vyötärölihavuuteen, mikä viittaa siihen, että herkän CRP:n pitoisuus kertoo metabolisesta riskistä ensipsykoosissa. Olantsapiini oli yleisimmin määrätty psykoosilääke ensipsykoosiryhmässä, vaikka lääkkeen käyttöön liittyy suurin painonnousun riski. Ensisijaiseksi lääkitykseksi ensimmäisessä psykoosissa tulisi harkita psykoosilääkkeitä, joihin liittyy vähäisempi painonnousun riski. Psykoottisista häiriöistä kärsiviä tulisi tukea tupakoinnin lopettamiseen häiriöihin liittyvän korkean kuolleisuuden vähentämiseksi. Korkeampi kuolleisuus ei-affektiivisissa psykooseissa ei selittynyt kokonaan sosioekonomisilla tekijöillä, elintavoilla tai fyysisillä sairauksilla. Ennenaikaisen kuolleisuuden taustalla voi olla tekijöitä, jotka liittyvät psykoottisista häiriöistä kärsivien fyysisten sairauksien hoidon laatuun.

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CONTENTS

Abstract 4

Tiivistelmä 6

Acknowledgements 8

List of original publications 14

Abbreviations 15

1 Introduction 17

2 Review of the literature 19

2.1 What are psychotic disorders? 19

2.2 Diagnostic classification of psychotic disorders 20

2.2.1 Schizophrenia 21

2.2.2 Brief psychotic disorder 24

2.2.3 Schizophreniform disorder 24

2.2.4 Schizoaffective disorder 24

2.2.5 Delusional disorder 25

2.2.6 Substance-induced psychotic disorder 25

2.2.7 Psychotic disorder due to another medical condition 25

2.2.8 Psychotic disorder not otherwise specified 26

2.2.9 Bipolar disorders 26

2.2.10 Major depressive disorder with psychotic features 26

2.3 Prevalence and incidence of psychotic disorders 27

2.4 Pharmacological treatment of psychotic disorders 27

2.5 Metabolic effects of antipsychotics 29

2.5.1 Antipsychotic-induced weight gain 29

2.5.1.1 Physiological regulation of energy homeostasis, appetite and satiety 32

2.5.1.2 How antipsychotics modify the regulation of energy homeostasis 33

2.5.1.3 Influence of genetic variants in antipsychotic-related weight gain 34

2.5.2 Antipsychotics' effects on glucose metabolism 35

2.5.2.1 Blood glucose regulation and insulin resistance 35

2.5.2.2 The effect of antipsychotics on glucose metabolism 35

2.5.2.3 Are antipsychotic-induced metabolic changes evident without a psychotic disorder? 37

2.5.3 Effects of antipsychotics on lipid metabolism 37

2.6 Course and prognosis of first-episode psychosis 38

2.7 Metabolic changes in first-episode psychosis 40

2.7.1 Anthropometric and metabolic parameters in drug-naïve patients 40

2.7.2 Medication further increases metabolic changes in first-episode psychosis patients 41

2.8 Low-grade inflammation in psychotic disorders 43

2.8.1 Mechanisms of low-grade inflammation 43

2.8.2 C-reactive protein as a marker for low-grade inflammation 44

2.8.3 Evidence of low-grade inflammation in psychotic disorders 45

2.8.3.1 Is high CRP causally correlated with risk of psychosis? 46

2.9 Physical comorbidity and mortality in psychotic disorders 48

2.9.1 Cardiovascular risk factors and cardiovascular disease in people with psychotic disorders 48

2.9.2 Increased mortality in psychotic disorders 53

2.10 Summary of the literature review 55

3 Aims of the study 57

4 Methods 58

4.1 Helsinki Early Psychosis Study (Studies I & II) 58

4.1.1 Study design and subjects 58

4.1.2 Measurement of height, weight, waist circumference and blood pressure 59

4.1.3 Measures of physical activity, diet and smoking 59

4.1.4 Definitions of clinically significant weight gain, overweight, obesity and metabolic syndrome 61

4.1.5 Laboratory analytical methods 62

4.2 The Health 2000 survey and the Psychoses in Finland Study (Study III) 67

4.2.1 Mental health assessment 67

4.2.2 Study population 68

4.2.3 Predictors of mortality 69

4.2.3.1 Antipsychotic medication 69

4.2.3.2 Socioeconomic factors 69

4.2.3.3 Lifestyle and health-related variables 69

4.2.3.4 Chronic physical disease 69

4.2.3.5 Low-grade inflammation 70

4.2.4 Mortality and causes of death 70

4.3 Statistical methods 70

4.3.1 Study I 70

4.3.2 Study II 71

4.3.3 Study III 71

5 Results 73

5.1 Predictors of weight gain and waist circumference increase in first-episode psychosis (Study I) 73

5.1.1 Characteristics of study participants 73

5.1.2 Changes in anthropometric measures during follow-up 75

5.1.3 Predictors of change in anthropometric measures during follow-up 76

5.2 Development and predictors of low-grade inflammation in first-episode psychosis (Study II) 78

5.2.1 Characteristics of study participants..... 78

5.2.2 Baseline metabolic and anthropometric measures of patients and controls 81

5.2.3 Changes in metabolic measures and hs-CRP during follow-up..... 81

5.2.4 Predictors of hs-CRP during the follow-up 85

5.3 Mortality in non-affective psychosis (Study III)..... 86

6 Discussion..... 88

6.1 Summary of the main findings 88

6.2 Weight gain and increase of waist circumference in FEP 88

6.2.1 Baseline predictors of changes in weight and waist circumference (Study I) 90

6.3 Changes in glucose metabolism and lipids 91

6.4 Development of low-grade inflammation in FEP (Study II)..... 92

6.5 Mortality in non-affective psychosis (Study III)..... 94

6.6 Strengths and limitations..... 96

6.6.1 Strengths and limitations in Studies I and II 96

6.6.2 Strengths and limitations in Study III..... 97

7 Conclusions and future research 97

7.1 Main conclusions 98

7.2 Clinical implications..... 99

7.3 Future research 100

8 References 102

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Keinänen, J., Mantere, O., Kieseppä, T., Mäntylä, T., Torniainen, M., Lindgren, M., Sundvall, J., Suvisaari, J., 2015. Early insulin resistance predicts weight gain and waist circumference increase in first-episode psychosis--A one year follow-up study. Schizophr Res. Dec 169(1-3), 458-463.

II Keinänen, J., Suvisaari, J., Reinikainen, J., Kieseppä, T., Lindgren, M., Mäntylä, T., Rikandi, E., Sundvall, J., Torniainen-Holm, M., Mantere, O. Low-grade inflammation in first-episode psychosis is determined by increased waist circumference. (Submitted)

III Keinänen, J., Mantere, O., Markkula, N., Partti, K., Perälä, J., Saarni, SI., Härkänen, T., Suvisaari, J., 2018. Mortality in people with psychotic disorders in Finland: A population-based 13-year follow-up study. Schizophr Res. Feb 192, 113-118.

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

AHA	American Heart Association
aHR	adjusted hazard ratio
AMP	adenosine monophosphate
ApoB	apolipoprotein B
ATPIII	Adult Treatment Panel III
AUDIT	Alcohol Use Disorders Identification Test
BIC	Bayesian information criterion
BMI	body mass index
BPRS	Brief Psychiatric Rating Scale
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CHD	coronary heart disease
CRP	C-reactive protein
DKA	diabetic ketoacidosis
DSM	Diagnostic and Statistical Manual
EPS	extrapyramidal symptoms
EUFEST	The European First-Episode Schizophrenia Trial
FEP	first-episode psychosis
FGA	first generation antipsychotics
GAF	Global Assessment of Functioning
HbA1c	glycated haemoglobin
HDL	high-density lipoprotein cholesterol
HOMA	homeostatic model assessment
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
ICD-10	International Classification of Diseases, Tenth Edition
IDF	International Diabetes Federation
IQR	interquartile range
LDL	low-density lipoprotein cholesterol
M-CIDI	Munich Version of the Composite International Diagnostic Interview
MetS	metabolic syndrome
MR	mendelian randomization
MRI	magnetic resonance imaging
MRR	mortality rate ratio
NAP	non-affective psychosis
NHLBI	National Heart, Lung, and Blood Institute
PIF	Psychoses in Finland
POMC	pro-opiomelanocortin
RAISE	Recovery After an Initial Schizophrenia Episode
RCT	Randomised controlled trial
RSWG	Remission in Schizophrenia Working Group

SANS	Scale for the Assessment of Negative Symptoms
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SGA	second generation antipsychotics
SMD	standardized mean difference
SMI	serious mental illness
SMR	standardized mortality rate
SNP	single nucleotide polymorphism
SREBP	sterol regulatory element-binding protein
T2D	type 2 diabetes

1 INTRODUCTION

Psychotic disorders are complex and serious mental disorders with varying course and prognosis. In Finland, approximately 3% of the population is affected by a psychotic disorder at some point in their life (Perälä et al., 2007). The majority of people with a psychotic disorder have an episodic course of illness, with over a half experiencing remission during five years after the first episode, and over a third recovering (Lally et al., 2017). However, about a fifth do not respond to antipsychotic treatment from illness onset (Demjaha et al., 2017), and only a minority with a more chronic course of psychotic illness recover (Jääskeläinen et al., 2013).

The mortality in chronic psychotic disorders is substantially increased, resulting in life expectancies 15-20 years shorter than in the general population (Laursen et al., 2014). The excess premature mortality is mostly due to chronic physical disease, such as cancer, cardiovascular and respiratory disease (Olfson et al., 2015). People with psychotic disorders have an increased risk for metabolic syndrome (MetS) and type 2 diabetes (T2D) (Mitchell et al., 2013b; Suvisaari et al., 2016). Suicides account for most of the excess mortality during the early course of psychotic illness (Simon et al., 2018) and, overall, lifetime suicide risk in schizophrenia is approximately 5% (Palmer et al., 2005).

The mortality gap between the lower life expectancy of people with serious mental illness (SMI, i.e. severe major depression, bipolar disorder, and schizophrenia and related psychoses) and the general population has not narrowed in recent decades. In fact, some studies have shown that the mortality gap has widened despite the progress in the diagnostics and treatment of cardiovascular disease and cancer (Lumme et al., 2016; Manderbacka et al., 2017; Osby et al., 2016).

The onset of psychosis is usually in adolescence or early adulthood, when the affected individuals are generally physically healthy. Although there is evidence that people with first-episode psychosis (FEP) differ from their healthy peers in terms of lipid levels and glucose metabolism (Misiak et al., 2017; Pillinger et al., 2017b, 2017a), antipsychotic medication has a strong propensity to cause weight gain (Bak et al., 2014; Leucht et al., 2013). Antipsychotics also have a detrimental effect on lipid and glucose metabolism (Meyer and Koro, 2004; Newcomer, 2005). These adverse effects of antipsychotics are associated with an increased risk of several physical diseases (Correll et al., 2015). Psychotic illness is also associated with smoking, poor diet and low level of physical activity, which further undermines the physical health of patients (De Leon and Diaz, 2005; Dipasquale et al., 2013; Stubbs et al., 2016).

Different risk factors for weight gain and metabolic changes in FEP, such as young age and low premorbid body mass index (BMI), have been

identified but with limited consistency (Perez-Iglesias et al., 2014; Strassnig et al., 2007). Early recognition of patients with the greatest risk for harmful metabolic changes would offer a way to prevent physical comorbidity in psychotic disorders, and thus help to reduce the excess mortality in SMI.

Low-grade inflammation is associated with obesity and increased all-cause mortality in the general population (Choi et al., 2013; Ridker, 2016). Meta-analytic evidence implies that C-reactive protein (CRP) is increased in schizophrenia and related chronic psychotic disorders (Fernandes et al., 2016). Whether increased CRP is inherently connected with the disease process of psychotic disorders or reflects the increase in weight and abdominal obesity, it would nonetheless be of great importance to identify factors that drive the development of pro-inflammatory activation in FEP.

The aim of this thesis was to investigate longitudinal changes in weight, waist circumference, metabolic parameters related to glucose and lipids and low-grade inflammation, as measured by high-sensitivity CRP assay (hs-CRP), in FEP during the first year of treatment. Additionally, mortality in non-affective psychosis (NAP) was investigated to examine the extent of increased mortality in this group of people in Finland, and to find factors explaining the mortality increase.

2 REVIEW OF THE LITERATURE

2.1 WHAT ARE PSYCHOTIC DISORDERS?

Psychosis is characterized by a distorted sense of reality. Psychotic symptoms include hallucinations, delusions, negative symptoms (i.e. flattening of emotions, lack of motivational drive, social withdrawal and reduced motor activity), symptoms of disorganization (e.g. incoherent speech or behaviour) and catatonic symptoms (characterized by extreme psychomotor retardation/immobility or excitation/hyperactivity). Cognitive impairment and disturbances in mood (manic and depressive symptoms) also constitute dimensions of symptoms in psychotic disorders (van Os and Kapur, 2009). The mental disorders with psychotic symptoms as the most prominent feature are classified as psychotic disorders. However, psychotic symptoms are not present exclusively in psychotic disorders, as mood disorders may also present with psychotic symptoms.

The current view is that none of the psychotic symptoms are "pathognomonic", i.e. specific to a particular psychotic disorder. Psychotic disorders, like all other psychiatric disorders, are syndromes, defined by constellations of symptoms of certain durations. Historically, attempts have been made to categorize hallucinations and delusions by their quality and content. The Schneiderian first-rank symptoms (named after the German psychiatrist Kurt Schneider, 1887-1967) are, depending on the classification system, still used to define the typical psychotic symptoms of schizophrenia (Carpenter et al., 1973). These first-rank symptoms include hallucinations, such as voices conversing with each other or commenting on the person's behaviour, experiences of thought withdrawal (thoughts being removed from the mind), thought insertion (thoughts being inserted into the person's mind by an external agent), thought broadcasting (person's thoughts are made observable by others) and made feelings and actions (feelings, impulses and actions sensed as imposed by an external agent). However, the specificity of first-rank symptoms for schizophrenia has been questioned and the symptoms were removed from the latest diagnostic manual, the DSM-5, as they may also be present in other psychotic disorders (Ihara et al., 2009). Similarly, lack of insight, although common in acute psychosis and a predictor of poor outcome (Novick et al., 2015), is not a prerequisite for a diagnosis of a psychotic disorder.

A dichotomous distinction between psychotic and non-psychotic states may be an artificial categorization, as psychotic experiences exist on a continuum and are relatively common in the general population (Van Os et al., 2009). Most of the psychotic experiences in the population are transitory and do not involve significant distress. The risk of transitioning to a more persistent state of psychotic symptoms and further to a psychiatric disorder

depends on the individual's genetic risk and environmental factors (Van Os et al., 2009).

The variation in the course, duration and severity of psychotic disorders is substantial. The duration of psychotic disorders ranges from a brief episode, measured in days, to a chronic illness that persists for decades. Illness onset can be gradual, with a clear phase of prodromal symptoms, including, e.g. symptoms of depression and anxiety, and a decline in daily functioning before the onset of psychosis, or the onset can be sudden with a rapid shift to psychosis. Similar variation applies for recovery, ranging from a fast recuperation with a return of the premorbid level of functioning to a persisting state of symptoms interfering constantly with daily life.

According to a meta-analysis, 38% of individuals with FEP experienced long-standing absence of symptoms and good level of functioning after the first psychotic episode during an average follow-up of seven years (Lally et al., 2017). However, a significant proportion of individuals with FEP have recurrent episodes with unfavourable consequences on the ability to achieve goals in life and physical health. Psychotic disorders are one of the gravest mental disorders, as measured by subjective experience, premature mortality and economic costs to the individual and society. Schizophrenia, which is the most common of psychotic disorders, has been estimated to encompass a significant health burden, as measured by disability-adjusted life years (DALYs). DALYs combines excess mortality (life years lost due to premature death) and the chronicity of the disorder (years lived with disability). Schizophrenia was the 8th leading cause of DALYs globally among people aged 15-44 years in a 2001 World Health Report (World Health Organization, 2001). Furthermore, taking into account the relative rarity of psychotic disorders, the direct and indirect economic costs of psychotic disorders are perhaps greater than in any other psychiatric disorder (Rössler et al., 2005).

2.2 DIAGNOSTIC CLASSIFICATION OF PSYCHOTIC DISORDERS

The classification systems currently in use in psychiatry are the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) published by the American Psychiatrist Association in 2013 (American Psychiatric Association, 2013) and the International Classification of Diseases, Tenth Edition (ICD-10) Classification of Mental and Behavioural Disorders published by the World Health Organization (WHO) (World Health Organization, 1992). While ICD-10 criteria are used in most countries of the world, DSM-5, which is the official classification system in the United States, dominates in psychiatric research (Tyrer, 2014). The predecessor of DSM-5 was the DSM-IV-TR (Diagnostic and Statistical Manual of Mental

Disorders, Fourth Edition, Text Revision), published in 2000 (American Psychiatric Association, 2000). In the following paragraphs, the diagnostic criteria of the major psychotic disorders in DSM-IV-TR, DSM-5 and ICD-10 are compared.

2.2.1 SCHIZOPHRENIA

The comparison of DSM-IV-TR, DSM-5 and ICD-10 criteria for schizophrenia is presented in Table 1. A major difference in the criteria is that DSM-IV-TR and DSM-5 require a minimum total duration of illness of 6 months with at least 1 month of active symptoms, while ICD-10 requires only 1-month total duration of the illness. Further differences are that DSM-IV-TR required only one psychotic symptom in Criterion A if the delusions were bizarre, or if the hallucinations consisted of a running commentary of the person's behaviour or thoughts or voices conversing with each other. This criterion reflected the Schneiderian first-rank symptoms of schizophrenia, and was removed from the DSM-5, leading to the requirement of two Criterion A symptoms for the diagnosis of schizophrenia. DSM-IV-TR and DSM-5 require deterioration in the level of social and occupational functioning, while ICD-10 does not. All the schizophrenia subtypes were eliminated from DSM-5. ICD-10 includes a diagnosis of simple schizophrenia which is diagnosed in the absence of positive symptoms, while the equivalent "Residual type" in DSM-IV-TR was removed from DSM-5.

Table 1. Comparison of ICD-10, DSM-IV-TR and DSM-5 diagnostic criteria for schizophrenia

	ICD-10	DSM-IV-TR	DSM-5
	G1: 1) At least one of the following a) Thought echo, thought insertion or withdrawal, thought broadcasting b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception c) Hallucinatory voices: running commentary on person's behaviour, or discussing about the person, or voices coming from some part of the body d) Persistent delusions that are culturally inappropriate and completely impossible 2) Or at least two of the following: e) Persistent hallucinations in any modality, every day at least 1 month f) Neologisms, incoherence or irrelevant speech g) Catatonic behaviour h) Negative symptoms	A: Two or more* of the following present for a significant portion of time over a 1-month period (or less if successfully treated): 1) delusions 2) hallucinations 3) disorganized speech 4) grossly disorganized or catatonic behaviour 5) negative symptoms	A: Two or more of the same symptoms as in DSM-IV-TR. One of these must be 1, 2 or 3.
	G2: Most commonly used exclusion criteria: If the patient meets the criteria for manic or depressive episode, the criteria listed above must have been met before the onset of the mood disorder	B: Since the onset of the disorder, at least one major area of functioning (work, social relations, self-care) is below the level achieved prior to the onset for a significant portion of time	B: As in DSM-IV-TR

Table 1. (continued)

	ICD-10	DSM-IV-TR	DSM-5
	G3: The disorder is not attributable to organic brain disease, or to alcohol- or drug-related intoxication, dependence or withdrawal.	C: Continuous signs of the disturbance for at least 6 months (must include at least one month, or less if successfully treated, symptoms meeting Criterion A, and may include periods of prodromal/residual symptoms)	C: As in DSM-IV-TR
		D: Schizoaffective disorder and mood disorder with psychotic features have been excluded	D: As in DSM-IV-TR, considering the revised criteria for schizoaffective disorder in DSM-5
		E: The disorder is not due to the direct physiological effect of a substance or a general medical condition	E: As in DSM-IV-TR
		F: If there is history of autistic disorder or another pervasive developmental disorder, the diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present ≥ 1 month	F: If there is history of autism spectrum disorder or communication disorder of childhood onset, the diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present ≥ 1 month

*Only one is required if delusions are bizarre, or hallucinations consist of a running commentary on the person's behaviour or thoughts, or voices conversing with each other

DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ICD-10, International Statistical Classification of Mental and Behavioural Disorders, 10th Revision

2.2.2 BRIEF PSYCHOTIC DISORDER

According to DSM-IV-TR and DSM-5, brief psychotic disorder has a sudden onset of psychotic symptoms that last at least 1 day but less than 1 month. The psychotic symptoms required are the same as in Criterion A for schizophrenia, except for negative symptoms which are not included in brief psychotic disorder. After full remission of the symptoms within the 1-month duration of the disorder, patients regain the level of function they had before the onset of the disorder.

Similar to brief psychotic disorder, ICD-10 defines an acute and transient psychotic disorder (with delusions, hallucinations or incoherent speech) with onset within 2 weeks and full remission within 1-3 months. Those who meet the criteria for ICD-10's acute and transient psychotic disorders fall under many different categories in DSM-IV-TR or DSM-5, including brief psychotic disorder, schizophreniform disorder and psychotic disorder not otherwise specified.

2.2.3 SCHIZOPHRENIFORM DISORDER

Both DSM-IV-TR and DSM-5 define schizophreniform disorder similarly. The Criterion A is the same as for schizophrenia, except that the total duration of the illness in schizophreniform disorder is 1-6 months (including prodromal, active and residual symptoms). Although there may also be disturbed functioning in work or social relations in schizophreniform disorder, it is not required in DSM-IV-TR or in DSM-5. The disturbance does not meet the criteria for schizoaffective or mood disorder with psychotic features.

ICD-10 does not include schizophreniform disorder. Many of those diagnosed with DSM schizophreniform disorder would be classified as having schizophrenia according to ICD-10. An acute schizophrenia-like psychotic disorder can be diagnosed according to ICD-10 if the criteria for schizophrenia are met, and the onset of symptoms is rapid (within 2 weeks), but the duration is shorter than the 1 month required for schizophrenia.

2.2.4 SCHIZOAFFECTIVE DISORDER

DSM-IV-TR states that an essential feature of schizoaffective disorder is an uninterrupted period of illness with a major depressive, manic or mixed episode concurrent with symptoms that meet Criterion A for schizophrenia. Also, during the same period of illness, there has been a 2-week period with delusions or hallucinations but without prominent mood symptoms. It is also required that mood episodes are present for a substantial portion of the total duration of the active and residual periods of the illness.

DSM-5 specifies that delusions or hallucinations must have been present for at least 2 weeks in the absence of a mood episode during the lifetime

duration of the illness, and that the mood episodes are present for the majority of the total duration of the active and residual phase of the illness.

In ICD-10, schizoaffective disorder is defined as a concurrent mood episode of at least moderate severity, with psychotic symptoms similar to schizophrenia, present at least 2 weeks. The mood episode and psychotic symptoms must coincide "for at least some time of the episode", and both must be prominent in the clinical picture. ICD-10 also requires a balance between the number, severity and duration of the affective and psychotic symptoms.

2.2.5 DELUSIONAL DISORDER

In DSM-IV-TR's definition of delusional disorder, non-bizarre delusions are required to persist for at least 1 month. Hallucinations may be present but not prominent. Ability to function is generally preserved and behaviour is not markedly odd or bizarre. Brief mood episode can co-occur with delusions but their duration has to be short relative to the duration of the delusional periods.

DSM-5 is identical to DSM-IV-TR in the definition of delusional disorder, except that DSM-5 does not require that the delusions are non-bizarre.

ICD-10 states that the delusions have to be other than those listed as typical schizophrenic delusions and they must have been present for at least 3 months. Persistent hallucinations in any modality are not allowed, but occasional auditory hallucinations are possible if they are not those listed for typical schizophrenic hallucinations.

2.2.6 SUBSTANCE-INDUCED PSYCHOTIC DISORDER

According to DSM-IV-TR and DSM-5, substance or medication-induced psychotic disorder is diagnosed when delusions or hallucinations have developed soon after use or withdrawal of a substance that is capable of inducing such symptoms, and the disorder is not better explained by an independent psychotic disorder. DSM-IV-TR and DSM-5 specify that the hallucinations and delusions must not be recognized by the individual as substance induced.

Similarly, in ICD-10 psychotic disorder due to psychoactive substance use is diagnosed when psychotic symptoms occur during or immediately after substance use (usually in 48 hours, but a late-onset psychotic disorder with onset more than 2 weeks after substance use can be diagnosed as well). The disorder resolves at least partially in 1 month and fully in 6 months.

2.2.7 PSYCHOTIC DISORDER DUE TO ANOTHER MEDICAL CONDITION

The definitions of DSM-IV-TR and DSM-5 of psychotic disorder due to another medical condition are identical: they require prominent hallucinations or delusions with evidence that the symptoms are the direct physiological consequence of a medical condition, and the disturbance is not better accounted for by another mental disorder.

ICD-10 divides the category of "other mental disorders due to brain damage and dysfunction and to physical disease" into organic hallucinosis, with persistent or recurrent hallucinations, and organic delusional (schizophrenia-like) disorder, characterized by recurrent delusions.

2.2.8 PSYCHOTIC DISORDER NOT OTHERWISE SPECIFIED

According to DSM-IV-TR, psychotic disorder not otherwise specified (NOS) is diagnosed if psychotic symptoms are present but there is inadequate or contradictory information to make a specific diagnosis, or symptoms do not meet the criteria for any specific psychotic disorder.

DSM-5 splits psychotic disorder NOS into the categories of "other specified schizophrenia spectrum and other psychotic disorder" and "unspecified schizophrenia spectrum and other psychotic disorder". The former category applies to situations where the symptoms do not meet full criteria for any specific psychotic disorders, and the latter for situations where information for making a specific diagnosis is inadequate.

According to ICD-10, a diagnosis of other non-organic psychotic disorder is made when the psychotic symptoms do not meet the criteria for any specific psychotic disorder. ICD-10 also lists a diagnosis of unspecified non-organic psychosis.

2.2.9 BIPOLAR DISORDERS

In DSM-IV-TR, bipolar I and II disorders were listed under the heading of mood disorders, while in DSM-5 the disorders were placed under a separate heading of Bipolar and Related Disorders to better recognize that bipolar disorders share common genetic factors and symptoms with both mood disorders and psychotic disorders. Bipolar disorders are characterized by recurrent depressive and manic or hypomanic episodes. DSM-IV-TR and DSM-5 require one or more manic episodes for a diagnosis of bipolar I disorder, while a diagnosis of bipolar II disorder requires at least one hypomanic episode. The definition of a mixed episode was eliminated from DSM-5; instead a depressive episode can be diagnosed with a specifier "with mixed features". ICD-10 requires at least two mood episodes, of which at least one has to be a hypomanic, manic or mixed episode, for a diagnosis of

bipolar disorder. Psychotic symptoms can occur in manic and depressive episodes.

2.2.10 MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES

In DSM-IV-TR, DSM-5 and ICD-10, major depressive disorder with psychotic features (or severe depressive episode with psychotic symptoms in ICD-10) is diagnosed when psychotic symptoms (delusions or hallucinations) are present during a major depressive disorder.

2.3 PREVALENCE AND INCIDENCE OF PSYCHOTIC DISORDERS

Prevalence and incidence are measures used in epidemiological research to describe how many persons at risk in a certain population are affected by a disease. Prevalence is reported as the ratio of affected persons per 100 or 1000 persons in the population. Prevalence can be measured as point prevalence, giving an estimate of the prevalence at a given time, or as prevalence over a certain period. Incidence is a measure of new cases in a population at risk over a given period.

The lifetime prevalence of DSM-IV schizophrenia in the Finnish Health 2000 study among persons aged over 30 years was 0.87 % (Perälä et al., 2007). A systematic review of prevalence studies conducted in 46 countries reported a 0.40% lifetime prevalence of schizophrenia without a statistical significant difference in the prevalence between males and females (Saha et al., 2005). The prevalence estimates were higher in migrant groups compared to native population (Saha et al., 2005). Other psychotic disorders have somewhat lower prevalence estimates compared to schizophrenia: in the aforementioned study by Perälä et al., the prevalence was 0.32% for schizoaffective disorder, 0.07% for schizophreniform disorder, 0.18% for delusional disorder, 0.05% for brief psychotic disorder, 0.45 for psychotic disorder NOS, 0.24% for bipolar I disorder, 0.35% for major depressive disorder with psychotic features, 0.42% for substance-induced psychotic disorders and 0.21% for psychotic disorders due to a general medical condition (Perälä et al., 2007).

A systematic review yielded a median incidence rate of schizophrenia of 15.2 per 100,000 with males having an increased rate compared to females (median rate ratio 1.40) (McGrath et al., 2004). Urbanicity was associated with higher incidence rate, as well as migrant status (McGrath et al., 2004). The incidence rate is at its highest among men aged 20-24 years and in women aged 25-29, although for women an increase in the incidence after age 40 is observed. Similar findings of lower age of onset in males compared

to females and declining incidence with increasing age has also been observed in other psychoses (Sutterland et al., 2013).

A systematic review of incidence studies conducted in England between 1950-2009 reported a higher incidence rate for non-affective psychoses than affective psychoses (23.2/100,000 person years vs. 12.4/100,000 person years) (Kirkbride et al., 2012). The incidence rates for non-affective psychoses declined with age, and women had another peak in the rate in mid to late 40s. In affective psychoses, women had higher incidence rates after the age of 45 than men, but before that there were no statistically significant gender differences (Kirkbride et al., 2012).

2.4 PHARMACOLOGICAL TREATMENT OF PSYCHOTIC DISORDERS

Antipsychotic medication is the mainstay of the treatment of psychotic disorders with well-established evidence of efficacy in reducing psychotic symptoms and preventing relapse (Leucht et al., 2011). The first antipsychotic agent, chlorpromazine, was discovered by a French surgeon Henri Laborit in a serendipitous manner. He administered chlorpromazine to patients undergoing surgery and observed that the drug made patients less anxious without a significant decrease in the level of consciousness. The effects of the newly discovered drug were tested by Laborit's colleagues on patients with agitation and hallucinations with dramatic effects. The drug reduced psychotic symptoms and anxiety, a finding that marked a significant advancement in the treatment of chronically ill patients with psychotic disorders, for whom effective treatment methods were practically non-existent at the time (Ban, 2007).

After the discovery of chlorpromazine, similar molecules were developed, such as thioridazine and fluphenazine, belonging to the same molecule class of phenothiazines as chlorpromazine. Drugs belonging to other chemical classes, such as haloperidol (butyrophenones) and zuclopenthixol (thioxanthenes), were also developed, but their effectiveness was essentially the same as chlorpromazine, although adverse effects differed. In 1958, a Swiss pharmaceutical company developed clozapine, which was later found to have superior effectiveness in reducing psychotic symptoms resistant to other antipsychotics. Clozapine was tested during the 1960s and released on to the market in the early 1970s. However, due to the finding that clozapine caused severe cases of agranulocytosis (Idänpään-Heikkilä et al., 1975), the drug was withdrawn. In 1990, after studies showing that clozapine was superior to other antipsychotics in reducing psychotic symptoms resistant to other drugs, clozapine was reinstated (Kane and Correll, 2010).

In the 1990s, new antipsychotic agents that were classified as second-generation antipsychotics (SGA), or atypical antipsychotics, were developed. Correspondingly, antipsychotics that were developed before the return of

clozapine in the 1990s were now categorized as first-generation (FGA), also referred to as typical or conventional antipsychotics in the literature. Originally, it was thought that the categories of different generations of antipsychotics would be based on differences in receptor binding affinities, but in fact the division has no clear-cut pharmacological boundaries, as both generations of antipsychotics have similar pharmacological actions.

FGA in general have high affinity for the dopamine D2 receptor. D2 antagonism is the main antipsychotic mechanism of action of FGA, which can be divided into high-potency and low-potency drugs by their affinity for the D2 receptor. A distinction between FGA and SGA is their differing propensity to cause extrapyramidal symptoms (EPS) such as rigidity, tremor and movement disorders (Meltzer, 2013). SGA generally cause less EPS than FGA. In particular, high-potency FGA cause significant EPS (Miyamoto et al., 2005). The low-potency drugs, such as chlorpromazine, also have, in addition to the D2 antagonism, antagonistic effects on histamine, adrenergic and muscarinic receptors. These other receptor effects are associated with sedation, weight gain, orthostatic hypotension and anticholinergic effects, which are typical adverse effects for low-potency FGA. SGA in turn are also potent antagonists of the serotonin 5-HT2A receptors (Nasrallah, 2008). The 5-HT2A receptor antagonism contributes to the antipsychotic action of the SGA and to the low risk of EPS (Meltzer, 2013). SGA target histamine, muscarinic and adrenergic receptors as well. These receptor actions are associated with the adverse effects of the SGA, but the significance for the antipsychotic effect is unclear (Meltzer, 2013).

2.5 METABOLIC EFFECTS OF ANTIPSYCHOTICS

Because antipsychotics target a multitude of receptors which are also involved in the central and peripheral energy metabolism and homeostasis, it is not surprising that antipsychotics also have extensive metabolic effects. Unfortunately, these metabolic effects, described in detail in the following paragraphs, are detrimental to health. They include weight gain, impaired glucose tolerance, dyslipidemia and an increased risk for MetS, T2D and cardiovascular complications.

2.5.1 ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

In the era of FGA, concern for the weight gain potential of antipsychotics was surpassed by the more acute adverse effects of the FGA such as EPS and increased prolactin levels. After the introduction of the SGA, awareness of the high prevalence of weight gain in people using antipsychotics increased. Weight gain affects a major percentage of people with psychotic disorders treated with antipsychotics, with proportion estimates ranging from 15% to 72% (De Hert et al., 2011b). Weight gain is not only a physical risk factor,

contributing to the risk for dyslipidemia, diabetes, hypertension and other cardiovascular disease, but it is also a significant reason for non-adherence to drug treatment (Velligan et al., 2009). Antipsychotic-related weight gain is rapid during the first six to 12 months, and continues for at least the first three years of antipsychotic treatment (Bushe et al., 2012; Perez-Iglesias et al., 2014).

Of the FGA, the low-potency antipsychotics (e.g. chlorpromazine) are more associated with higher average weight gain than high-potency antipsychotics (e.g. haloperidol) (De Hert et al., 2011c; Leucht et al., 2013). SGA, especially olanzapine and clozapine, are associated with the greatest weight gain of all antipsychotics (Leucht et al., 2013). Quetiapine, risperidone, paliperidone and sertindole are considered as having an intermediate propensity to cause weight gain, while aripiprazole and ziprasidone are generally associated with low risk for weight gain (De Hert et al., 2011c; Leucht et al., 2013). However, there is individual variation in the amount of weight gain, and none of the antipsychotics have been shown to be consistently weight neutral. In a meta-analysis, only haloperidol, aripiprazole and lurasidone were not associated with significantly more weight gain than placebo (Leucht et al., 2013). In another meta-analysis, aripiprazole, amisulpride and ziprasidone were deemed weight neutral (Bak et al., 2014). A meta-analysis investigating weight gain in first-episode psychosis found that only ziprasidone was not associated with increased risk of clinically significant weight gain (Tek et al., 2016). The average weight gain difference compared to placebo in first-episode psychosis was 3.22kg in the short-term (studies with <12 weeks of antipsychotic treatment) and the corresponding BMI change was 1.46kg/m^2 (Tek et al., 2016). In the long-term (>12 weeks), the average weight gain was 5.30kg and BMI change 1.86kg/m^2.

Identifying reliable risk factors for antipsychotic-related weight gain would be useful to guide antipsychotic choice. There are a number of suggested risk factors, mediators and moderators for antipsychotic-related weight gain, but the findings have been inconsistent. Table 2 lists some of the findings of studies on antipsychotic-induced weight gain. Other suggested risk factors for weight gain, mentioned in a review, include family history of obesity and overeating as a stress response (De Hert et al., 2009). Young age and low pre-treatment BMI are the most consistently reported risk factors. However, these too have been questioned, as young age itself might not be a risk factor, but rather a proxy for less previous antipsychotic exposure (Correll et al., 2009). Moreover, the tendency for individuals with low pre-treatment BMI to gain more weight might reflect a statistical artifact called regression to the mean, which means that extreme observations will tend to move closer to the mean of observations on the next measurement (Allison et al., 2009a). Taken together, from the clinical point of view, no single factor can be used to reliably identify individuals vulnerable to antipsychotic-related weight gain.

Table 2. Predictors of weight gain in psychosis

Predictor	Comments	References
Lower baseline BMI	Low premorbid BMI has been associated with more weight gain. In Gebhardt et al. (2009) high premorbid BMI associated with more total BMI change and low premorbid BMI associated with higher acceleration of BMI change	Basson et al., 2001; Kinon et al., 2001; Lee et al., 2011; Lipkovich et al., 2009; Neovius et al., 2007; Saddichha et al., 2008; Strassnig et al., 2007; Verma et al., 2009
Young age	Young patients have increased risk for weight gain	Lee et al., 2011; Lipkovich et al., 2009; Safer, 2004; Strassnig et al., 2007; Verma et al., 2009
Gender	Perez-Iglesias et al. found male gender to be associated with short-term (≤3 months), but not long-term weight gain. Other studies have reported an association between female gender and more weight gain	Gebhardt et al., 2009; Hakko et al., 2006; Homel et al., 2002; Lee et al., 2011; Lipkovich et al., 2009; Neovius et al., 2007; Perez-Iglesias et al., 2014; Verma et al., 2009
Negative symptoms	High level of negative symptoms associated with weight gain	Strassnig et al., 2007
Poor social functioning	Poor social functioning associated with weigh gain	Perez-Iglesias et al., 2014
Schizophrenia subtype	More weight gain in undifferentiated vs. paranoid subtype	Saddichha et al., 2008
Co-medications and antidepressants	Polypharmacy associated with weight gain	Strassnig et al., 2007
Non-white ethnic background	Weight gain associated with non-white ethnic background	Basson et al., 2001; Chan et al., 2013; De Leon et al., 2007; Krakowski et al., 2009; Lipkovich et al., 2009; Stauffer et al., 2010
Smoking	Less weight gain in smokers	Gebhardt et al., 2009
Cannabis use	Less weight gain and metabolic risk factors in cannabis users	Bruins et al., 2016; Scheffler et al., 2018; Waterreus et al., 2016

2.5.1.1 Physiological regulation of energy homeostasis, appetite and satiety

The hypothalamic arcuate nucleus is a centre for appetite and satiety control, and contains two main cell types involved in maintaining energy homeostasis: orexigenic neuropeptide Y/Agouti-related peptide (NPY/AgRP) neurons and anorexigenic pro-opiomelanocortin (POMC) neurons (Manu et al., 2015). The hypothalamus receives signals from peripheral tissues by circulating metabolites (i.e. amino acids, fatty acids, glucose), hormones such as gut-related ghrelin, glucagon-like peptide 1 and peptide YY, and leptin and adiponectin produced by adipocytes (Skolnik and Ryan, 2014). Leptin's main functions in maintaining energy homeostasis include appetite suppression and reducing insulin secretion. Production of leptin is directly proportionate to fat mass. In obesity, leptin resistance often develops, meaning that leptin loses its appetite suppressing and homeostasis maintaining effects (Skolnik and Ryan, 2014). Adiponectin is a hormone produced by adipocytes with decreasing levels in obesity. Adiponectin increases insulin sensitivity and glucose uptake to adipocytes (Nigro et al., 2014).

Appetite and energy metabolism are not only regulated by these homeostatic mechanisms. Reward-dependent motivational mechanisms also determine eating behaviour. The pleasure obtained from eating foods with high energy content has helped people to survive in nutrient scarce environments. In modern society, with the abundance of energy-rich foods and daily activities requiring less physical activity than before, the reward mechanisms related to eating may have significant downsides, as they increase the craving for energy-rich foods (Chaput et al., 2011). The reward system involves dopaminergic mesocorticolimbic circuits arising from the ventral tegmental area and projecting to the nucleus accumbens, various other limbic areas, and to the prefrontal cortex (Arias-Carrián et al., 2010). There is interplay between the brain's reward system and the hormones transmitting signals from peripheral energy metabolism. For example, leptin can inhibit the mesolimbic dopaminergic pathways and reduce food intake (Berthoud, 2012). In contrast, ghrelin may increase food intake by increasing the dopaminergic activity in ventral tegmental area and nucleus accumbens (Berthoud, 2012; Lenard and Berthoud, 2008).

As reviewed by Mazier et al. (2015), another mechanism involved in regulating energy consumption and expenditure is the endocannabinoid system, which consists of the endocannabinoids and the centrally and peripherally located endocannabinoid receptors. N-arachidonoylethanolamide (anandamide) and 2-arachidonoylglycerol are the most studied endocannabinoids. They act on CB1 and CB2 endocannabinoid receptors, which are found in several brain areas and peripheral organs. In the brain, endocannabinoid receptors in the hypothalamus and nucleus accumbens interact with orexigenic and anorexigenic signalling. The main function of the endocannabinoid system is to preserve and store energy: in the central nervous system, endocannabinoids increase food intake and

craving for palatable food, and also decrease centrally regulated energy expenditure and thermogenesis. Peripherally, endocannabinoids increase insulin secretion, lipogenesis and glucose uptake. In the gastrointestinal tract, endocannabinoids increase fat preference and intake by interacting with orexigenic mediators such as ghrelin (Mazier et al., 2015).

2.5.1.2 How antipsychotics modify the regulation of energy homeostasis

The potential mechanisms of antipsychotic-induced weight gain are complex and involve disturbance of energy homeostasis by disrupting the balance between caloric intake and energy expenditure. Antipsychotics increase the craving for food and suppress or delay satiety signalling which can lead to overeating (Correll et al., 2011). Antipsychotics have a variety of receptor targets, and many of these, including dopamine, serotonin and histamine receptor antagonism, are associated with weight gain.

The main antipsychotic action of antipsychotic drugs is based on dopamine D2 antagonism. Antipsychotics with D2-specific receptor affinity, e.g. amisulpride, are also associated with weight gain, albeit to a lesser extent than antipsychotics with a wider array of receptor targets (Leucht et al., 2013). In otherwise healthy individuals, obesity is associated with lower D2 receptor density in the brain, possibly reflecting decreased activity in the reward pathways which may lead to increased food intake (Wang et al., 2001). An interesting example of how dopamine antagonism can affect weight regulation comes from a study investigating the association of reward system activity, measured by functional magnetic resonance imaging during a monetary reward task, with amisulpride-related weight gain in people with schizophrenia (Nielsen et al., 2016). Weight gain in the study was predicted by lower striatal reward system activity before six-week treatment with amisulpride. Weight gain was also associated with increase in the reward system activity after treatment. The result suggests that reward deficiency may moderate the amount of weight gain associated with dopamine antagonism.

Antagonism of the serotonin 5-HT2C receptor is associated with weight gain (Correll et al., 2011). Hypothalamic 5-HT2C receptors expressed by POMC neurons are crucial for serotonergic regulation of energy homeostasis (Xu et al., 2008). In animal studies, mice with deficient 5-HT2C receptors have disturbed regulation of feeding behaviour and are overweight (Tecott et al., 1995). Furthermore, pharmacological blockade of 5-HT2C receptors is also associated with increased feeding in animals (Correll et al., 2011). A putative mechanism by which serotonin antagonism increases food intake is the delayed onset of satiety signalling which can lead to increased meal sizes and binge eating (Correll et al., 2011).

Antipsychotic antagonism on histamine H1 receptors is associated with weight gain (Kroeze et al., 2003), possibly by a leptin-dependent mechanism,

as mice with H1 receptor deficiency display leptin resistance (Masaki et al., 2001). In addition, as reviewed by Correll et al. (2011), antagonism of the H1 receptors in animal studies increases feeding. Another mechanism by which SGA may affect the regulation of food intake via H1 receptors is suggested by a mouse study, showing that by blocking H1 receptors SGA stimulate the hypothalamic adenosine monophosphate-activated protein kinase (AMP kinase) (Kim et al., 2007). The AMP kinase activity in the hypothalamus is under normal circumstances inhibited by leptin, producing leptin's anorexigenic effect. Furthermore, this stimulation of AMP kinase by SGA, which overrides the effect of leptin, can be blocked by H1 receptor gene deletion in animal models (Kim et al., 2007).

2.5.1.3 Influence of genetic variants in antipsychotic-related weight gain

A meta-analysis, investigating genetic associations with antipsychotic medication-related weight gain, analysed 38 single nucleotide polymorphisms (SNPs) in 20 genes or genetic regions and found variations associated with weight gain in 9 genes (Zhang et al., 2016). The genetic variations most consistently associated with weight gain were located in genes that code for proteins which are also targets of antipsychotic drugs: serotonin 2C receptor (*HTR2C*), dopamine receptor D2 (*DRD2*) and alpha-2A adrenergic receptor (*ADRA2A*). Other genes that were also associated with weight gain were the genes encoding for G protein subunit beta 3 (*GNB3*), melanocortin 4 receptor (*MC4R*), brain-derived neurotrophic factor (*BDNF*) and insulin-induced gene 2 (*INSIG2*) (Zhang et al., 2016).

HTR2C encodes the serotonin receptor 5-HT2C. The receptor has a role in appetite regulation and food intake (Vickers et al., 2003). Most atypical antipsychotics are potent antagonists of the receptor (Markowitz et al., 1999). Mutation of *HTR2C* in animal models is associated with hyperphagia, obesity and increased insulin resistance (Nonogaki et al., 1998; Xu et al., 2008). By contrast, agonists of 5-HT2C receptor can cause weight loss by decreasing food intake (Smith et al., 2010).

Dopamine receptor D2, encoded by *DRD2*, is the main target of antipsychotics. Variation in the *DRD2* gene has been linked with clinical response to antipsychotics in patients with schizophrenia (Zhang et al., 2010). Dopamine is involved in pathways regulating feeding, motivation and sense of well-being (Blum et al., 2014). In animal models, *DRD2* function is associated with hyperphagia, addictive behaviour and binge drinking (Blum et al., 2014).

Adrenergic receptors are also the target of many atypical antipsychotics. Alpha 2A receptor has an inhibitory effect on fatty acid mobilization from adipose tissue. The SNP associated with weight gain in the meta-analysis of Zhang et al. is also associated with fat accumulation in the general population

(Garenc et al., 2002) and may affect plasma glucose, insulin and cortisol levels (Rosmond et al., 2002).

GNB3 encodes a beta 3 subunit in heterotrimeric (i.e. constituting three subunits) G proteins, which are involved in intracellular signal pathways and transmitting signals from extracellular stimuli. The SNP identified to have an association with antipsychotic-induced weight gain is also associated with atherosclerosis, insulin resistance and obesity in the general population (Siffert, 2005).

MC4R has also been linked with obesity in the general population (Zobel et al., 2009). The so-called melanocortin system in the hypothalamus is a neuronal circuit involved in maintaining energy homeostasis. Activation of the MC4R neurons causes decreased food intake and increases energy expenditure, while inhibition of these neurons results in decreased energy expenditure and weight increase (Kim et al., 2014).

Of other genes associated with obesity or energy regulation in the general population, only *BDNF* and *INSIG2* were modestly associated with antipsychotic-related weight gain in the meta-analysis. However, the results were not consistent, as *BDNF* was only linked with a categorical outcome of clinically significant weight gain (>7%), and the sample size of *INSIG2* was small (Zhang et al., 2016).

2.5.2 ANTIPSYCHOTICS' EFFECTS ON GLUCOSE METABOLISM

2.5.2.1 Blood glucose regulation and insulin resistance

Blood glucose levels are regulated by insulin and glucagon with opposite effects. Insulin is released from pancreatic β-cells in response to increasing levels of blood glucose. It reduces blood glucose levels by increasing the storage of glucose in liver, skeletal muscle and fat. When the glucose level is low, insulin secretion decreases, and glucagon is released from pancreatic α-cells, inducing glucose utilization and release from the liver and muscle, thereby increasing the level of glucose in the blood. Cortisol and the catecholamines adrenaline and noradrenaline also take part in the regulation of blood glucose levels by increasing the blood glucose concentration.

Insulin resistance is a condition where the physiological effects of insulin are reduced, leading to increased levels of blood glucose and accelerated release of lipids from the adipocytes and glucose from the liver (Reilly and Saltiel, 2017). Obesity, especially abdominal obesity, has a strong association with insulin resistance (Despres and Lemieux, 2006), and insulin resistance is a major risk factor for developing type 2 diabetes (Kahn et al., 2006).

2.5.2.2 The effect of antipsychotics on glucose metabolism

Apart from the effect on glucose metabolism that is mediated by weight gain, antipsychotics also alter glucose metabolism independently of weight. The effects on glucose metabolism (e.g. on insulin resistance) can occur substantially more rapidly than the effects on weight gain (Deng, 2013). Several receptor targets of antipsychotics disturb the physiological regulation of glucose levels by effects on insulin secretion, insulin sensitivity and appetite regulating mediators, such as leptin (Nasrallah, 2008).
An example of the potential of antipsychotics to disturb glucose metabolism is diabetic ketoacidosis (DKA), which is a rare adverse effect of antipsychotics. In DKA, production of insulin is not adequate to control the blood glucose level and ketone bodies from free fatty acids cause acidosis (Guenette et al., 2013). DKA is a medical emergency with a considerable mortality rate. The risk of DKA is greatest with the antipsychotics that also cause the greatest weight gain, olanzapine and clozapine, but there are reports of aripiprazole-related DKA as well (Guenette et al., 2013; Vuk et al., 2017).

Olanzapine and clozapine are most consistently connected with elevated glucose levels and insulin resistance in schizophrenia. In the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study, a prospective randomized clinical study investigating the effectiveness of antipsychotics in patients with schizophrenia, olanzapine treatment was associated with increased HbA1c and glucose levels compared to risperidone, ziprasidone, perphenazine or quetiapine (Nasrallah, 2008). The risk of diabetes is greatest with SGA use, but FGA such as haloperidol and amisulpride are also associated with increased glucose levels (Deng, 2013; Nasrallah, 2008).

Antipsychotics are associated with increased insulin resistance. Studies using homeostatic model assessment (HOMA, calculated as fasting glucose [mmol/l] x fasting insulin [mU/l]/22.5) as a measure of insulin resistance (Matthews et al., 1985) have shown that treatment with olanzapine, clozapine or risperidone is associated with increased insulin resistance (Deng, 2013). When comparing olanzapine and risperidone, the former seems to cause a larger decrease in insulin sensitivity measured by oral glucose tolerance test (Deng, 2013). HOMA measurement and hyperinsulinemic-euglycemic glucose clamp process (measurement of blood glucose levels under a constant insulin infusion (Muniyappa et al., 2007)) have also been used in animal studies, showing that treatment with olanzapine or clozapine causes insulin resistance and dysregulation of glucose metabolism (Deng, 2013). A study using a method of frequently sampled intravenous glucose tolerance test, where glucose and insulin levels are measured minute-by-minute after an intravenous glucose bolus, found that non-obese olanzapine- and clozapine-treated patients with schizophrenia had increased insulin resistance and decreased glucose effectiveness (i.e. measure of glucose clearance rate due to an increase in blood glucose independent of insulin) compared to patients treated with risperidone (Henderson et al., 2005).

Of antipsychotics' receptor targets, 5-HT2C, H1 and muscarinic receptor affinities have been associated with increased risk of diabetes (Matsui-Sakata et al., 2005). 5-HT1A antagonism decreases insulin secretion and increases glucose levels by interfering with pancreatic beta-cell function. Moreover, 5-HT2A receptor antagonism has been found to decrease glucose uptake to skeletal muscle and thus increase glucose levels. In animal studies, 5-HT2C-deficient mice display insulin resistance, increased blood glucose and weight gain. The mechanism by which histamine H1 receptor antagonism is associated with increased glucose level may be leptin dependent. H1 blockade interferes with leptin-mediated anorexigenic signalling (Matsui-Sakata et al., 2005; Nasrallah, 2008). Muscarinic acetylcholine M3 receptors are expressed in pancreatic beta-cells where they take part in the regulation of insulin secretion. Olanzapine and clozapine, which both have antagonistic effect on M3 receptors, impair acetylcholine-mediated insulin secretion in animal studies (Nasrallah, 2008).

2.5.2.3 Are antipsychotic-induced metabolic changes evident without a psychotic disorder?

A meta-analysis aiming to clarify the connection between insulin resistance and weight gain during antipsychotic treatment, independent of the effect of the psychiatric disease, pooled together studies done with healthy volunteers (Burghardt et al., 2018). Atypical antipsychotics were found to reduce insulin sensitivity (standardized mean difference [SMD] -0.437) and increase weight (SMD 0.591) in healthy volunteers. Insulin resistance was dependent on treatment length but not on weight gain. It is of note that the range of length of the studies included in the meta-analysis was from single-dose to 28 days. Most of the studies compared 10mg of olanzapine to placebo. Significant reduction in insulin sensitivity was observed in studies ranging 3-14 days, and weight gain was observed only in studies of 14-28 days.

The meta-analysis by Burghardt et al. (2018) indicates that antipsychotics also induce insulin resistance and weight gain in individuals without a psychiatric disorder. Antipsychotic-induced insulin resistance seems to precede weight gain, which takes more time to develop. In addition to disturbing glucose metabolism, antipsychotics also have effects on lipids which will be reviewed in the next section.

2.5.3 EFFECTS OF ANTIPSYCHOTICS ON LIPID METABOLISM

The first studies addressing the effect of FGA on lipid levels showed that the use of FGA was associated with increased levels of triglycerides and total cholesterol (Meyer and Koro, 2004). Phenothiazine compounds, such as chlorpromazine, were noted to be more strongly associated with increased lipid levels than high-potency butyrophenones, such as haloperidol (Meyer

and Koro, 2004). Of SGA, olanzapine and clozapine use has been shown to increase triglyceride and both total and low-density lipoprotein (LDL) cholesterol, while risperidone use in comparison to the former has a lower propensity to increase lipid levels. Antipsychotics that have a lower risk for weight gain, e.g. ziprasidone and aripiprazole, are also associated with smaller effects on lipids (Gonçalves et al., 2015; Meyer and Koro, 2004).

In animal models, treatment with antipsychotics induces the synthesis of phospholipids, triglycerides and free fatty acids in the liver, which are then either stored in the hepatocytes or released into the circulation in very low-density lipoprotein particles (Gonçalves et al., 2015). Olanzapine has also been found to decrease lipolysis, which further contributes to the increase in fat tissue (Albaugh et al., 2012).

Antipsychotics have been found to upregulate SREBP (sterol regulatory element-binding proteins) controlled genes (Fernø et al., 2005). SREBPs are transcription factors that bind to a specific DNA sequence called the sterol regulatory element and thereby increase the transcription of enzymes taking part in cholesterol and fatty acid biosynthesis (Brown and Goldstein, 1997). However, antipsychotics' effects on the lipid biosynthesis pathways are complex and involve feedback mechanisms that result in rapid changes in the enzyme activities. This is reflected in a study investigating the in vitro effects of different SGA on lipid biosynthesis (Canfran-Duque et al., 2013). All the SGA included (clozapine, risperidone and ziprasidone) inhibited cholesterol synthesis by altering the activity of various enzymes involved in the pathway (Canfran-Duque et al., 2013). After the removal of the antipsychotic from the culture medium, a rebound effect was detected with an increase in cholesterol, phospholipid and triglyceride synthesis (Canfran-Duque et al., 2013). Taken together, antipsychotics modify lipid metabolism resulting in increased levels of total and LDL cholesterol and triglycerides. Antipsychotics have complex effects on lipid biosynthesis but the net effect seems to be an increase in the synthesis rate. The effects of antipsychotics are at least partly independent of weight gain, although antipsychotics with the greatest weight gain potential are also most strongly associated with dyslipidemia.

2.6 COURSE AND PROGNOSIS OF FIRST-EPISODE PSYCHOSIS

Outcome in psychotic disorders varies widely (Revier et al., 2015). Key concepts in defining the course of a disease are remission, meaning a significant reduction in symptoms to a level that is not detrimental to functioning or causing distress, and recovery, absence of significant symptoms and regaining the premorbid level of functioning for a prolonged period of time.

Remission and recovery in psychosis, and factors associated with varying outcomes, have been less of a focus for research than the factors affecting the

onset of psychoses. This is perhaps because dementia praecox, the predecessor of schizophrenia as a disease entity, was originally defined by Kraepelin as a chronic, unremitting illness, and recovery was thought to be rare and anomalous. The poor outcome itself was one of the defining features of the disease. Despite observations that a significant proportion of patients remitted at times, and that there were cases of partial recovery, the intractable and declining nature of schizophrenia was still considered a hallmark of schizophrenia during the era of Kraepelin. With the development of antipsychotic pharmacotherapy from the middle of the 20th century onwards, remission and recovery rates became of more interest, as new possibilities in treating psychotic disorders gave hope for a better prognosis in psychotic disorders (Frese et al., 2009).

In the past decades, definitions of remission and recovery in psychosis varied, as there was no official agreement on these concepts. The Remission in Schizophrenia Working Group (RSWG) was established to formulate a consensus on remission criteria in schizophrenia, which it published in 2005 (Andreasen et al., 2005). RSWG defined *remission* in schizophrenia as a period of at least 6 months with only mild or no symptoms (a corresponding BPRS score of ≤3 in certain items measuring psychotic symptoms and disorganization, and SANS score ≤2 in each item) such that the symptoms do not interfere with behaviour and functioning. The working group stated that remission is a necessary but not sufficient step towards recovery, which it defined as a process of longer duration, but for which it provided no operational criteria. *Recovery* has been defined multidimensionally, including symptom-level and functional (social, occupational and educational function) improvement (Emsley et al., 2011; Jääskeläinen et al., 2013; Warner, 2009).

A meta-analysis (Lally et al., 2017) found that 57-59% of patients with FEP met the criteria for remission during an average follow-up period of 5.5 years (using the RSWG remission criteria with and without the 6-month duration requirement). The rate of remission was higher in more recent studies, possibly reflecting the improved care of FEP in specialized tertiary clinics. The other potential moderators did not have a significant effect on the rate of remission, including duration of untreated psychosis, adherence to antipsychotic medication, ethnicity, employment status or being single.

The meta-analysis by Lally et al. also analysed recovery rates using criteria for recovery as in Jääskeläinen et al. (2013) (i.e. domains of clinical and social recovery with only mild symptoms, at least one of them persisting for minimum two years). The pooled recovery rate was 38% during a follow-up of 7.2 years. The rate of recovery was lower in more recent studies (published between 1997-2016) (32%) compared to older studies (1976-1996) (45%). The rate of recovery was not reduced with a longer duration of follow-up (2-6 years of follow-up compared to over 6 years), implying that the course of psychotic disorders is not necessarily deteriorating and the early

recovery rate is maintained over longer periods of follow-up (Lally et al., 2017).

Using a stricter definition of recovery than the RSWG, a meta-analysis by Jääskeläinen et al. (2013), comprising 50 studies on multi-episode and first-episode schizophrenia, found that only 13.5% of people with schizophrenia recovered with a median annual recovery rate of 1.4%. This proportion was smaller than previous estimates of approximately 40% of patients with good outcome in schizophrenia or FEP (Hegarty et al., 1994; Menezes et al., 2006).

To summarize, the recent meta-analysis by Lally et al. (2017) suggests that the prognosis in FEP is considerably better in terms of recovery rates than in schizophrenia. Unlike remission rates, the recovery rates in FEP seem not to have improved during recent decades, a finding that warrants further research. FEP does not necessarily show a deteriorating course, as the recovery rate does not seem to decline in time. Nevertheless, the prognosis in schizophrenia is relatively poor, with only a minority of individuals experiencing an extended period of time with minimal symptoms and good functioning.

2.7 METABOLIC CHANGES IN FIRST-EPISODE PSYCHOSIS

2.7.1 ANTHROPOMETRIC AND METABOLIC PARAMETERS IN DRUG-NAÏVE PATIENTS

Whether people with first-episode psychosis have an inherent vulnerability for weight gain and metabolic disturbances, independent of the effects of antipsychotic medication, is a topic of great interest and clinical importance. In historical publications, before the era of the first antipsychotic agent chlorpromazine, people with dementia praecox were described to have glucose levels similar to those of patients with diabetes (Kohen, 2004). These reports, which were case studies or small inpatient cohorts, found hyperglycaemia and decreased glucose tolerance in patients with dementia praecox. Another observation that prompted the early research on glucose metabolism in psychosis was an observation made when treating patients with psychotic symptoms with insulin-induced hypoglycaemic coma therapy, which was a widely used treatment method from the first half of the 20th century until the late 1950s. With poor results and causing tremendous suffering to the patients, repeated insulin injections were given in order to produce a hypoglycaemic state with convulsions and coma. Some clinicians administering the insulin noted that patients with schizophrenia had a decreased response to insulin compared to people without the illness. This led researchers to speculate whether the carbohydrate metabolism of the central nervous system was also disturbed in psychotic disorders (Kohen, 2004).

One potential factor resulting in harmful metabolic changes in people with FEP is a reduction of physical activity and other changes in lifestyle associated with the declining ability to function. The prodromal period, which often precedes the onset of psychosis, is characterized by symptoms of depression and anxiety, social withdrawal and a decline in the level of functioning. This, with the onset of positive symptoms, may lead to reduction in physical activity and to a lifestyle that is detrimental to physical health. Both sedentary lifestyle (Stubbs et al., 2016) and poor diet (Dipasquale et al., 2013) are common among people with schizophrenia.

A systematic review on metabolic changes in people with FEP, comprising 25 studies, found that among 7 studies reporting case-control differences before antipsychotic treatment, three studies found higher waist-to-hip ratio in patients, and one study that matched for BMI reported significantly more intra-abdominal fat in patients compared to controls (Foley and Morley, 2011). Patients and controls did not have differences in BMI, total body fat, weight or waist circumference before antipsychotic treatment. Also, no systematic differences were found in laboratory parameters such as lipid or glucose metabolism, nor in adiponectin or leptin levels (Foley and Morley, 2011).

Recent meta-analyses have examined changes in glucose and lipid parameters in patients with first-episode psychosis with minimal or no antipsychotic exposure. Increased fasting glucose, impaired glucose tolerance and insulin resistance were detected in FEP patients (Pillinger et al., 2017a). In another meta-analysis, FEP patients had reduced total and LDL cholesterol and increased triglyceride levels compared to controls, while no differences were detected in high-density lipoprotein (HDL) cholesterol levels (Pillinger et al., 2017b). However, in sensitivity analysis matched for ethnicity, the differences in total cholesterol and triglycerides were no longer significant. Furthermore, in a sensitivity analysis matched for BMI, the difference in triglycerides was not significant. In a meta-analysis investigating lipid levels in antipsychotic-naïve patients with first-episode non-affective psychosis, patients had lower total, LDL and HDL cholesterol levels, and higher triglyceride levels compared to controls (Misiak et al., 2017).

In the European First-Episode Schizophrenia Trial (EUFEST), among drug-naïve patients with first-episode schizophrenia (n=157) the prevalence of MetS was 5.7%, similar to the general population of the same age (Fleischhacker et al., 2013).

A meta-analysis, assessing metabolic abnormalities in unmedicated patients with FEP, found that the prevalence of metabolic syndrome and metabolic risk factors were low in relation to medicated multi-episode psychosis patients (Mitchell et al., 2013a). Of unmedicated patients with FEP, 9.8% had metabolic syndrome using any of the standardized criteria, and the prevalence of each of the individual metabolic risks (increased waist

circumference, hypertension, hyperlipidemia) was above 20%. (Mitchell et al., 2013a).

In conclusion, metabolic changes in FEP seem to be already partly present before medication. Dysregulated glucose metabolism and high triglycerides are among the most consistently reported findings. This is suggested to be due to intrinsic factors like dysregulated HPA axis, or external factors like stress. Unfortunately, these changes seem to further escalate during psychotropic medication, as described in the next paragraphs.

2.7.2 MEDICATION FURTHER INCREASES METABOLIC CHANGES IN FIRST-EPISODE PSYCHOSIS PATIENTS

With increasing duration of illness and antipsychotic medication, several studies show significant changes in anthropometric and metabolic parameters in FEP. In a systematic review by Foley and Morley (2011), weight gain and increase in waist circumference were already evident after one month of treatment with antipsychotics. Olanzapine was associated with more weight gain by 8 weeks than risperidone or haloperidol. By 8 weeks, increases in insulin resistance, glucose levels, as well as cholesterol and triglyceride levels were observed. In studies with a follow-up of 3-4 months, weight gain was consistently reported but changes in metabolic parameters were inconclusive, with some studies reporting increases in glucose and lipid levels while others did not find similar differences (Foley and Morley, 2011). In studies with a follow-up of one year, olanzapine was again associated with the greatest weight gain (11-17kg). Significant increases in insulin, insulin resistance, total and LDL cholesterol, triglyceride, leptin and ghrelin levels were reported in studies following patients for one year (Foley and Morley, 2011).

A study reporting the baseline results from the US-based RAISE (Recovery After an Initial Schizophrenia Episode) study found that of the 394 first-episode schizophrenia patients included in the study, 48% were overweight, 51% smoked, 57% had lipid abnormalities, 10% had hypertension and 13% had metabolic syndrome (Correll et al., 2014). In addition, 15% of patients had HbA1c-defined prediabetes. The patients had a mean lifetime antipsychotic treatment of 47 days. Antipsychotic treatment duration was associated with higher non-HDL cholesterol, triglycerides, lower HDL cholesterol and systolic blood pressure. Duration of illness was associated with anthropometric measures (weight, fat mass and percentage, waist circumference). Although the prevalence of overweight and obesity in this sample did not differ from findings in the general population in the United States, MetS and dyslipidemia were more common than in the general population of similar age. Furthermore, smoking was more common among patients than the general population (respective percentages among men 55.9% vs. 36.7% and women 36.8% vs. 24.9%).

In the EUFEST study, 52-week changes in body weight, waist circumference, hyperglycaemia, insulin resistance and lipids were compared across groups of first-episode schizophrenia patients treated with five different antipsychotics (amisulpride, haloperidol, olanzapine, quetiapine and ziprasidone). Increase in weight ranged from 0.18kg/month (ziprasidone) to 0.98kg/month (olanzapine). In the amisulpride and olanzapine groups, a statistically significant rise in insulin resistance was observed. Proportions of patients with a shift from normal triglyceride levels to hypertriglyceridemia and a reduction in HDL cholesterol levels were greatest in the amisulpride (29.2% and 22.5% respectively) and olanzapine (21.4% and 24.1%) groups over the 52-week study period. All antipsychotics were associated with increase in glucose levels with no statistically significant differences between treatment groups (Fleischhacker et al., 2013).

Providing further evidence of the longitudinal increase in cardiometabolic risk in FEP with antipsychotic treatment, a study examined differences in the incidence and prevalence of MetS in FEP patients treated with FGA compared to patients treated with SGA (De Hert et al., 2008). During a 3-year follow-up, an almost 5-fold increase in the prevalence of MetS was detected in the SGA group over the study period (baseline prevalence 5.6% vs. 3-year prevalence 30.6%). This was a markedly higher increase than the prevalence in the FGA group (baseline prevalence 5.7% vs. 3-year prevalence 13.1%). The higher increase in the prevalence in the SGA group was mostly due to the harmful metabolic effects of clozapine and olanzapine. Patients treated with clozapine at the 3-year measurement had a MetS prevalence of 58.3%, and those treated with olanzapine 47.1%. In contrast, the prevalence of MetS was lowest in those treated with aripiprazole (10.0%). Another study on medication-naïve FEP patients found a 12.1kg mean weight gain among 170 patients during a 3-year follow-up (Perez-Iglesias et al., 2014). The weight gain was rapid during the first year of antipsychotic treatment, accounting for 85% of the total weight gain. Total cholesterol, LDL cholesterol and triglycerides increased significantly from baseline to the one-year assessment, while the change in HDL cholesterol was slower, reaching a statistical significance at the two-year assessment. Changes in glucose, insulin and HOMA levels were not statistically significant, although a trend for increases in HOMA and insulin were observed (Perez-Iglesias et al., 2014).

In conclusion, studies consistently show how weight gain and an unfavourable lipid profile develop rapidly during the first months of psychopharmacological treatment, and this development continues even longer. While these metabolic changes already increase cardiovascular risk considerably, the changes are accompanied by a systemic low-grade inflammation adding to the risk.

2.8 LOW-GRADE INFLAMMATION IN PSYCHOTIC DISORDERS

2.8.1 MECHANISMS OF LOW-GRADE INFLAMMATION

Inflammation is an organism's response to factors that are perceived as threatening the survival of the organism (e.g. infection or physical injury). Inflammation has adaptive functions: initiating the process of removal of the threat (e.g. bacteria or viruses causing an infection) and the healing of damaged tissue. By recruiting a variety of defense mechanisms, the organism aims to prevent any further damage by the infectious or other physically insulting agent. The immune system is divided into the innate and adaptive immune systems (Chaplin, 2010). The innate immune system consists of physical barriers (e.g. epithelial layers of gastrointestinal and respiratory tracts, mucus and saliva), immune cells, complement system and cytokines. Immune cells of the innate system, neutrophils and monocytes, and the cells deriving from monocytes (dendritic cells, macrophages, mast cells and eosinophils) take part in clearing out the infectious agent by detecting foreign substances and attempting to neutralize them. By antigen presentation, dendritic cells also activate the T and B lymphocytes of the adaptive immune system. The B lymphocytes secrete pathogen-specific antibodies and thus activate a range of immune mechanisms against the pathogen. T lymphocytes have differing functions, including elimination of the pathogen and regulation of the immune response. Cytokines and chemokines, secreted by the immune cells and various other cell types, orchestrate the immune activation by increasing or decreasing the inflammatory activity (Chaplin, 2010).

In addition to providing vital protection for the survival of the host organism, inflammation can also be maladaptive, causing effects that are harmful for the survival and well-being of the host. In the case of infection or physical damage, inflammation is a transient process, usually leading to successful removal of the insulting agent and healing of the tissues. In chronic inflammation, such that is present in obesity, the immune system is not able to remove the inflammation-inducing factors. This leads to a persisting pro-inflammatory activation. The low-grade, chronic inflammation is associated with obesity and the many complications of obesity, such as insulin resistance, T2D and cardiovascular disease (Gregor and Hotamisligil, 2011).

In obesity, excessive fat accumulation causes a pathological state in the adipocytes which are forced to adapt to an environment with abundant nutrients and increased levels of insulin (Reilly and Saltiel, 2017). Increased number of adipocyte cell death, mechanical stress of cell and tissue expansion and hypoxia all contribute to an inflammatory reaction, which in itself is adaptive, aiming to increase the chance of survival of the adipocytes,

e.g. by increasing vascularization of the adipose tissue. In response to increased pro-inflammatory cytokine production by the adipocytes, pro-inflammatory macrophages, mast cells and T cells invade the adipose tissue (Gregor and Hotamisligil, 2011). In addition, obesity is associated with increased permeability of the intestinal mucosa, which may lead to leakage of gut-derived antigens, such as lipopolysaccharide (LPS), the major component of the outer membrane of gram-negative bacteria, to the blood. LPS is detected by the adipocytes in the mesenteric adipose tissue surrounding the gut. Ingested lipids may also act as antigens, provoking further pro-inflammatory activation (Reilly and Saltiel, 2017).

2.8.2 C-REACTIVE PROTEIN AS A MARKER FOR LOW-GRADE INFLAMMATION

CRP is the most widely available inflammatory marker in clinical medicine. CRP is an acute-phase protein produced mainly by hepatic cells in response to inflammatory cytokines, primarily interleukin-6 (Castell et al., 1990). In addition to liver cells, adipocytes may also produce CRP in obese individuals (Anty et al., 2006). CRP takes part in the innate immune process of host defense by binding to the surface of microbes or to components released from damaged cells, which leads to activation of the complement cascade (Pepys and Hirschfield, 2003).

Low-grade inflammation can be measured with hs-CRP with better sensitivity than regular assays. CRP correlates with BMI and waist circumference in the general population (Choi et al., 2013). Hs-CRP is an independent risk factor for cardiovascular disease of the same magnitude as LDL cholesterol and independent of it (Ridker, 2016). Values of hs-CRP below 1mg/l mark low cardiovascular risk, values between 1-3mg/l intermediate risk and above 3mg/l increased risk (Ridker, 2016). Furthermore, hs-CRP is a risk factor for vascular and non-vascular mortality in the general population (Emerging Risk Factors Collaboration et al., 2010). In the general population, significant changes in hs-CRP levels are not common; in fact, just as cholesterol and blood pressure levels, hs-CRP has been observed to stay relatively unchanged in individuals over a number of years (Emerging Risk Factors Collaboration et al., 2010).

2.8.3 EVIDENCE OF LOW-GRADE INFLAMMATION IN PSYCHOTIC DISORDERS

Low-grade inflammation has been observed in many psychiatric disorders, including major depression, bipolar disorder, schizophrenia and post-traumatic stress disorder (Pinto et al., 2017). These disorders do not have specific inflammatory biomarker profile as many of the same biomarkers are shared by the disorders (Pinto et al., 2017). This may reflect the fact that the psychiatric disorders also share similarities in their molecular background

(Gandal et al., 2018), and that the disorders are associated with lifestyle factors, stress and metabolic changes which can all induce pro-inflammatory activation (Black, 2003).

Four meta-analyses have been published on the association between CRP levels and schizophrenia or related psychoses. A meta-analysis by Miller et al. (2011) included eight individual cross-sectional studies measuring CRP in people with schizophrenia or related psychoses (schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified, delusional disorder and schizoaffective disorder) and in healthy controls. The studies consisted of altogether 767 patients and 745 controls. According to the meta-analysis, people with schizophrenia or related psychoses had increased levels of CRP by a small-to-medium effect size of 0.45 (95% CI 0.34-0.55, $p<0.001$) (Hedge's g; where 0.2 is considered to indicate small effect, 0.5 a moderate effect and 0.8 a large effect (Higgins and Green, 2011)). However, after excluding one (Fawzi et al., 2011) of the eight studies in a sensitivity analysis, the effect size dropped to 0.10 and was no longer statistically significant ($p=0.10$). In their meta-analysis, Miller et al. also looked into the prevalence of abnormal CRP (defined as CRP value >5mg/l) in five studies consisting of altogether 575 subjects with schizophrenia or related psychoses, and found that 28.0% of the subjects had an abnormal level of CRP. A limitation of the meta-analysis was, as discussed by the authors, that many of the included studies did not control for factors known to affect CRP levels, such as BMI, smoking or antipsychotic use.

The largest meta-analysis on CRP levels and psychotic disorders published to date was conducted by Fernandes et al. (2016), including 26 cross-sectional or longitudinal studies and 85000 participants diagnosed with schizophrenia, schizophreniform or schizoaffective disorder. The authors did a between-group meta-analysis, consisting of 19 studies, to investigate differences in CRP levels between patients with psychotic disorders and healthy controls. They also conducted two within-group meta-analyses consisting of six and three studies to clarify the effects of antipsychotic initiation and antipsychotic change on CRP levels. The between-group meta-analysis showed that people with psychotic disorders had higher CRP levels than controls with an effect size of 0.66 (95% CI 0.43-0.88, $p<0.0001$). In meta-regression analyses, CRP levels were associated with positive symptom severity, but no association between CRP levels and negative symptoms were detected. There was a positive association with BMI and CRP levels (slope=0.21, 95% CI 0.04-0.29, $p=0.004$). However, the authors detected no association between CRP and waist circumference (slope=0.01, 95% CI –0.07-0.09, $p=0.867$). The within-group meta-analyses showed that there were no statistically significant differences in CRP levels before and after the initiation of antipsychotic treatment (range of follow-up 4-52 weeks) or after a switch of antipsychotic, regardless of whether the switch was within or across the classes of FGA and SGA.

Inoshita et al. (2016) included 14 case-control studies (1664 patients with schizophrenia, 3070 controls) in their meta-analysis on CRP levels in schizophrenia. They reported significantly higher CRP levels in patients with schizophrenia (SMD 0.62, 95% CI 0.24-0.99, p=0.0014). No analysis of the possible confounding effect of BMI or waist circumference in CRP levels was included.

Wang et al. (2017) based their meta-analysis on 18 case-control studies on schizophrenia and related psychoses. They found moderately increased CRP levels in people with psychoses (SMD 0.53, 95% CI 0.30-0.76). Similar to the meta-analysis by Fernandes et al., Wang et al. reported that increase in CRP was not explained by higher BMI in people with psychosis, and with increasing age the difference in CRP levels between people with schizophrenia and controls decreased.

It is noteworthy that the meta-analyses conducted on CRP levels in schizophrenia have high heterogeneity among individual studies. Heterogeneity can be measured by I^2 which varies between 0% and 100%, and reflects inconsistency in the findings of individual studies (Higgins et al., 2003). The meta-analyses on CRP and schizophrenia all have an I^2 above 90%, indicating that there is marked heterogeneity among the studies included. This might arise because of differences in the selection of participants for the studies (e.g. stage of illness, duration of antipsychotic use), differences in exclusion criteria (eg. infections, chronic physical illnesses), and differences in the method of selection of control subjects. The reasons underlying high heterogeneity were further explored in the meta-analysis by Fernandes et al. (2016), where heterogeneity was higher in clinical studies than in population-based studies, but was not explained by any other single variable.

2.8.3.1 Is high CRP causally correlated with risk of psychosis?

Mendelian randomization (MR) is a method of analysing the genetic variation of a risk factor and its association with an outcome. It can be utilized to clarify possible causal connections between a putative risk factor and the associated outcome when there is a known genetic variation affecting the risk factor, and when this genetic variation does not directly influence the outcome. MR studies conducted on CRP and risk of schizophrenia use information of certain SNPs that affect levels of CRP in large samples, and aim to test whether this genetically determined level of CRP is connected to the risk of schizophrenia. MR eliminates the common problems of observational studies, reverse causation (meaning that the observed outcome influences the exposure) and confounding factors (unaccounted factors affecting both the exposure and outcome variables, thus leading to a false association) (Hartwig et al., 2016).

Several MR studies have been conducted to clarify whether genetically predicted CRP levels are causally connected with the risk of schizophrenia

(Hartwig et al., 2017; Inoshita et al., 2016; Prins et al., 2016; Wium-Andersen et al., 2014). The results have been inconsistent, as some studies have found the genetic variations connected with elevated CRP levels to be associated with increased risk of schizophrenia (Inoshita et al., 2016; Wium-Andersen and Wium-Andersen, 2016), while other studies have reported an inverse finding (Hartwig et al., 2017; Prins et al., 2016). For example, a MR study by Hartwig et al. (2017) found that genetic predisposition for higher CRP levels had a protective effect: with each 2-fold increase in the predicted CRP level, risk of schizophrenia decreased by an odds ratio of 0.90 (random effects 95% CI 0.84–0.97, p=0.005). The mechanism behind the association of lower levels of CRP and schizophrenia risk is unknown. The authors suggested that higher levels of CRP might provide protection from early life infections and thus decrease the risk of schizophrenia (Hartwig et al., 2017). Interestingly, this hypothesis is in accordance with another study that reported higher levels of acute-phase proteins in newborns associating with lower risk of later non-affective psychosis (Gardner et al., 2013).

In summary, studies attempting to clarify whether there is a causal connection between CRP levels and schizophrenia have come up with discordant results. Even if no genetic mechanism behind CRP levels and risk of schizophrenia were found, this does not necessarily exclude a role for inflammatory activity in the aetiology of psychotic disorders. Nevertheless, there are a multitude of confounding factors when measuring inflammation in psychotic disorders, including physical disease, obesity, stress and medication (Manu et al., 2014). Revealing distinct inflammatory processes with aetiological significance would require more studies that control for these factors and follow individuals throughout the disease process from at-risk states to psychosis.

2.9 PHYSICAL COMORBIDITY AND MORTALITY IN PSYCHOTIC DISORDERS

2.9.1 CARDIOVASCULAR RISK FACTORS AND CARDIOVASCULAR DISEASE IN PEOPLE WITH PSYCHOTIC DISORDERS

People with chronic psychotic disorders have a high prevalence of co-occurring physical disease, i.e. physical comorbidity (Crump et al., 2013b; Laursen et al., 2011). Various factors predispose people with psychotic disorders to physical comorbidity, including low level of physical activity, smoking, low quality diet and antipsychotic medication. Table 3 shows major physical comorbidities and their estimated prevalence or incidence in psychotic disorders or other SMI.

Obesity is defined as BMI ≥30kg/m^2. The global prevalence of obesity has been increasing during recent decades, tripling since 1975. Globally in 2016, 15% of women and 11% of men were obese (WHO World Health Organization, 2018). In Finland, one fourth of the adult population is obese (Koponen et al., 2018). Obesity increases the risk of cardiovascular disease, diabetes, cancer and musculoskeletal disease, such as arthrosis (Bray, 2004). In the general population, obesity is associated with increased all-cause, vascular, diabetic and cancer mortality (Prospective Studies Collaboration, 2009). As reviewed in section 2.5.1, antipsychotic medication is a major driver for obesity in people with psychotic disorders. Fat accumulation that is associated with antipsychotic use concentrates especially in the abdomen, leading to abdominal obesity, subsequent metabolic dysregulation (i.e. inflammation, hypertriglyceridemia and insulin resistance) and increased risk of physical comorbidity (Gonçalves et al., 2015).

MetS consists of abdominal obesity, hyperglycaemia, increased triglycerides, low HDL and hypertension (Alberti et al., 2009). MetS is associated with a 2-fold increased risk of cardiovascular disease over 5-10 years and with a 5-fold risk of type 2 diabetes in comparison to people without the syndrome (Alberti et al., 2009). There have been various modifications to the criteria for MetS. In 2001, the National Cholesterol Education Program of the United States published the ATPIII (Adult Treatment Panel III) criteria for MetS (Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults, 2001). The new criteria abandoned the insulin resistance/glucose intolerance criterion, which was included in previous definitions of MetS, with the rationale that waist circumference is correlated with insulin resistance, and in the clinical setting fasting glucose is more easily available than measures of insulin resistance. The International Diabetes Federation (IDF) introduced their criteria for MetS in 2005, modifying the ATPIII criteria with ethnicity-specific cut points for waist circumference and lower cut point (5.6mmol/l) for elevated fasting glucose (International Diabetes Federation, 2006). The IDF criteria also emphasized the significance of abdominal obesity in MetS by making increased waist circumference a prerequisite for the diagnosis.

The American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) made minor changes to the ATPIII criteria in 2005: they lowered the fasting glucose cut point from 6.1mmol/l to 5.6mmol/l to correspond with the American Diabetes Association's definition for impaired fasting glucose (Grundy et al., 2005). In the manner of IDF, AHA/NHLBI set ethnicity-specific cut points for waist circumference, specifying that some people with marginally increased waist circumference (especially people with Asian ethnicity, for whom lower cut points for waist circumference should be used) will have a genetic predisposition for insulin resistance and should therefore be treated accordingly, even if the required limit of ≥102cm in men or ≥88cm in women is not met (Grundy et al., 2005). Table 4 shows the AHA/NHLBI and IDF criteria for MetS.

Table 3. Major physical comorbidities in psychotic disorders. Adapted from Eskelinen, 2017

Physical comorbidity	Prevalence/incidence of the comorbidity in people with SZ or related psychotic disorder	Comments	References
Obesity	In chronic SZ, obesity is approximately two times more common than in the general population. Prevalence estimates in different studies range from 17-52%	Factors increasing the risk of obesity: psychotropic medication, poor diet, low level of physical activity	Allison et al., 2009b; Bradshaw and Mairs, 2014
Metabolic syndrome	Prevalence between 30-60% of people with chronic SZ or other psychotic disorders	Especially in young people with psychotic disorders, the prevalence of MetS is higher compared to the general population	Gardner-Sood et al., 2015; Mitchell et al., 2013b; Suvisaari et al., 2007
Type 2 diabetes mellitus	In chronic SZ, the prevalence is 2-5 times more common than in the general population. A meta-analysis by Stubbs et al. suggested a prevalence of type 2 DM of approximately 10% in SZ		Stubbs et al., 2015; Suvisaari et al., 2008; Ward and Druss, 2015
Dyslipidemia	In a meta-analysis, the prevalence of hypertriglyceridemia in SZ and related disorders was 39.3% and of low HDL 42.6%. In Finland, the respective prevalence: 46.2% and 50.8%	Suvisaari et al. (2007) found that hypertriglyceridemia and low HDL were more prevalent in SZ, but not in other other psychotic disorders, than in the general population	Mitchell et al., 2013b; Suvisaari et al., 2007
Cardiovascular disease	A meta-analysis by Fan et al. found that in SZ the risk ratio was 1.5 for CVD, 1.2 for CHD, 1.7 for stroke, and 1.8 for CHF	Findings for the prevalence of hypertension in SZ and related disorders are inconsistent; some studies suggest higher, some lower prevalence than in the general population	Bresee et al., 2010; Fan et al., 2013; Suvisaari et al., 2007

Respiratory disease	A US-based study reported a self-reported COPD prevalence in SMI (SZ, schizoaffective disorder, recurrent MDD, BD) of 22.6%. Another study utilizing inpatient and outpatient administrative claims in Iowa, USA, reported an OR of 1.88 for COPD. In a study based on Swedish register data, HR for COPD was over 2-fold. In a Finnish study, the OR for COPD was 4.2 and for chronic bronchitis 3.8	Carney et al., 2006; Crump et al., 2013b; Himelhoch et al., 2004; Partti et al., 2015
Cancer	Risk of most cancer types in SMI may not be increased compared to the general population. However, a recent meta-analysis showed that women with SZ may have increased risk of breast cancer	Catts et al., 2008; Kisely et al., 2013; Zhuo and Triplett, 2018
Infections	In a study using Swedish register data, the age-adjusted HR for influenza or pneumonia diagnosis in SZ was over 2-fold. In a Finnish study, risk for hospitalization due to pneumonia was 5-fold in SZ compared to the general population. Clozapine and other SGA use are associated with an increased risk of pneumonia. Risk of pneumococcal septicaemia and meningitis are also higher in SMI	Crump et al., 2013b; Kuo et al., 2013; Partti et al., 2015; Seminog and Goldacre, 2013

BD, bipolar disorder; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; OR, odds ratio; HR, hazard ratio; MDD, major depressive disorder; SZ, schizophrenia; SMI, serious mental illness; MetS, metabolic syndrome; HDL, high-density lipoprotein cholesterol

Table 4. ATPIII criteria modified by AHA/NHLBI and IDF criteria for metabolic syndrome

	AHA/NHLBI modification of ATPIII (2005)	IDF (2005)
Required	Any 3 of the 5 criteria	Elevated waist circumference + 2 of the 4 criteria
Waist circumference	≥102cm in men, ≥88cm in women	Ethnicity specific.* European ancestry: ≥94cm in men, ≥80cm in women
Elevated triglycerides	≥1.7mmol/l or specific treatment	≥1.7mmol/l or specific treatment
Reduced HDL	<1.03mmol/l in men, <1.3mmol/l in women, or specific treatment	<1.03mmol/l in men, <1.29mmol/l in women, or specific treatment
Elevated blood pressure	≥130mmHg systolic or ≥85mmHg diastolic, or antihypertensive treatment	≥130mmHg systolic or ≥85mmHg diastolic, or antihypertensive treatment
Elevated fasting glucose	≥5.6mmol/l or treatment for elevated glucose	≥5.6mmol/l or treatment for elevated glucose

*If BMI >30kg/m^2, elevated waist circumference can be assumed.
AHA/NHLBI, American Heart Association / National Heart, Lung, and Blood Institute; ATPIII, Adult Treatment Panel III; IDF, International Diabetes Federation; HDL, high-density lipoprotein cholesterol; BMI, body mass index

Diabetes mellitus is traditionally divided into type 1 (with deficient insulin production) and type 2 (characterized by insulin resistance). However, this division is not definite, as many individual patients with diabetes fall somewhere between the two categories. The global prevalence of diabetes has almost doubled from 4.7% in 1980 to 8.5% in 2014 (WHO World Health Organization, 2017). In Finland, it is estimated that approximately 500 000 people have diabetes, and the number of people having a right for reimbursement for medication used to treat diabetes has doubled during the previous 12 years. Most of this increase is due to the increase in the prevalence of T2D (Working group set up by the Finnish Medical Society Duodecim the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society, 2018). In addition to genetic risk factors (Almgren et al., 2011), obesity and lack of physical activity are the main risk factors for T2D (WHO World Health Organization, 2017). T2D is diagnosed when in two separate measurements fasting glucose is ≥7.0mmol/l or after 2-hour oral glucose tolerance test >11mmol/l, or HbA1c is ≥48mmol/mol (≥6.5%) in a single measurement. In addition, a single

measurement of blood glucose >11mmol/l is sufficient for the diagnosis if classical symptoms of diabetes (thirst, weight loss, excessive urination) are present (Working group set up by the Finnish Medical Society Duodecim the Finnish Society of Internal Medicine and the Medical Advisory Board of the Finnish Diabetes Society, 2018).

Dyslipidemia is a major risk factor for atherosclerosis and cardiovascular disease (including coronary heart disease, stroke and peripheral arterial disease). Dyslipidemia is diagnosed when total plasma cholesterol exceeds 3.0mmol/l, triglycerides >1.7mmol/l, or HDL <1.0mmol/l in men or <1.2mmol/l in women. In 2008, the global prevalence of elevated total cholesterol was 39% (WHO World Health Organization, 2011). In Finland, nearly 60% of the population over 30 years of age have increased total cholesterol and about 50% have increased LDL cholesterol (Koponen et al., 2018). In addition to antipsychotics, a diet with high saturated fat and low fibre content, low level of physical activity, smoking, high alcohol use and genetic factors may increase lipid levels and the risk of atherosclerotic vascular disease. Hypertriglyceridemia and low HDL are associated with insulin resistance and T2D (Li et al., 2014), although the causal connection between hypertriglyceridemia and low HDL with T2D is unclear (De Silva et al., 2011; Haase et al., 2015; Qi et al., 2012).

Risk of cancer is generally increased by high alcohol consumption, smoking, obesity, low level of exercise and low intake of fruit and vegetables. Thus, it might be reasonable to expect the risk of cancer to be higher in people with psychotic disorders than in the general population. However, the findings on cancer have been inconsistent, and generally pointing in the direction that cancer incidence is not increased in people with psychosis (Kisely et al., 2013). The shorter lifespan of people with psychotic disorders due to other causes, and lower participation of cancer screening, may result in lower incidence rates of cancer in this population (De Hert et al., 2011b).

2.9.2 INCREASED MORTALITY IN PSYCHOTIC DISORDERS

In epidemiological studies on mortality, mortality rates are often reported. Mortality rate is defined as number of deaths per year per 1000 individuals. Mortality rates in different populations can be compared by mortality rate ratio (MRR) or standardized mortality rate (SMR). MRR is defined as the mortality rate in a population of interest divided by the mortality rate in a comparison group. SMR is calculated by dividing the mortality rate in a specific population by the mortality rate in the general population. Another way to express differences in mortality is to calculate differences in years people in different populations live. For instance, the average age of death in people with schizophrenia is compared to the average age of death in the general population, and the difference is reported. Causes of mortality are divided into natural causes (i.e. disease) and unnatural causes (i.e. accident, suicide, homicide, poisonings or overdose).

People with schizophrenia die 15-20 years earlier than the general population (Laursen et al., 2014). Even higher differences have been

reported: in a US study, the years of life lost per deceased with schizophrenia was 28.5 years (Olfson et al., 2015). The excess mortality is mainly due to medical comorbidity in particular cardiovascular disease, diabetes, cancer and respiratory disease (Crump et al., 2013b; Olfson et al., 2015; Suvisaari et al., 2013; Termorshuizen et al., 2013). In people with psychotic disorders, the mortality due to medical conditions is disproportionally high compared to morbidity, which may be partly explained by under-diagnosis or poor quality of treatment of physical comorbidities (Crump et al., 2013b). A systematic review on mortality in schizophrenia gathered 37 studies from 25 nations, and reported an SMR of 2.58 (10% and 90% quantiles 1.18-5.76) (Saha et al., 2007). In a Finnish study, the all-cause SMR of people with SMI compared to the total population was 3.48 in men and 3.75 in women between 2008-2010 (Lumme et al., 2016).

Various studies indicate that although in the general population mortality due to cardiovascular disease and cancer has been steadily decreasing, similar improvement is not observed in people with SMI (Lumme et al., 2016; Osby et al., 2016; Saha et al., 2007). However, studies have also reported decreasing differences in mortality between people with SMI and the general population in Finland, Denmark and Sweden (Wahlbeck et al., 2011; Westman et al., 2012). In an Australian study, cancer patients with SMI received less surgical treatment and chemotherapy than patients without SMI (Kisely et al., 2013). Similarly, a recent Finnish study showed that cancer mortality increased in people with SMI and was partly explained by poorer quality of treatment (Manderbacka et al., 2017). The less intensive treatment received by people with SMI is not limited to cancer. In a Finnish study, examining access to coronary care in people with psychotic disorders in 1998-2009, people with psychotic disorders had particularly poor access to hospital treatment for coronary heart disease and revascularization treatment (Manderbacka et al., 2012). In addition, medication use for cardiovascular disease has been observed to be lower in patients with schizophrenia than in the general population (Laursen et al., 2014).

As described above, various factors increasing mortality risk accumulate for people with psychotic disorders and other SMI. These include lifestyle-related factors, potential intrinsic factors to SMI and shared genetic risk between physical disease and SMI (Andreassen et al., 2013). Antipsychotic treatment further increases unfavourable metabolic changes resulting in a systemic inflammation.

Antipsychotics have adverse effects that result in increased risk of cardiovascular disease and diabetes, as reviewed above. A systematic review consisting of 12 studies concluded that long-term exposure to antipsychotics increased mortality in schizophrenia, although the heterogeneity in the methods, follow-up times and outcomes in the individual studies was evident (Weinmann et al., 2009). Register-based studies from Finland and Sweden, investigating the association between antipsychotic use and mortality in schizophrenia, have found higher mortality risk in the groups with no

exposure to antipsychotics (Tiihonen et al., 2009; Torniainen et al., 2015). Specifically, antipsychotic, but also antidepressant, use has been associated with lower mortality in schizophrenia, whereas exposure to benzodiazepines may increase mortality (Tiihonen et al., 2016). In a Finnish study, antipsychotic use was not associated with mortality in people with schizophrenia (Suvisaari et al., 2013). However, in people over 65 years without a primary psychotic disorder antipsychotic use was associated with increased mortality (Suvisaari et al., 2013), concordant with the finding of increased mortality in people with dementia using antipsychotics (Koponen et al., 2017). In a recent study using Finnish register data, mortality in people hospitalized due to first-episode schizophrenia was higher during the 16.4-year follow-up in those who discontinued antipsychotic medication within the first year after the first hospitalization compared to those using antipsychotics continuously (HR 2.74, 95% CI 1.09–6.89) (Tiihonen et al., 2018). Mortality was even higher among patients who never used antipsychotics after the first hospitalization (HR 3.14, 95% CI 1.29–7.68).

In studies examining mortality in FEP, unnatural cause mortality for suicides and accidents is higher than natural cause mortality, which is understandable given that the onset of FEP is typical in young adulthood when deaths due to natural causes are rare. The lifetime risk of suicide in psychotic disorders has been estimated to be 5.6%, and the highest risk is during the first year of treatment during which 10% of patients attempt suicide (Nordentoft et al., 2015). In the ÆSOP-10 study, 557 patients with FEP from Southeast London and Nottinghamshire, UK, were followed for 10 years. Suicide was the leading cause of death; a 20-fold increase compared to the local general population. Unnatural cause mortality was in total 13-fold higher and natural cause mortality 2-fold higher than in the general population (Reininghaus et al., 2015). Interestingly, a study based on Danish, Finnish and Swedish register data found that the observed/expected ratio of natural cause mortality was also highest during the first year after first hospitalization due to a psychiatric disorder (Nordentoft et al., 2013).

2.10 SUMMARY OF THE LITERATURE REVIEW

Psychotic disorders are accompanied by substantial physical comorbidity and excess mortality. Although it seems that individuals with FEP do not differ from the general population of the same age in terms of weight or waist circumference, some metabolic risk factors, such as disturbances of glucose metabolism and elevated triglyceride levels, may already be present in drug-naïve individuals with FEP. However, weight gain and increase in metabolic and cardiovascular risk factors, including glucose, insulin and lipid levels, is substantial after the initiation of antipsychotic medication. It is currently not possible to accurately predict which individuals will suffer most from the adverse metabolic effects of antipsychotics.

There is meta-analytic evidence of increased CRP in psychotic disorders. This increase has been observed in early psychosis as well as in chronic disease. There are a multitude of potential confounding factors when measuring CRP in psychosis, including obesity, stress, smoking and antipsychotic medication, which should be considered. Furthermore, the longitudinal course of pro-inflammatory activity marked by CRP is unknown in psychotic disorders.

The mortality in psychotic disorders is increased compared to the general population, and this is mostly due to natural causes. The excess mortality in psychotic disorders, i.e. the mortality gap between people with psychosis and the general population, has not been decreasing during the last decades. Under-diagnosis and poor quality of treatment of physical comorbidities may be some reasons underlying the excess mortality in psychotic disorders. Even though antipsychotics increase the risk of some physical comorbidities, their use is not associated with increased mortality.

3 AIMS OF THE STUDY

The aim of the study was to clarify baseline differences between FEP patients and controls, and longitudinal changes during a 12-month follow-up in FEP patients in anthropometric measures (weight, waist circumference), metabolic parameters (glucose homeostasis, lipid levels) and low-grade inflammation. This study also aimed to investigate mortality in psychotic disorders, and to clarify the effect of sociodemographic status, physical disease, lifestyle-related factors, smoking and antipsychotic medication on mortality risk.

Specific aims of the studies were:

I. To identify baseline risk factors for changes in weight and waist circumference in FEP patients during a 12-month follow up.

II. To examine baseline differences in anthropometric and metabolic measures between FEP patients and controls, and changes in the measures during a 12-month follow-up. Furthermore, baseline differences and longitudinal changes in low-grade inflammation measured by hs-CRP were investigated, with the aim of detecting factors associated with low-grade inflammation.

III. To identify predictors of mortality in people with psychotic disorders during a 13-year follow-up, and to examine associations between previously known sociodemographic and health-related factors with mortality.

4 METHODS

4.1 HELSINKI EARLY PSYCHOSIS STUDY (STUDIES I & II)

4.1.1 STUDY DESIGN AND SUBJECTS

The subjects in the Helsinki Early Psychosis Study were FEP patients between 18-40 years receiving their first treatment due to psychosis. They were recruited from the catchment areas of the Helsinki University Hospital and Helsinki Psychiatric Services from December 2010 to June 2016. Receiving a score of at least 4 in Unusual thought content or Hallucinations in the Brief Psychiatric Rating Scale–Expanded (BPRS-E) (Ventura et al., 1993) and fluency in Finnish language were used as inclusion criteria to the study. Patients with substance-induced psychotic disorders and psychotic disorders due to a general medical condition were not included.

Controls matched by age, gender and region of residence were identified from the Population Register Centre. Controls were assessed at baseline and at 12 months using the same protocol as described for the patients. The exclusion criteria for controls were lifetime history of psychotic disorder, chronic neurological, endocrinological or cardiovascular disease, or any condition that prevents magnetic resonance imaging (MRI).

Patients were assessed three times. The baseline assessment was done after the patient had entered treatment and as soon as the patient was able to give informed consent. The follow-up assessments were done at two and 12 months after the baseline assessment. The number of participants and the psychiatric diagnoses of FEP patients in Studies I and II are shown in Table 5 and 6. Table 7 shows the measures and scales used in the evaluation of FEP patients in each assessment. MRI using a 3 Tesla scanner was done at baseline and at 12-month follow-up for patients and controls (Mäntylä et al., 2015). Blood and stool samples were collected from patients and controls at each assessment. Psychiatric diagnostic interviews were done at the follow-ups of two and 12 months. The diagnostic assessments were based on the Research Version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 2002) and available medical records. After the interview, the interviewer confirmed the diagnosis with a senior psychiatrist. If there was uncertainty, three senior psychiatrists determined a consensus diagnosis.

The study protocol was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa (257/12/03/03/2009) and by the institutional review boards of the National Institute for Health and Welfare, Helsinki, Finland, and the University of Helsinki. All participants gave a

written informed consent. The treating psychiatrist assessed the patient's capacity to give informed consent.

4.1.2 MEASUREMENT OF HEIGHT, WEIGHT, WAIST CIRCUMFERENCE AND BLOOD PRESSURE

A wall-mounted stadiometer was used to measure height. Weight was measured by using a standard portable scale. At baseline and at 12 months, the same scale was used (OBH Nordica 6251). At the 2-month follow-up, a scale in the treating clinic or at the National Institute for Health and Welfare was used, depending on the location of the interview.

Waist circumference was measured during light expiration with a flexible tailor's measuring tape while the subject was in a standing position with the legs slightly apart. The measuring tape was positioned at the midpoint between the lowest rib bone and the high point of the iliac crest.

The interviewer measured blood pressure after a five-minute rest using Omron M6 Comfort digital blood pressure monitor.

4.1.3 MEASURES OF PHYSICAL ACTIVITY, DIET AND SMOKING

The Gothenburg scale (Wilhelmsen et al., 1972) was used to measure the physical activity of the study subjects. The participants were asked how much they exercised or strained themselves. Participants were classified physically active when they reported: 1) walking, bicycling or otherwise moving at least four hours per week; *or* 2) exercising at least three hours per week; *or* 3) training for competitive sports. Otherwise participants were classified as having a sedentary lifestyle.

Consumption of different foods and drinks during the past week was assessed using a questionnaire from the Health Behaviour and Health among the Finnish Adult Population survey (Helldán et al., 2013; Männistö et al., 2010). The answers ranged from "not at all" (0 points) to "on 6-7 days" (3 points). For assessing unhealthy diet, a sum score of the frequency of consumption of high-energy foods and drinks rich in fat and/or sugar (pizza, hamburgers, chocolate and sweets, cookies, pastries, juices and beverages containing sugar) was calculated.

Current smoking was defined as current, regular smoking and having smoked at least 100 cigarettes as reported by the participants.

Table 5. Data available throughout Studies I & II

	Interview		Laboratory analyses		Weight		Waist circumference		Information on current smoking	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
Baseline										
Study I	60	27	57-58[a]	27	59	27	60	27	51	25
Study II	95	62	84-85	51	94	61	95	61	79	53
Two months										
Study I	43	NA	43	NA	48	NA	49	NA	NA	NA
Study II	77	NA	67-68	NA	75	NA	77	NA	NA	NA
12 months										
Study I	22	NA	20-22	NA	33	NA	34	NA	NA	NA
Study II	61	NA	52-53	NA	59	NA	59	NA	NA	NA

[a]The number of successful plasma and serum sample analyses differed in some of the laboratory measures

Table 6. Psychiatric diagnoses of FEP patients in Studies I and II

Diagnosis	n	%
Schizophrenia		
Study I	24/60	40
Study II	35/95	37
Schizophreniform disorder		
Study I	13/60	22
Study II	22/95	23
Psychotic disorder not otherwise specified		
Study I	11/60	18
Study II	19/95	20
Bipolar disorder with psychotic features		
Study I	7/60	12
Study II	8/95	8
Major depressive disorder with psychotic features		
Study I	0/60	0
Study II	4/95	4
Schizoaffective disorder		
Study I	2/60	3
Study II	3/95	4
Brief psychotic disorder		
Study I	2/60	3
Study II	3/95	3
Delusional disorder		
Study I	1/60	2
Study II	1/95	1

4.1.4 DEFINITIONS OF CLINICALLY SIGNIFICANT WEIGHT GAIN, OVERWEIGHT, OBESITY AND METABOLIC SYNDROME

As per the criteria defined by the World Health Organization, BMI ≥25.0kg/m² was defined as overweight and BMI ≥30.0kg/m² as obesity.

For MetS, the IDF criteria were applied: MetS was diagnosed when the participant had elevated waist circumference (≥94cm in men and ≥80cm in women) and met at least two of the following criteria: triglycerides ≥1.7mmol/L, HDL <1.03mmol/L in men and <1.29mmol/L in women, blood pressure ≥130/85mmHg, fasting glucose ≥5.6mmol/L (Zimmet *et al.* 2005).

Clinically significant weight increase was defined as 7% increase from the baseline weight, in accordance with the definition of the Food and Drug

Administration for clinically significant weight increase for studies of psychotropic medication (Sachs and Guille 1999).

4.1.5 LABORATORY ANALYTICAL METHODS

A fasting blood sample was collected between 8 and 10 am. Serum and plasma samples were immediately aliquoted and stored at −80°C. Serum total cholesterol, HDL cholesterol, triglycerides, hs-CRP, insulin, apolipoprotein A-I and apolipoprotein B (ApoB), and plasma glucose were measured on an Abbott Architect ci8200 analyser (Abbott Laboratories, Abbott Park, IL, USA) in the laboratory of the Genomics and Biomarkers Unit at the National Institute for Health and Welfare. The laboratory has been accredited by the Finnish Accreditation Service and it fulfills the requirements of the standards SFS-EN ISO/IEC 17025:2005.

HOMA was used to assess insulin resistance (Muniyappa et al., 2007). HOMA was calculated using the formula: fasting glucose (mmol/l) x fasting insulin (mU/l)/22.5.

Table 7. Evaluation of FEP patients in the Helsinki Early Psychosis study

	Domain	Measure	Baseline	Two months	12 months
	Blood and *stool* samples		x	x	x
	Brain imaging (MRI)		x		x
	Cognitive assessment	Described in (Lindgren et al., 2018)		x	x
Questionnaire	*Depressive symptoms*	Beck Depression Inventory (BDI) (Beck et al., 1961)	x	x	x
	Anxiety	Beck Anxiety Inventory (BAI) (Beck et al., 1988)	x	x	x
	Obsessive-compulsive symptoms	Obsessive-Compulsive Inventory – Revised (OCI-R) (Foa et al., 1998)	x	x	x
	Harmful alcohol use	Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001). At 2-month assessment AUDIT-C (Bush et al., 1998)	x	x	x
	Manic symptoms, lifetime	Mood Disorder Questionnaire (Hirschfeld et al., 2000)	x	x	x
	Physical activity	Gothenburg Scale (Wilhelmsen et al., 1972)	x	x	x
	Diet	Questions on eating habits and frequency of consumption of selected foods during previous 7 days	x	x	x
	Smoking	Current smoking (Kestilä et al., 2006)	x	x	x

Table 7. (continued)

Questionnaire		Fagerström Nicotine Dependence Scale (Heatherton et al., 1991)	**x**		**x**
	Substance use (other than alcohol and tobacco)	Questionnaire on substance use (Suvisaari et al., 2009)	**x**	**x**	**x**
	Dissociation	Cambridge Depersonalization Scale (Sierra and Berrios, 2000)	**x**	**x**	**x**
	Social support	Perceived social support scale – Revised (Blumenthal et al., 1987)	**x**	**x**	**x**
	Attitudes toward antipsychotic treatment	Questions from the Attitudes Toward Neuroleptic Treatment Questionnaire (Kampman et al., 2000)		**x**	**x**
	Satisfaction with care	Patient Satisfaction Questionnaire (Mattsson et al., 2005)		**x**	
	Insight	Cognitive Insight Scale (Beck et al., 2004)	**x**	**x**	**x**
	Sense of mastery	Sense of Mastery Scale (Pearlin and Schooler, 1978)	**x**	**x**	**x**
	Childhood adversities	11-item questionnaire on childhood adversities (Kestilä et al., 2006; Pirkola et al., 2005a)	**x**		
	Childhood trauma and distressing experiences	Trauma and Distress Scale (TADS) (Salokangas et al., 2016)			**x**
Interview	Sociodemographic factors	Questions regarding living situation, family, education, occupation, employment	**x**	**x**	**x**

Psychotic symptoms	24-item version of the Brief Psychiatric Rating Scale-Expanded (BPRS-E) (Ventura et al., 1993), including the current severity and severity during the worst period before the baseline assessment, complemented by 3 domains (alogia, anhedonia-asociality and avolition-apathy) from the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982)	**x**	**x**	**x**
Positive symptoms	Sum of BPRS items Hallucinations (10), Unusual thought content (11), Bizarre behaviour (12) and Conceptual disorganization (15); BPRS items were rescaled from 1-7 to 0-6 for calculating the sum score	**x**	**x**	**x**
Negative symptoms	BPRS item Blunted affect (16) and SANS items Alogia, Anhedonia and Avolition; BPRS item was rescaled from 1-7 to 0-6 for calculating the sum score	**x**	**x**	**x**
Current manic symptoms	Young Mania Rating Scale (YMRS) (Young et al., 1978)	**x**	**x**	**x**
Psychiatric diagnosis	Research version of the Structured Clinical Interview for DSM-IV disorders (First et al., 2002)		**x**	**x**
Functioning	Global Assessment of Functioning (GAF), Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 2000; Hilsenroth et al., 2000)	**x**	**x**	**x**

Table 7. (continued)

Interview	Weight, height, blood pressure and waist circumference		**x**	**x**	**x**
	Family history of psychiatric disorders		**x**		
	Insight	Schedule for the Assessment of Insight (SAI-E) (David, 1990)	**x**	**x**	**x**
Assessed based on interview and case records	Medication	Duration of antipsychotic medication, type of medication, dosage	**x**	**x**	**x**
	Substance use	Substance use assessed based on all available data (self-report, case records, laboratory screening)	**x**	**x**	**x**
	Psychiatric diagnosis	Evaluated by a senior psychiatrist based on SCID interview and case record data from all lifetime treatment contacts		**x**	**x**

Italics used to denote measures not analysed in Studies I and II

4.2 THE HEALTH 2000 SURVEY AND THE PSYCHOSES IN FINLAND STUDY (STUDY III)

The sample in the Finnish Health 2000 survey consisted of 8028 persons aged 30 years or older. A two-staged stratified cluster sampling procedure was used to get a nationally representative sample (Heistaro, 2008). The sampling frame was regionally stratified according to the five university hospital regions of Finland. Sixteen healthcare districts were sampled from each five regions as clusters, i.e. overall 80 healthcare districts, including 160 municipalities. The 15 largest cities in Finland were included in the sample, the other 65 areas were selected by systematic probability proportional to population size sampling in each stratum. The persons were selected from the areas by systematic sampling, also including institutionalized and homeless persons. Oversampling (2:1) was used for persons over 80 years of age within the clusters to make sure that the oldest participants were adequately covered.

The data were collected in the time period between September 2000 and June 2001. The fieldwork consisted of a home interview, a health examination (or for those unable to attend a health examination at a local healthcare centre, a condensed interview and health examination at home) and a telephone interview or mailed questionnaire for the remaining participants.

Altogether, 93% (7419) of subjects contacted at the first phase of the survey participated in at least one study phase (Aromaa and Koskinen, 2004).

4.2.1 MENTAL HEALTH ASSESSMENT

During the health examination the physician assessed whether the participant had a probable or definite psychotic disorder. Further, questionnaires and the Munich Version of the Composite International Diagnostic Interview (M-CIDI) (Wittchen et al., 1998) were used to assess mental disorders. The Finnish version of M-CIDI is computerized and a fully structured interview assessing 12-month diagnoses of mood, anxiety, psychotic and substance use disorders, and, in addition, lifetime diagnoses of alcohol/other substance dependence and psychotic experiences (Pirkola et al., 2005b).

A second phase study, Psychoses in Finland (PIF) was conducted to confirm psychotic diagnoses in those screened in the Health 2000 study as having a probable psychotic diagnosis (Perälä et al., 2007). Psychotic diagnoses were screened based on either self-reported psychotic disorder, probable psychotic disorder as assessed by the physicians conducting the

health examination or psychotic or manic symptoms reported in the questionnaires used in the Health 2000 survey and the M-CIDI. In addition, information from the healthcare registers was used to complement the screening: hospital treatment due to psychotic disorder according to the Hospital Discharge Register, reimbursement for outpatient antipsychotic medication, disability pension due to psychotic disorder and mood stabilizing medication without a diagnosis of epilepsy or other neurological disease.

Those with a probable psychotic diagnosis were assessed with the SCID-I interview. Lifetime case notes for psychiatric problems were also collected, as well as for those who did not take part in the SCID-I interview. Final best estimate diagnoses were made utilizing the information from the SCID-I interview and the case notes.

The ethics committees of the National Public Health Institute (the National Institute for Health and Welfare since 2009) and the Hospital District of Helsinki and Uusimaa approved the Health 2000 Survey (407/E3/2000) and the PIF study (644/E3/2001). Participants gave a written informed consent.

4.2.2 STUDY POPULATION

In Study III, persons aged 70 years and over, and persons with substance use disorder or psychotic disorder due to a general medical condition were excluded. The age restriction was made due to the high mortality of the oldest age groups, potentially confounding the analysis. Of the original study sample of persons aged less than 70 years (n=6334), 89.1% (n=5642) had participated in the Health 2000 study and were followed up in Study III. Non-response was corrected by weighting.

Study III focused on people with non-affective psychosis (NAP) (Figure 1). Predictor analysis was not possible for people with affective psychoses due to no deaths in that group of people aged less than 70 years.

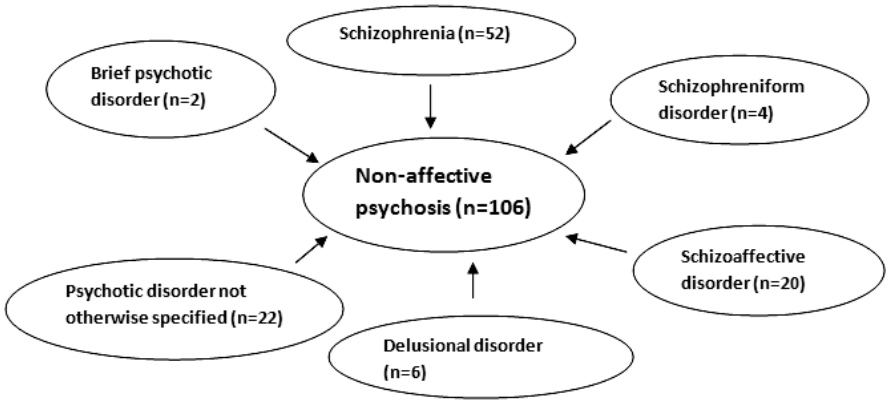

Figure 1. Diagnoses pertaining to the non-affective psychosis group in Study III

4.2.3 PREDICTORS OF MORTALITY

4.2.3.1 Antipsychotic medication

Antipsychotic medication use was coded at study baseline based on the self-reported medication use by the participants. They brought prescriptions or medications to the interview to assist in recording the medication use.

4.2.3.2 Socioeconomic factors

Information on family income was determined from the registers of the Finnish Tax Administration. Family income was divided into quintiles and adjusted for family size. Marital status at baseline was coded as married or cohabiting, or unmarried (including divorced, never-married or widowed).

4.2.3.3 Lifestyle and health-related variables

BMI was calculated as weight divided by height squared (kg/m^2). Smoking was coded based on self-report of the participants as current smokers and non-smokers. Current smoking was defined as having smoked at least 100 cigarettes during lifetime, regular smoking during the past year and most recently during the past month.

4.2.3.4 Chronic physical disease

The WHO 1999 criteria was used to diagnose T2D (World Health Organization Expert Committee, 1999). Diagnosis was based on self-reported diagnosis of T2D, confirmed in the clinical examination; antidiabetic medication use reported by the participant or according to the National Prescription Register of the Social Insurance Institution; reimbursed antidiabetic medication because of T2D according to the Medication Reimbursement Register of the Social Insurance Institution.

Coronary heart disease (CHD) was diagnosed based on health examination, electrocardiogram and register data (Kattainen et al., 2006).

MetS was diagnosed based on the National Cholesterol Education Program's Adult Treatment Panel III criteria (Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults, 2001), requiring a minimum of three of the following: 1) central obesity (waist circumference >102cm in men and >88cm in women); 2) high fasting triglycerides (≥1.7mmol/l); 3) low HDL cholesterol (<1.03mmol/l in men and

<1.29mmol/l in women); 4) elevated systolic blood pressure (systolic blood pressure ≥130mmHg or diastolic pressure ≥85mmHg) and 5) impaired fasting glucose (≥6.1mmol/l).

4.2.3.5 Low-grade inflammation

Categorical variable based on the highest quintile of CRP concentration (2.43mg/l) was used to mark low-grade inflammation.

4.2.4 MORTALITY AND CAUSES OF DEATH

Information on mortality and causes of death were obtained from the Cause of Death statistics kept by Statistics Finland (up to December 31st 2013). The cause of death is determined by the treating physician if the cause is known, and in cases of unknown or suspected unnatural causes of death an autopsy is performed. As the forensic autopsy rate is high in Finland, the Cause of Death statistics can be considered reliable (Lunetta et al., 2007).

Causes of death were classified into natural causes (ICD-10 A00–R99), including alcohol-related diseases and accidental poisoning by alcohol (F10, G312, G4051, G621, G721, I426, K292, K70, K852, K860, O354, P043, Q860, X45), and unnatural causes, including suicide (X60–X84, Y870) and other unnatural causes (V01–X44, X46–X59, X85–Y86, Y871–Y89).

4.3 STATISTICAL METHODS

In Studies I and II, most of the variables were non-normally distributed. Thus, descriptive statistics for sociodemographic and clinical variables were calculated using Pearson's χ^2 (or Fisher's exact test) or Mann-Whitney *U* test in between-group comparisons. In Study III, Student's *t*-test was used for comparisons of continuous variables. To test differences between baseline, 2-month and 12-month follow-up measures in patients (Studies I and II), Friedman's ANOVA (for continuous variables) and McNemar's and Cochran's Q tests (for categorical variables) were used. Alpha level for statistical significance was set at <0.05. Bonferroni correction was used to adjust the p-values for post hoc pairwise tests conducted after Friedman's ANOVA and Cochran's Q tests. SPSS statistical software versions 23 and 24 were used for statistical comparisons.

4.3.1 STUDY I

General linear regression models were used to examine predictors of change in weight and waist circumference among FEP patients. First, correlations

between continuously or ordinally distributed variables and change in weight and waist circumference were calculated using the Spearman's rank order correlation. For categorical variables, median change in weight and waist circumference was compared across the categories using the Mann-Whitney *U* test. Next, variables that were significantly associated with change in weight or waist circumference were chosen for general linear models which were calculated using PROC GLM in SAS statistical software. Shapiro-Wilk test was used to check if the assumption of normally distributed residuals held. There were two patients with pre-existing diabetes who were both excluded from the regression analysis.

4.3.2 STUDY II

To examine which variables were associated with longitudinal changes in hs-CRP, mixed-effects regression modelling was used. Advantages of mixed-effects models in a study with repeated measures include: 1) accounting for the correlation of repeated measures observations, and 2) the variability in time between assessments for each subject. Furthermore, 3) time-dependent covariates can be used, and 4) data with different number of repeated measurements for each subject can be analysed (Gueorguieva and Krystal, 2004).

For the mixed-effects models in Study II, hs-CRP was logarithm-transformed to reduce the skewness of its distribution. Since the focus was on chronic low-grade inflammation hs-CRP values ≥10mg/l, indicative of acute infection, were excluded. Bayesian information criterion (BIC) (Schwarz, 1978) was used to select the variables for the model. BIC gives an estimate of how well the model fits the data and includes a penalty for the number of predictor variables in the model to avoid overfitting. Waist circumference and BMI were analysed as time dependent, as there were marked changes in them over the study period. Information on smoking status was used only from baseline, as there were few patients that either started or quitted smoking during the follow-up, and there were fewer missing data on smoking at baseline. Other variables that were considered as possibly associated with hs-CRP were insulin, HOMA, clozapine and olanzapine use and cannabis use.

The final model included a random intercept for each patient. As the fixed effects, gender, time of assessment (days from baseline measurement), antipsychotic use at each assessment, baseline cigarette smoking and waist circumference were included. The analysis was run using PROC MIXED in SAS statistical software.

4.3.3 STUDY III

The sampling design of Health 2000 survey was taken into account in the statistical analyses, and post-stratification weights were used to adjust for

non-response. Seven Cox's proportional hazards regression models, all adjusted for age and gender, were built to examine the effects of different variables on mortality using SUDAAN software's SURVIVAL procedure. The explanatory variables in each model are presented in Table 8. All-cause mortality and mortality from disease and medical conditions were analysed separately. For the final model (Model VII), the proportional hazards assumption was checked by running the Kolmogorov-type supremum test with SAS's PHREG procedure. The test indicated that the proportional hazards assumption held for all variables.

In people with NAP, predictors of mortality were analysed with Cox's proportional hazards model using SAS's PHREG procedure. Due to the small number of cases in the NAP group (n=106), sampling design was not taken into account. Explanatory variables were the same as presented for Model VII, except for CHD because the number of cases was small. All-cause mortality and mortality from disease and medical conditions were analysed separately.

Table 8. Explanatory variables used in Cox's regression models (Study III)[a]

Model I	Diagnosis of NAP
Model II	NAP + antipsychotic medication
Model III	Variables in Model II + low-grade inflammation
Model IV	Variables in Model II + marital status + income
Model V	Variables in Model II + BMI + smoking
Model VI	Variables of Model II + T2D + MetS + CHD
Model VII	All variables used in Models I-VI

BMI, body mass index; CHD, coronary heart disease; MetS, metabolic syndrome; NAP, non-affective psychosis; T2D, type 2 diabetes

[a]All models were adjusted for age and gender

5 RESULTS

5.1 PREDICTORS OF WEIGHT GAIN AND WAIST CIRCUMFERENCE INCREASE IN FIRST-EPISODE PSYCHOSIS (STUDY I)

5.1.1 CHARACTERISTICS OF STUDY PARTICIPANTS

Blood sample data were available for 60 FEP patients and 27 controls at the study baseline. At two and 12 months, the number of blood samples from patients was 43 and 22 (72% and 37% of the baseline sample), respectively. At 12 months, weight and waist circumference measurements were respectively available from 33 and 34 patients. No statistically significant differences in age, symptom severity, anthropometric measures or laboratory values were found between patients followed during the whole study period and those who dropped out, either during the study or were recruited less than 12 months before the data was analysed.

Patients had lower education, were more often unemployed and had a more sedentary lifestyle at baseline compared to controls (Table 9). Otherwise patients and controls were similar in terms of potential confounding factors. There were no differences in baseline BMI or waist circumference between patients and controls (Table 10).

At baseline, olanzapine and risperidone were each prescribed to 37% of patients (n=22), quetiapine to 23% (n=14) and other antipsychotics to 22% of patients (n=13). Eight percent of patients (n=5) were not using antipsychotics at baseline. The median duration of antipsychotic use at baseline was 26 days.

Table 9. Baseline demographic and clinical variables in FEP patients and controls

	FEP patients (n=60)	Controls (n=27)	P-value[a]
Age	24.5 (21.5, 29.5)	25.0 (23.3, 33.9)	0.183
Male	39/60 (67%)	13/27 (48%)	0.138
Living with parents	19/60 (32%)	3/27 (11%)	**0.041**
No vocational or higher education	33/60 (55%)	6/27 (22%)	**0.004**
Employed, military or student	38/60(63%)	26/27 (96%)	**0.001**
Smoking	16/51 (31 %)	4/25 (16 %)	0.153
No illicit substance use lifetime	29/56 (52 %)	17/25 (68 %)	0.174
Active lifestyle[b]	31/50 (62 %)	22/25 (88 %)	**0.020**
Consumption of highly palatable foods[c]	4 (0-9)	4 (1-7)	0.634
Positive symptoms[d]	7 (4, 10)	0 (0, 0)	**<0.001**
Negative symptoms[e]	5 (3.25, 9.0)	0 (0, 0)	**<0.001**
AUDIT	6 (2, 13)	6 (3, 7)	0.646
GAF	35 (30, 40)	85 (75, 90)	**<0.001**

AUDIT Alcohol use disorder identification test, BMI Body mass index, GAF Global assessment of functioning scale

[a]Continuous variables: Mann-Whitney *U* test. Categorical variables: chi-squared test.

[b]Easy exercise at least 4 hours per week, self-reported

[c]Sum score of the frequency of consumption of high-energy foods and drinks rich in fat and/or sugar (pizza, hamburgers, chocolate and sweets, cookies, pastries, juices and beverages containing sugar)

[d]Sum score of BPRS-E items 10 (hallucinations), 11 (unusual thought content), 12 (bizarre behavior) and 15 (conceptual disorganization)

[e]Sum score of BPRS-E item 16 (blunted affect) and SANS-score (alogia, avolition-apathy, anhedonia-asociality)

Table 10. Anthropometric measures of FEP patients and controls at baseline

Variable	FEP patients	Controls	P-value[a]
BMI	22.7 (20.9, 25.6)	23.9 (21.8, 26.6) (n=27)	0.204
Waist circumference (total)	84.0 (79.0, 89.0)	82 (77.0, 93.0)	0.734
Waist circumference (men)	85.0 (81.0, 89.0)	89.0 (77.5, 96.0)	0.783
Waist circumference (women)	79.0 (70, 87.5)	81.0 (72.0, 85.75)	0.761

[a]Mann-Whitney *U* test

5.1.2 CHANGES IN ANTHROPOMETRIC MEASURES DURING FOLLOW-UP

The median waist circumference increased 6.0cm from baseline to the 12-month assessment (baseline 84cm [IQR 79-89cm], 12-month 90cm [IQR 84–96cm], p<0.001) in FEP patients. BMI increased from 22.7kg/m² (IQR 20.9-25.6kg/m²) to 25.9kg/m² (IQR 23.3-29.5kg/m², p<0.001). Olanzapine medication at baseline (n=22) was associated with the greatest 12-month weight gain (mean 17.7kg [SD 8.7kg] in olanzapine users vs. 8.5kg [SD 6.9kg] in other patients, t=3.39, p=0.002). Weight change during the study period correlated statistically significantly with baseline unhealthy diet (Spearman´s rho 0.46, p=0.01) and positive symptoms (Spearman´s rho 0.39, p=0.03). Change in waist circumference correlated with baseline insulin (Spearman´s rho 0.35, p=0.04) and positive symptoms (Spearman´s rho 0.35, p=0.04). Of categorical variables, olanzapine use and insulin resistance at baseline (defined as the highest quartile of HOMA due to the highly skewed distribution) were associated with weight gain (Table 11).

Table 11. Associations of baseline variables with change in weight and waist circumference during the 12-month follow-up

	Weight change (kg)		Change in waist circumference (cm)	
	Mean (SD)	P-value[a]	Mean (SD)	P-value[a]
Gender				
Men	12.0 (7.7)	0.78	10.4 (7.7)	0.29
Women	11.6 (10.3)		7.5 (7.1)	
Olanzapine				
Yes	17.7 (8.7)	**0.003**	12.0 (7.5)	0.13
No	8.5 (6.9)		7.6 (7.3)	
Sedentary lifestyle				
Yes	11.1 (5.9)	0.98	11.8 (9.2)	0.19
No	11.4 (9.8)		7.5 (5.9)	
Insulin resistance[b]				
Yes	15.3 (6.8)	0.26	17.0 (7.4)	**0.01**
No	11.2 (9.0)		7.6 (6.6)	

[a] Mann-Whitney *U* test
[b] Defined as HOMA index above 75th percentile

5.1.3 PREDICTORS OF CHANGE IN ANTHROPOMETRIC MEASURES DURING FOLLOW-UP

Table 12 shows the p-values for the predictors of weight gain and waist circumference increase in the regression models for weight change and change in waist circumference. Olanzapine use and insulin resistance at baseline were statistically significant predictors for 12-month weight gain. Insulin resistance was a significant predictor for 12-month increase in waist circumference.

Table 12. P-values and R^2 for predictors in the regression models for weight change (Model 1) and for change in waist circumference (Model 2)

Predictors	Model 1: weight change	Model 2: change in waist circumference
Insulin resistance	**0.025**	**0.0036**
Olanzapine use	**0.0076**	0.09
Unhealthy diet	0.07	0.08
Severity of positive symptoms	0.20	0.72
R^2	0.55	0.49

5.2 DEVELOPMENT AND PREDICTORS OF LOW-GRADE INFLAMMATION IN FIRST-EPISODE PSYCHOSIS (STUDY II)

5.2.1 CHARACTERISTICS OF STUDY PARTICIPANTS

Altogether 97 FEP patients and 62 controls took part in the study at baseline. Two of the patients were diagnosed with a substance-induced psychotic disorder and were excluded from the analyses. Table 13 and Table 14 show the demographic and clinical characteristics of the participants. Of patients, 93% (n=88) reported using antipsychotic medication at baseline. The median duration of antipsychotic medication at baseline was 22 days (IQR 10-49 days) among the FEP patients. Olanzapine (n=35), risperidone (n=34) and quetiapine (n=18) were the most commonly prescribed antipsychotics at baseline. Figure 2 and Table 15 show the distribution of psychotropic medication used throughout the study period. Sixty per cent (n=57) of patients were hospitalized at the time of baseline assessment.

Table 13. Baseline clinical and demographic characteristics of all 95 first-episode psychosis (FEP) patients, FEP patients with 12-month follow-up data available (n=52) and 62 controls

	FEP patients, n (%) or median (25%, 75%)	FEP patients with follow-up data available[a], n (%), or median (25%, 75%)	Controls, n (%), or median (25%, 75%)	P-value[b]
Age	24.9 (21.6, 29.4)	25.4 (22.6, 30.1)	24.0 (21.7, 28.7)	0.828
Male	65/95 (68%)	31/52 (60%)	40/62 (65%)	0.611
Living with parents	35/95 (37%)	18/52 (35%)	10/62 (16%)	**0.005**
No vocational or higher education	38/95 (40%)	15/52 (29%)	11/62 (18%)	**0.003**
Employed, military or student	73/95 (77%)	41/52 (79%)	59/62 (95%)	**0.002**
Smoking	20/78 (26%)	9/47 (19%)	11/53 (21%)	0.518
No illicit substance use lifetime	40/74 (54%)	27/45 (60%)	26/51 (51%)	0.735
Active lifestyle[c]	50/72 (69%)	33/44 (75%)	39/51 (77%)	0.391
Consumption of highly palatable foods[d]	4.5 (0-9) (n=70)	4.5 (0-9) (n=44)	4 (1-9) (n=51)	0.932
Positive symptom score[e]	6 (3, 9)	6.5 (3, 9)	0 (0, 0)	**0.001**
Negative symptom score[f]	5 (3, 8)	5 (3, 8)	0 (0, 0)	**0.001**
AUDIT	5 (2, 12) (n=74)	4 (1, 12) (n=45)	6 (3, 9)	0.797
GAF	35 (31, 40)	35 (30, 40)	86 (77, 90)	**0.001**

AUDIT, Alcohol use disorder identification test; BMI, Body mass index; GAF, Global assessment of functioning scale

[a]With 12-month CRP available. [b]Comparison of all FEP patients and controls. Mann-Whitney *U* test for continuous variables; chi-squared test for categorical variables. [c]Easy exercise at least 4 hours per week, self-reported. [d]Sum score of the frequency of consumption of high-energy foods and drinks rich in fat and/or sugar (pizza, hamburgers, chocolate and sweets, cookies, pastries, juices and beverages containing sugar). [e]Sum score of BPRS-E items 10 (hallucinations), 11 (unusual thought content), 12 (bizarre behavior) and 15 (conceptual disorganization). [f]Sum score of BPRS-E item 16 (blunted affect) and SANS-score (alogia, avolition-apathy, anhedonia-asociality)

Table 14. Body mass index and waist circumference measures of patients and controls at baseline (Study II)

Measure	FEP patients	FEP patients with 12-month data (CRP) available	Controls	P-value[a]
Body mass index	22.9 (21.1, 25.9)	23.0 (20.9, 25.8)	23.8 (21.8, 25.8)	0.356
Waist circumference (cm; total)	83.0 (78.0, 90.0)	82.5 (75.5, 89.0)	82.0 (77.0, 90.0)	0.519
Waist circumference (cm; men)	85.0 (81.0, 91.0)	84.0 (79.0, 89.0)	86.0 (78.0, 92.0)	0.443
Waist circumference (cm; women)	78.5 (69.8, 86.3)	79.0 (71.0, 84.5)	79.0 (72.8, 85.8)	0.584

[a]Comparison of all FEP patients and controls. Mann-Whitney *U* test.

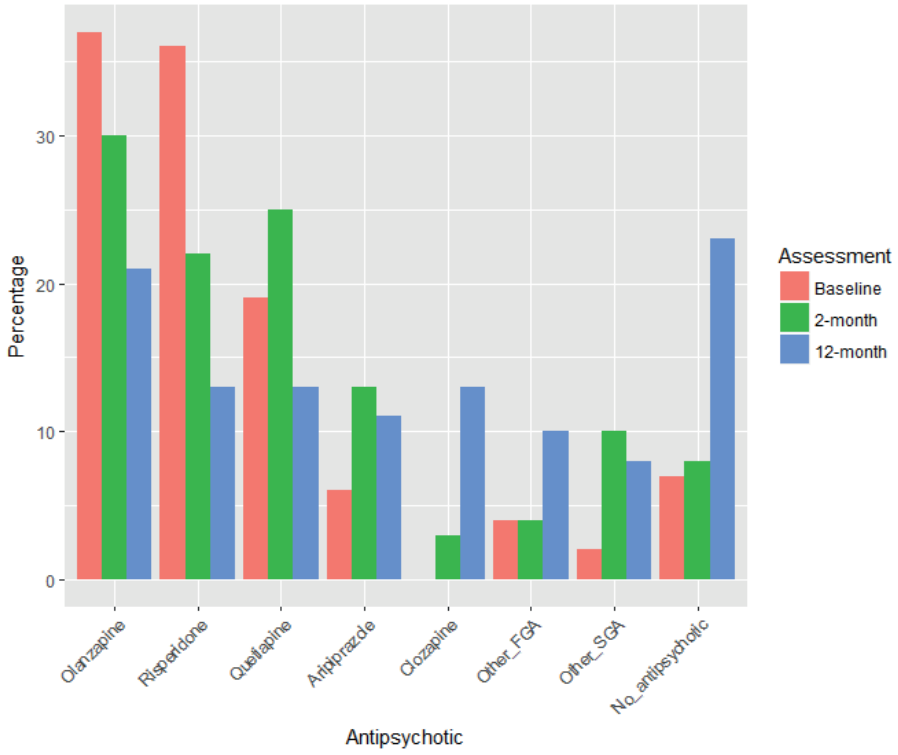

Figure 2. Percentage of antipsychotics in use at baseline (n=95), 2-month (n=77) and 12-month assessment (n=61)

Table 15. Prevalence of antipsychotic monotherapy and mood-stabilizing medication in FEP patients

	Baseline (n=95)	Two months (n=77)	12 months (n=61)
Antipsychotic monotherapy	78 (88%)[a]	61(86%)[a]	38 (81%)[a]
Lithium	2 (2%)	2 (3%)	1 (2%)
Valproate	2 (2%)	3 (4%)	5 (8%)
Lamotrigin	2 (2%)	1 (1%)	2 (3%)
Antidepressant	19 (20%)	22 (29%)	19 (31%)

[a]Percentage of those using antipsychotic medication (baseline n=88, two months n=71, 12 months n=47)

5.2.2 BASELINE METABOLIC AND ANTHROPOMETRIC MEASURES OF PATIENTS AND CONTROLS

At baseline, FEP patients had increased HOMA, total and LDL cholesterol, triglycerides and ApoB compared to controls (Figure 3). There were no significant differences in baseline measures of weight, waist circumference, hs-CRP, fasting glucose or HDL cholesterol between patients and controls. Of patients, 11% (9/84) met the criteria for MetS.

5.2.3 CHANGES IN METABOLIC MEASURES AND HS-CRP DURING FOLLOW-UP

By the 12-month assessment, patients had gained a median of 9.6kg of weight (IQR 1.5-13.6kg) and their waist circumference had increased by a median of 6.0cm (IQR 2.0-13.0cm). Forty of 59 patients (68%) had gained >7% of weight, a threshold considered clinically significant weight gain. The proportion of patients who had lost weight was 14% (n=8/59); range of weight loss was 0.2-3.5kg. The prevalence of MetS from baseline to the 12-month assessment rose from 11% (9/84) to 19% (10/53), which was not statistically significant. Apart from the increase in the proportion of patients meeting the criterion for elevated waist circumference (Figure 4, baseline to

2-month to 12-month: 27% [26/95]; 44% [34/77]; 54% [32/59], χ^2=21.444, p<0.001) the proportion meeting the criteria for other components of MetS did not increase significantly during the follow-up.

Those FEP patients who were using antipsychotics at the 12-month assessment had a median weight gain of 10.8kg (IQR 4.0-14.4), whereas those who were antipsychotic-free at the 12-month assessment gained 5.6kg (-1.7 to 10.0kg, U=201.5, p=0.043). The respective median changes in waist circumference during the 12-month study period were 1.0cm (IQR -1.0 to 7.0cm) and 8.5cm (IQR 4.0-15.3cm, U=160.5, p=0.011).

Hs-CRP increase during the study period was statistically significant in patients (Figure 5): baseline (median) 0.67mg/l (IQR 0.33-2.54mg/l); 2-month 0.79mg/l (0.39-1.92mg/l); 12-month 1.73mg/l (IQR 0.49-4.21mg/l), χ^2=6.731, p=0.035.

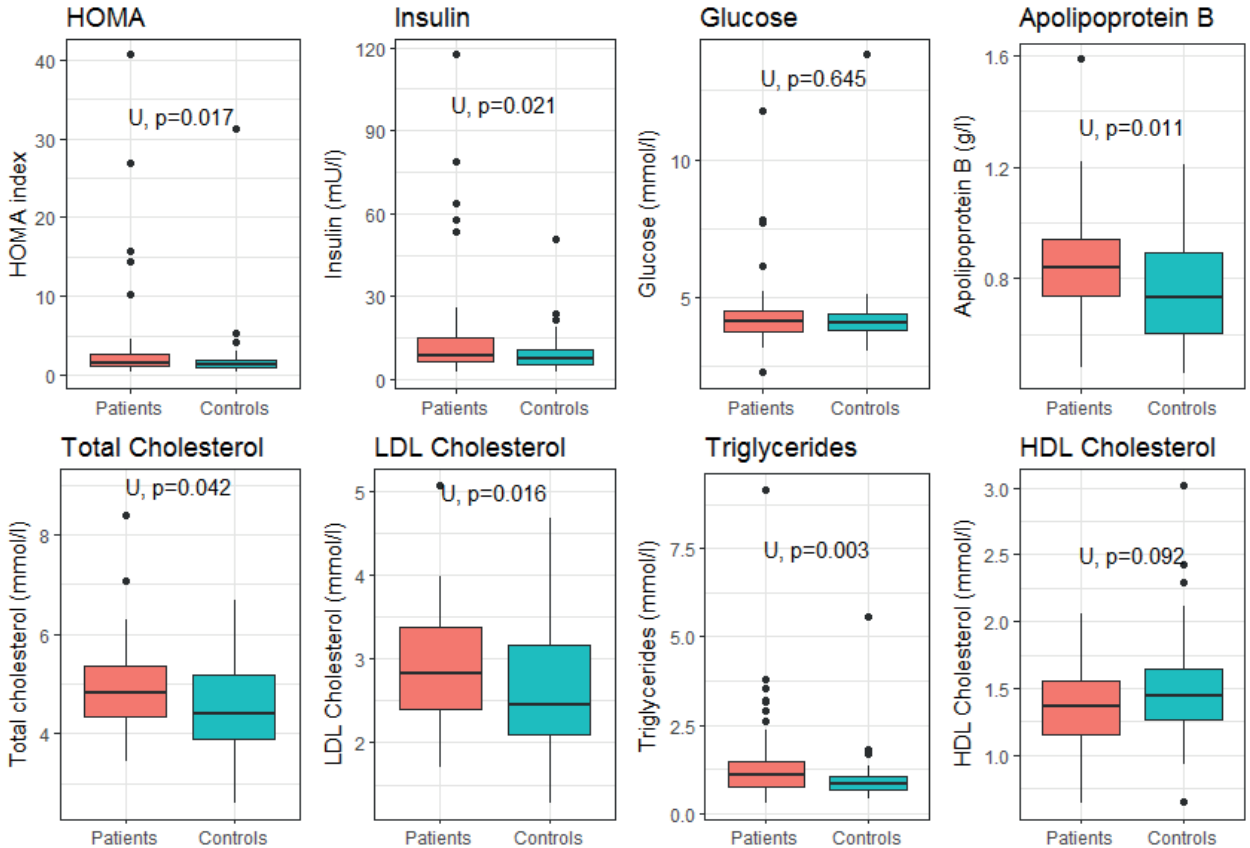

Figure 3. Comparison of baseline laboratory parameters in FEP patients and controls

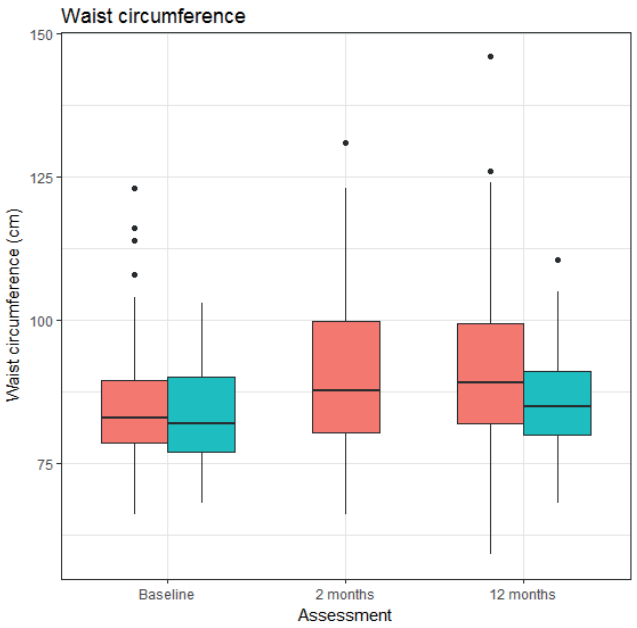

Figure 4. Waist circumference in FEP patients and controls

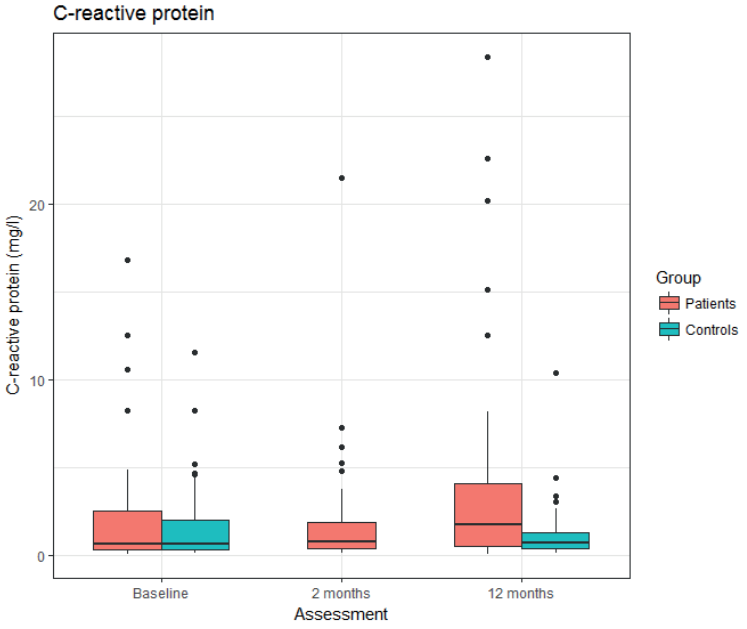

Figure 5. C-reactive protein in FEP patients and controls

5.2.4 PREDICTORS OF HS-CRP DURING THE FOLLOW-UP

In the final mixed-effects regression model analysis, waist circumference (β=0.05048, standard error [SE]=0.006646, p<0.0001) and female gender (β=0.4721, SE=0.1882, p=0.0140) were statistically significant predictors of higher logCRP (Table 16). Other variables used in the final model contributed to the model fit based on the BIC, but they did not reach statistical significance as predictors of logCRP. Other tested variables were not included in the model, as they were not significantly associated with logCRP and did not improve the model fit assessed by the BIC.

Replacing waist circumference with BMI as a predictive variable decreased the model's goodness of fit, but BMI was also a significant predictor of logCRP (β=0.1163, SE=0.01737, p<0.0001).

Table 16. Estimates, standard errors and p-values of the variables used in the final mixed-effects regression model predicting logCRP

Variable	Estimate	Standard error	P-value
Intercept	-4.4968	0.6291	**<0.0001**
Waist circumference	0.05048	0.006646	**<0.0001**
Female gender	0.4721	0.1882	**0.0140**
Time from baseline (days)	0.000328	0.000403	0.4179
Smoking at baseline	0.1639	0.2163	0.4507
No antipsychotic medication	0.3365	0.2382	0.1614

5.3 MORTALITY IN NON-AFFECTIVE PSYCHOSIS (STUDY III)

As there were no deaths in the affective psychosis group, analysis on mortality was done in the non-affective psychosis group (n=106). There were 25 deaths in the NAP group during the 13-year follow-up period. Cancer and cardiovascular disease were the most common causes of death, and altogether natural causes made up 84% (21/25) of all deaths (Figure 6).

In the NAP group, those who died during the follow-up were older (55.9, SD 9.3 vs. 48.8, SD 10.0, p=0.002), less often married or cohabiting (16% vs. 40%, p=0.03) and had a higher prevalence of T2D (36% vs. 12.3%, p=0.014) compared to those who survived.

In people diagnosed with NAP, the all-cause mortality hazard ratios (HR) ranged from 2.11 (95% CI 1.10-4.05) when adjusting for all relevant variables (age, gender, smoking, socioeconomic factors, antipsychotic use, CRP level, obesity, T2D, MetS and CHD) to 2.99 (95% CI 2.03-4.41) when adjusting only for age and gender (Figure 7).

HR for natural cause mortality among people with NAP did not reach significance when adjusting for all the relevant variables (HR 1.98, 95% CI 0.94-4.16), but was significantly elevated in all the other models (Figure 7).

In people with NAP, those who used antipsychotics at baseline had a reduced HR for natural cause mortality (HR 0.25, 95% CI 0.07-0.96). Smoking was associated with increased HR for natural cause mortality in people with NAP (HR 3.54, 95% CI 1.07-11.69).

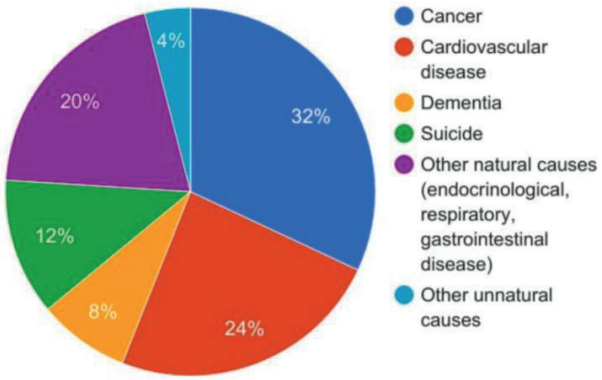

Figure 6. Causes of death in patients with non-affective psychosis. Total number of deaths 25.

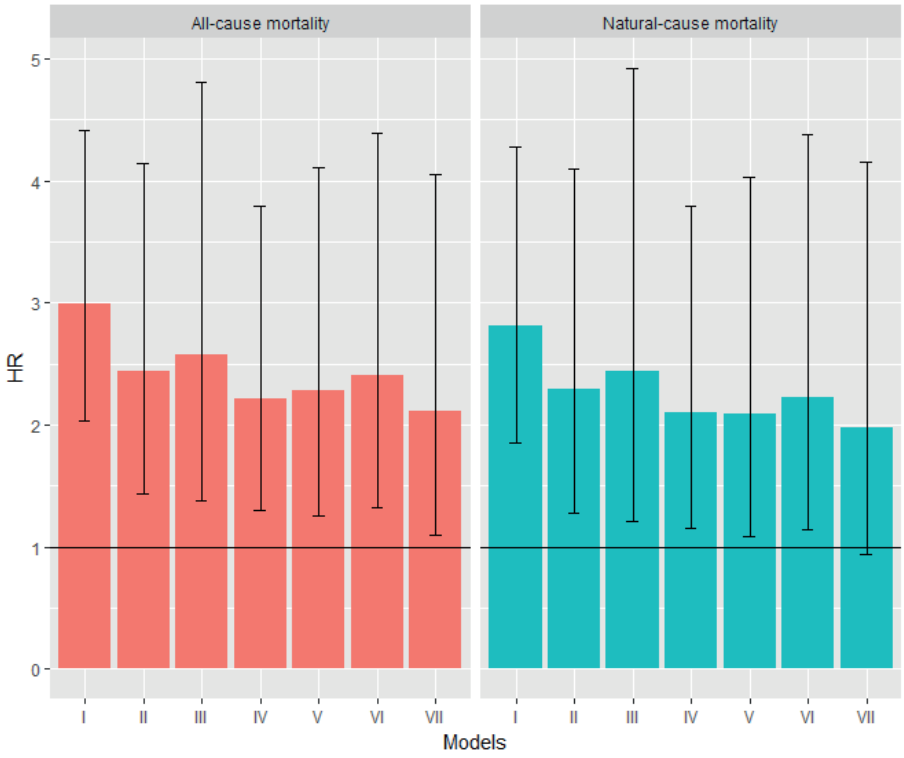

Figure 7. Cox proportional hazard models for all-cause and natural cause mortality hazard ratios (HR) in people with non-affective psychosis (n=106) adjusted with a different set of variables in each model I-VII. Solid horizontal line marks the mortality HR in the general population used as reference

Cox proportional hazard models presented in Figure 7 were adjusted for age and gender as well as in addition for the following variables:
Model I: diagnosis of NAP
Model II: NAP + antipsychotic medication
Model III: Model II + low-grade inflammation
Model IV: Model II + socioeconomic factors (marital status and income)
Model V: Model II + lifestyle-related factors (BMI and smoking)
Model VI: Model II + chronic physical disease (T2D, MetS and CHD)
Model VII: All variables from models I-VI

6 DISCUSSION

6.1 SUMMARY OF THE MAIN FINDINGS

Although FEP patients did not differ from healthy controls in BMI or waist circumference at baseline, remarkable weight gain and increase of waist circumference were observed during the first treatment year of FEP (Studies I and II). Of antipsychotics, olanzapine was associated with the greatest weight gain. Insulin resistance and olanzapine use at study baseline were significant predictors of weight gain during the first treatment year of FEP, and insulin resistance at baseline predicted waist circumference change (Study I).

At baseline, FEP patients had higher insulin, insulin resistance, total cholesterol, LDL cholesterol, triglyceride and apolipoprotein B levels than controls (Study II). There was no difference between FEP patients and controls in hs-CRP levels at baseline.

A significant increase in hs-CRP was detected in FEP patients during the first treatment year, and this increase was predicted by waist circumference and female gender in a mixed-effects regression model (Study II). BMI was also a statistically significant predictor of hs-CRP, although waist circumference was a better predictor in terms of model fit. No changes were observed in glucose or lipid parameters during the first treatment year of FEP, despite the notable increases in weight and waist circumference.

In a population sample, people with NAP had a 2-3-fold increased mortality risk during a 13-year observation period compared to the general population (Study III). The increased mortality was only partly explained by socioeconomic factors, cardiovascular and metabolic comorbidities, inflammation and lifestyle. Smoking was associated with increased natural cause mortality in NAP, while antipsychotic use was associated with reduced mortality risk.

6.2 WEIGHT GAIN AND INCREASE OF WAIST CIRCUMFERENCE IN FEP

No baseline differences were observed in weight, BMI or waist circumference between FEP patients and healthy controls. A rapid increase in weight and waist circumference was already evident at the 2-month measurement and continued until the 12-month measurement, in accordance with the literature describing significant risk of weight gain and abdominal obesity early in the treatment of FEP (Foley and Morley, 2011; Tek et al., 2016). The median weight gain of 9.6kg during the 12-month follow-up in Study II was of the same magnitude as in another study of 170 patients with FEP treated with

haloperidol, olanzapine or risperidone (Perez-Iglesias et al., 2014). The study by Perez-Iglesias et al. reported an increase of 10.3kg in mean weight during the first year of treatment, which constituted 85% of the total weight gain during a three-year follow-up (Perez-Iglesias et al., 2014). Another study, following patients with FEP for one year from the start of treatment, reported that patients using olanzapine throughout the study period (n=11) gained 16.9kg in weight, risperidone (n=43) 7.5kg, haloperidol (n=24) 4.1kg and perphenazine 1.5kg, while patients not using antipsychotics gained 1.5kg in weight (Strassnig et al., 2007). In Study II, antipsychotic switches were common and thus differences in weight gain between different antipsychotics were not compared, but olanzapine also showed the greatest weight gain potential in this study.

The prevalence of overweight and obesity approximately doubled from 30% to 59% among FEP patients during the first treatment year. About two-thirds of patients gained a clinically significant amount (>7%) of weight during 12 months. Similar percentages have been reported in the literature. In Strassnig et al. (2007), the proportion gaining >7% of weight was lower in those using FGA (38%) than in those using SGA (59%). Similarly, in a one-year randomized controlled trial (RCT) comparing haloperidol, amisulpride, olanzapine, quetiapine and ziprasidone in FEP, the proportion of patients having >7% weight gain ranged from 37% (ziprasidone) to 86% (olanzapine), although the between-group differences were not statistically significant (Kahn et al., 2008). Another RCT reported that 80% of patients with FEP had >7% weight gain during 52 weeks of olanzapine medication, 58% of those using risperidone and 50% of those using quetiapine (Mcevoy et al., 2007).

Antipsychotic use was also associated with weight gain and increase in waist circumference in Study II; those who were using antipsychotics at the 12-month assessment had an almost 2-fold increase in weight compared to those who were antipsychotic-free at the 12-month assessment, and the difference between medicated and non-medicated patients was even greater when comparing the increase of waist circumference.

Interestingly, olanzapine was the most commonly prescribed antipsychotic in Studies I and II. Although olanzapine is efficient in treating psychotic symptoms (Leucht et al., 2013), concerns have been raised whether olanzapine is an appropriate choice as a first-line antipsychotic in FEP due to its harmful metabolic effects (Buchanan et al., 2010). These concerns may not have yet affected antipsychotic prescription patterns. For example, in a nationwide US sample consisting of 404 first-episode schizophrenia spectrum patients, 17% of antipsychotic prescriptions were for olanzapine, and, compared to other antipsychotics, olanzapine was prescribed more often in doses exceeding the recommended maximum dose (Robinson et al., 2015). In Study II, olanzapine was prescribed to over one third of the patients at baseline, and although this proportion diminished during the follow-up,

olanzapine was still the most prescribed antipsychotic at 12-month assessment.

Olanzapine use at baseline was associated with the greatest weight gain in follow-up, but due to medication switches during the follow-up, no further analysis on the effects of specific antipsychotics on weight and waist circumference was done. A selection bias might affect the results of such analysis: those who were already overweight or obese at baseline may have been prescribed less olanzapine to avoid further metabolic harm. This is demonstrated by the fact that patients prescribed olanzapine at baseline showed a trend for lower baseline BMI (Mdn 22.7kg/m^2) compared to those who were not prescribed olanzapine (Mdn 23.4kg/m^2, p=0.10). Similarly, those who first gained a significant amount of weight with olanzapine may have had more switches to other antipsychotics with less weight gain potential.

6.2.1 BASELINE PREDICTORS OF CHANGES IN WEIGHT AND WAIST CIRCUMFERENCE (STUDY I)

In a linear regression model, insulin resistance and olanzapine use at baseline predicted weight gain during the 12-month follow-up, and insulin resistance at baseline, defined as HOMA in the highest quartile, predicted increase in waist circumference. In Study I, there were no differences between FEP patients and controls in glucose, insulin or HOMA at baseline.

Insulin resistance as a predictor of weight gain and increase in waist circumference in FEP is a novel finding. In the general population, abdominal obesity has been associated with subsequent development of insulin resistance (Park et al., 2010). However, the reverse association (i.e. insulin resistance preceding the development of abdominal obesity) has also been reported (Sossa et al., 2013). Some longitudinal studies have reported higher insulin levels or insulin resistance predicting weight gain in the general population (Sigal et al., 1997; Tong et al., 2005). However, other studies have not found this association (Silver et al., 2006; Zavaroni et al., 1998). In a study examining the metabolic risk of first-degree relatives of subjects with T2D, insulin resistance was superior to BMI or waist circumference in predicting MetS and overall metabolic risk, suggesting that in a genetically high-risk population, individuals with normal body weight who are insulin resistant have an increased metabolic risk compared to those who are obese but insulin sensitive (Utzschneider et al., 2010).

Glucose metabolism may be intrinsically dysregulated in psychotic disorders, as indicated by a meta-analysis showing evidence of insulin resistance in antipsychotic-naïve individuals with FEP (Perry et al., 2016). Although the reason for the association between psychosis and impaired glucose metabolism is unclear, some potential explanations have been discussed in the literature. There is inflammatory activity associated with T2D and psychotic disorders, and inflammation may play a part in glucose

dysregulation in both diseases (Calle and Fernandez, 2012). Also, psychosis has been associated with hyperactivity of the hypothalamus-pituitary-adrenal axis, which is a system regulating endocrine responses to stress and, among other functions, has an important role in energy metabolism (Borges et al., 2013). The higher level of circulating cortisol in patients with FEP could lead to disturbances in the glucose metabolism. Furthermore, people with psychotic disorders may have a genetic liability for insulin resistance and T2D. This is demonstrated by studies showing that T2D and schizophrenia share gene variants increasing the risk for both diseases (Hansen et al., 2011; Lin and Shuldiner, 2010). There is also evidence of increased risk of T2D in unaffected relatives of people with psychotic disorders (Mothi et al., 2015; Van Welie et al., 2013). A recent study found decreased insulin sensitivity both in FEP patients and their unaffected siblings compared to controls (Chouinard et al., 2018). The evidence suggests that the increased risk of T2D in schizophrenia is not only a consequence of poor health habits and antipsychotic medication, but may also be affected by shared genetic risk or factors intrinsic to schizophrenia.

Most of the FEP patients in Study I were using antipsychotics at baseline with a median of 26 days of antipsychotic use. Antipsychotics have rapid effects on glucose metabolism, as shown by a meta-analysis examining the effects of antipsychotics on insulin resistance in healthy volunteers (Burghardt et al., 2018). A reduction in insulin sensitivity was observed in studies in which antipsychotics were administered for 3 to 13 days (Burghardt et al., 2018). Weight gain was detected only in studies of longer duration, probably because weight gain requires a more long-standing imbalance of energy intake and expenditure. In Study I, FEP patients with insulin resistance at baseline may have been especially vulnerable to antipsychotic-related metabolic dysregulation. It is also possible that patients who were adherent to medication displayed greater antipsychotic-induced insulin resistance early in the treatment and more weight gain in the longer-term compared to those who had a lower adherence to medication.

6.3 CHANGES IN GLUCOSE METABOLISM AND LIPIDS

A somewhat surprising finding in Studies I and II was that the metabolic parameters of glucose and lipid levels did not change significantly during the follow-up in FEP patients. This is in contrast with several findings from studies showing increasing lipid, glucose and insulin resistance levels in FEP during the first year after treatment initiation (Fleischhacker et al., 2013; Foley and Morley, 2011; Perez-Iglesias et al., 2014). It is possible that the relatively short duration of antipsychotic use at baseline had already disturbed glucose and lipid metabolism, influencing the observed baseline differences in insulin resistance, non-HDL cholesterol and triglycerides.

An in vitro study indicated that antipsychotics have rapid effects on lipid metabolism by first inhibiting cholesterol biosynthesis, and then via a feedback mechanism, actually increasing the synthesis rate (Canfran-Duque et al., 2013). It is also possible that factors inherent to the psychotic illness result in disturbed lipid metabolism in FEP. According to two recent meta-analyses, FEP patients with minimal or no exposure to antipsychotics show differences in lipid levels compared to controls (Misiak et al., 2017; Pillinger et al., 2017b). Intriguingly, both meta-analyses reported lower levels of total and LDL cholesterol and higher triglycerides in FEP compared to controls. The meta-analysis by Misiak et al. also found lower levels of HDL cholesterol in FEP, but this was not observed in the meta-analysis by Pillinger et al. (2017).

These meta-analyses imply that dyslipidemia in chronic psychotic disorders results from factors such as sedentary lifestyle, poor diet and antipsychotic medication. The lower levels of total cholesterol and especially LDL cholesterol in FEP would signify lower cardiovascular risk, as LDL cholesterol is a major risk factor and also causal factor in cardiovascular disease (Ference et al., 2017). Pillinger et al. (2017) reported that in FEP the absolute reduction in total cholesterol was 0.26mmol/l, in LDL 0.15mmol/l, and an increase in triglycerides of 0.08mmol/l. The difference in LDL would translate to a cardiovascular risk reduction of 3% (Pillinger et al., 2017b). However, in Study II, total cholesterol, LDL and triglyceride levels were already higher in FEP patients at baseline.

6.4 DEVELOPMENT OF LOW-GRADE INFLAMMATION IN FEP (STUDY II)

In Study II, no baseline differences were observed between FEP patients and controls in hs-CRP. However, hs-CRP increased during the 12-month follow-up over 2.5-fold. Analysed with mixed-effects models, waist circumference, BMI and female gender were significant predictors of hs-CRP levels.

The finding of similar levels of low-grade inflammation measured by hs-CRP at baseline between FEP patients and controls is not in agreement with meta-analyses published on CRP levels in psychotic disorders, which uniformly report higher CRP levels in psychosis, and two reported that increased BMI did not explain the association (Fernandes et al., 2016; Wang et al., 2017). In addition, the meta-analysis by Fernandes et al. analysed separately studies where participants were drug-naïve or drug-free, and concluded that CRP levels were still higher in this group than in healthy controls. However, of the six studies including only unmedicated individuals with early psychosis that were included in the meta-analysis, three did not show significant differences between patients and controls, while the other three studies displayed large effect sizes ranging from 1.45–1.91. The wide

range of effect sizes shows that there is high variability between individual studies.

One factor potentially explaining some of the differences between individual studies is the selection of controls. In Study II, controls were recruited randomly from the general population with matching for age, gender and region of residence. There were no statistically significant differences between patients and controls at baseline in lifestyle factors, such as smoking and exercise, which could affect CRP levels (Fedewa et al., 2017; Ohsawa et al., 2005). If controls were to have healthier lifestyle habits than the average population, this could bias the comparison of CRP towards lower levels in controls.

Waist circumference was a highly significant predictor of hs-CRP levels in the mixed-effects model of Study II. This is consistent with results from general population studies showing that obesity correlates strongly with CRP levels, and waist circumference more strongly than BMI (Choi et al., 2013). Adipose tissue is not only a storage for excess energy but has active endocrine functions. For example, adipocytes monitor the energy status and aim to maintain energy homeostasis by secreting hormones, e.g. leptin which reduces food intake. Adipocytes can also regulate lipolysis by activating the sympathetic nervous system (Reilly and Saltiel, 2017). When nutrients are abundant, adipocytes are under constant anabolic effects of insulin and other hormones. Eventually the expanded adipocytes reach a threshold after which an inflammatory activation takes place. The pro-inflammatory activation leads to an increase in cardiovascular risk and mortality, for which CRP is an independent risk factor (Emerging Risk Factors Collaboration et al., 2010; Ridker, 2016). It is thus of great concern, that young, originally metabolically healthy adults with FEP show not only significant weight gain and increase in abdominal obesity, but also a remarkable rise in hs-CRP, indicating a state of low-grade inflammation which further adds to their cardiovascular risk.

Female gender was another statistically significant predictor of hs-CRP levels in the mixed-effects model. This is in agreement with findings of women having larger increases in CRP levels with increasing body fat mass compared to men (Cartier et al., 2009; Khera et al., 2009). This may be due to hormonal differences between women and men, e.g. oestrogens increasing the CRP concentration (Khera et al., 2009). Also, the hepatic CRP production may be stimulated more strongly by leptin in women (Hribal et al., 2014), as leptin levels have been shown to associate steeper with body fat parameters in women than in men (Abdullah et al., 2007).

In Study II, patients had a median of 22 days of antipsychotic treatment before the baseline assessment. There is evidence of antipsychotics reducing the levels of pro-inflammatory cytokines and increasing the levels of anti-inflammatory cytokines, thus attenuating pro-inflammatory activity (Fonseka et al., 2016; Tourjman et al., 2013). As reviewed by Baumeister et al. (2016), there is conflicting evidence from in vivo and in vitro studies and different studies showing opposing effects for same antipsychotics

(Baumeister et al., 2016). Nonetheless, the results of Study II suggest that if antipsychotics have anti-inflammatory effects, they are outweighed by the pro-inflammatory effect of increasing abdominal obesity.

It should be noted, that apart from antipsychotics, other drugs may also affect CRP levels and confound the comparison of results between different populations. For example, valproate and antidepressants have immunomodulatory effects (Baumeister et al., 2016; Sinn et al., 2007), and statins lower the level of CRP independent of the drug's effects on lipids (Devaraj et al., 2011).

6.5 MORTALITY IN NON-AFFECTIVE PSYCHOSIS (STUDY III)

In Study III, the all-cause mortality HR during a 13-year follow-up in NAP was 2.99 when adjusting for age and gender, and 2.1 when adjusting, in addition, for antipsychotic medication, socioeconomic factors, smoking, obesity, inflammation and chronic physical disease. The increased mortality was mostly due to natural causes, with cancer and cardiovascular disease accounting for over half of the all-cause mortality. Accidents and suicide accounted for 16% of the all-cause mortality. Smoking increased the mortality HR for natural causes while antipsychotic use decreased it.

Similar increased mortality risk in psychotic disorders has been reported previously. A systematic review assessing mortality in schizophrenia reported a SMR of 2.58 for all-cause mortality (Saha et al., 2007). In a study based on Swedish register data, people with schizophrenia had increased mortality from ischaemic heart disease (adjusted HR [aHR] for women 3.3 and for men 2.2) and cancer (aHR women 1.7, men 1.4), as well as increased total and natural cause mortality (Crump et al., 2013b). In the US, a study including over 1.1 million individuals with schizophrenia calculated a SMR of 3.7 for all-cause mortality (Olfson et al., 2015). In Finland, a study examining the Health 2000 sample up to September 2009 found that people with schizophrenia had a mortality HR of 3.0, and people with other NAP 1.8 (Suvisaari et al., 2013). Another Finnish study, including people with schizophrenia older than 65 years, found that the mortality rate for unnatural causes of death was significantly higher (SMR 11.0) than the mortality for natural causes (SMR 2.6), reflecting the low rate of unnatural deaths in the general population of same age (Talaslahti et al., 2012).

As the mortality HR in NAP remained high after adjusting for several factors such as lifestyle, socioeconomic differences and health status, the results of Study III suggest that there may be factors associated with the quality of physical care that explain a significant part of the excess mortality in people with NAP. There is evidence that the quality or intensity of care in cardiovascular disease and cancer is worse in NAP compared to the general population. For example, a Finnish study showed that coronary

revascularization was less frequently done to people with NAP who had CHD compared to other people diagnosed with CHD (Manderbacka et al., 2012). In addition, a recent study found increased cancer mortality in people with psychotic disorders which was also partly explained by poorer quality of treatment (Manderbacka et al., 2017). In the study by Manderbacka et al. (2017), the mortality gap in cancer mortality between people with psychotic disorders and those without mental illness increased over time, indicating that people with psychotic disorders are not benefiting from developments in cancer treatment as much as the general population. Similar findings of lower intensity or quality of care for people with chronic psychotic disorders have also been made concerning the treatment of cardiovascular disease, as reviewed by Laursen et al. (Laursen et al., 2014).

In Study III, about 40% of the NAP group were smokers, and smoking was associated with increased risk of natural cause mortality. The increased risk has also been found in other studies examining mortality in serious mental illness (Dickerson et al., 2016; Tam et al., 2016). Smoking is more common in people with serious mental illness than in the general population, and according to a British report, smoking among people with psychiatric disorders has not declined at the same rate as in the general population (Harker and Cheeseman, 2016). The risk of natural cause mortality was reduced by antipsychotic medication use. In another Finnish study, antipsychotics were found to increase mortality in people who did not have a psychotic disorder but not in those with a psychotic disorder (Suvisaari et al., 2013). Register-based studies have reported lower mortality risks in people with schizophrenia using antipsychotics compared to non-users (Crump et al., 2013b; Tiihonen et al., 2016; Torniainen et al., 2015). Antipsychotic use might reflect treatment adherence or insight and be therefore related to lower mortality. It is important to note that in Study III, the diagnoses of psychotic disorders were lifetime diagnoses and some of the disorders were in remission and no longer required medical treatment. There were also people who had dropped out of treatment and thus were no longer using antipsychotics.

Inflammation measured by CRP levels increased the mortality risk in the total population sample of Study III, in agreement with findings from other studies (Emerging Risk Factors Collaboration et al., 2010), although CRP was not an independent risk factor for mortality in the population with NAP. A trend for higher CRP levels was observed in those with NAP who died during the follow-up (2.17mg/l vs. 1.47mg/l, p=0.17). The relatively small sample of people with NAP may have reduced the statistical power of the study to detect an effect for CRP on mortality. A study reported that levels of CRP over 3mg/l increased the mortality risk in people with schizophrenia, bipolar disorder and depression (n=3034) during a follow-up of up to 12 years (aHR 1.56, 95% CI 1.02-2.38) (Horsdal et al., 2017). However, more studies are needed to clarify the significance of increased CRP to the mortality risk in SMI.

6.6 STRENGTHS AND LIMITATIONS

6.6.1 STRENGTHS AND LIMITATIONS IN STUDIES I AND II

The general strengths in Studies I and II include a reliable diagnostic process, utilizing structured diagnostic interview and all available information from medical records. Subjects with FEP were recruited from hospital and outpatient settings and they represent the population with FEP well. Controls were randomly recruited from the general population and matched for gender, age and region of residence to reduce sociodemographic bias. Laboratory measurements were conducted in a laboratory which is internationally accredited. The statistical method used in Study II to analyse the relationship between hs-CRP and anthropometric and clinical measures, mixed-effects regression analysis, accounts for the correlation of repeated observations in a longitudinal setting. Furthermore, in mixed-effects models, missing data resulting in different number of observations in different individuals does not prevent the usage of all the available data in the analysis.

The limitations include the relatively large loss to follow-up among people with FEP. Attrition in longitudinal studies is common and hard to completely avoid. There were no statistically significant differences in baseline metabolic measures between those with data available throughout the follow-up and those who dropped out. The majority of the patients with FEP were already using antipsychotic medication at baseline. However, the median duration of medication at baseline was relatively short (22 days in Study II) and it did not result in baseline differences in BMI or waist circumference. Switches in antipsychotic medication during the follow-up were common, and thus it was not possible to analyse antipsychotic-specific effects on metabolic parameters. Furthermore, data on medications commonly used on an “as-needed” basis, such as benzodiazepines and hypnotics, were not analysed. Antidepressant and mood stabilizing medications were used in addition to antipsychotic medication, but the prevalence of polypharmacy was lower than, for example, a Finnish study which reported that in recent-onset schizophrenia the prevalence of antipsychotic polypharmacy was 40%, and 56% had previous use of antidepressants (Suokas et al., 2013). Further limitations are the use of HOMA as a measure of insulin resistance instead of a more accurate measurement, such as the oral minimal model method described in Chouinard et al. (2018). There are also more accurate methods to measure abdominal obesity than waist circumference (i.e. imaging methods), but these are not readily clinically available, and waist circumference has been shown to correlate well with abdominal fat mass (Pouliot et al., 1994).

6.6.2 STRENGTHS AND LIMITATIONS IN STUDY III

Strengths of Study III include the large population sample, which represents well the total population, and reliable diagnostics using many sources of information (enabling the inclusion of individuals who had not actively sought treatment, as opposed to clinical or register-based studies) and the SCID-I interview. The final diagnoses were ascertained by multiple psychiatrists, increasing the diagnostic reliability. There was extensive information available on sociodemographic and lifestyle variables, and on chronic physical disease. The data on causes of death in Finland is reliable.

Limitations of Study III include the relatively small number of cases with NAP, which resulted in wide confidence intervals in the analysis of mortality risk. Another limitation is that there were no data available from the follow-up period on measures that potentially affect mortality, e.g. clinical information, sociodemographic variables and lifestyle. No deaths were observed in people with affective psychotic disorders, and thus the analysis was focused on NAP only. Other studies have found an increased mortality risk in mood disorders as well, although the risk may be lower than in schizophrenia (Crump et al., 2013a; Roshanaei-Moghaddam and Katon, 2009). Previous studies in the same sample of affective psychoses as in Study III have shown that the risks of T2D, MetS or CHD were not increased compared to the general population (Suvisaari et al., 2010, 2008, 2007). The sample consisted of individuals older than 30 years of age which automatically excluded those who had committed suicide at a younger age and lowered the rate of suicides observed in this study.

7 CONCLUSIONS AND FUTURE RESEARCH

7.1 MAIN CONCLUSIONS

The aim of this study was to examine changes in weight, waist circumference, metabolic measures and low-grade inflammation in patients with FEP during the first year of treatment. Factors predicting weight gain and increase of waist circumference were investigated. In addition, this study aimed to examine factors associated with mortality in psychotic disorders.

At the onset of FEP, some of the metabolic risk factors, i.e. insulin resistance, levels of total and LDL cholesterol and triglyceride levels, were already higher than in healthy controls of similar age, while BMI and waist circumference was similar across the groups. A significant increase in weight and waist circumference took place during the first year of treatment, accompanied by a rise in hs-CRP, indicating the development of chronic low-grade inflammation. Insulin resistance and olanzapine medication at baseline were related to greater weight gain during the first year of treatment in FEP. Insulin resistance was also related to greater increase in waist circumference, suggesting that early insulin resistance during the treatment of FEP may mark an increased vulnerability for developing abdominal obesity.

The increase in waist circumference observed in FEP, reflecting the development of abdominal obesity, was related to the increase in hs-CRP, a marker of low-grade inflammation. Thus, it seems that hs-CRP is not a reliable marker of progress or outcome in FEP, but it rather signals the pro-inflammatory activity associated with increased visceral fat.

This study showed that the mortality risk in NAP is increased 2-3-fold compared to the general population, a finding which is concordant with previous literature. The increased mortality risk was not completely explained by differences in socioeconomic factors, obesity, smoking, chronic physical conditions or inflammation, suggesting that there are other factors contributing to the risk that were not accounted for. For example, the quality of treatment of chronic physical conditions in people with psychotic disorders may be lower than average, and the risk of a delayed diagnosis of physical conditions may be higher. Smoking was associated with increased risk of natural cause mortality, demonstrating the importance of promoting smoking cessation and examining effective ways in helping people with chronic mental disorders to quit smoking.

7.2 CLINICAL IMPLICATIONS

This study showed that young people with FEP are extremely vulnerable to the development of metabolic risk factors that result in significant increases in the risk for cardiovascular disease and diabetes. The weight gain, increase in waist circumference and low-grade inflammation in FEP that were observed in this study during the first year of treatment are alarming and rapid changes in young adults that are physically healthy at the onset of FEP. The increase in waist circumference was accompanied by increased low-grade inflammation, an independent risk factor for cardiovascular disease and mortality.

The findings highlight the importance of regular monitoring of physical health and the need for effective methods for prevention of physical complications in people with FEP. Weight, waist circumference, as well as lipid and glucose parameters should be regularly monitored to enable early prevention of metabolic adversities. Increased waist circumference is related to chronic low-grade inflammation, which provides another justification for frequent measurement of the waistline. Guidance and support in making healthy lifestyle modifications should be an integral part of the treatment of chronic psychiatric disorders.

Early insulin resistance during the treatment of FEP may be a marker for increased risk of weight gain and abdominal obesity. However, more studies on the relationship between insulin resistance and the development of obesity in FEP are needed before any recommendation concerning the clinical use of measuring insulin resistance, in order to detect those with increased risk for adverse metabolic changes, can be made.

Olanzapine was the most prescribed antipsychotic in FEP despite its high potential for weight gain. As is already recommended in some of the clinical care guidelines, antipsychotics other than olanzapine should be considered for first-line medication in FEP due to the adverse metabolic profile of olanzapine. As almost every antipsychotic is associated with significant metabolic risks, regular monitoring of weight, waist circumference and lipid and glucose parameters is essential to identify patients with the highest risk. Early intervention to reduce the metabolic risks in this highly vulnerable population is critical. It is important to note that although antipsychotics cause adverse metabolic changes, their use in the treatment of psychotic disorders is always indicated. Antipsychotics are effective in reducing psychotic symptoms and their use has also been associated with lower mortality in several studies compared to non-use. Also, in this study antipsychotic use was associated with lower natural cause mortality.

This study showed that the increased mortality in NAP is partly due to factors that could be acted upon by improving the early detection of physical problems, and the quality of care of chronic physical illness. A review (De Hert et al., 2011a) looked into the barriers of treatment of physical comorbidities ranging from patient-specific factors (e.g. unawareness of

physical problems or late help-seeking due to cognitive problems, difficulties in adhering to the treatment of physical illness) to factors related to psychiatrists (e.g. lack of time/interest/knowledge of physical problems), other physicians (e.g. stigma, pessimistic view of the potential results of treatment) and overall health services (e.g. difficulties in accessing care, fragmentation of services among different providers, low resources in mental care). These barriers seem to remain stable. Both system and individual level actions are required to reduce the excess mortality. For example, facilitating collaboration between psychiatric and physical healthcare, improving access to physical care for people with SMI, as well as early monitoring of physical risk factors and interventions to reduce those risks are all essential.

Advocating smoking cessation among people with psychotic disorders is probably the single most effective way to reduce the excess mortality of this population. There are effective pharmacological and psychosocial interventions for people with SMI who want to stop smoking (Aubin et al., 2012). Their clinical use should be promoted. A significant proportion of people with mental illness are willing to quit smoking (Aubin et al., 2012), and this inclination should be endorsed by offering the means and support to succeed in quitting.

7.3 FUTURE RESEARCH

As yet, it is not possible to accurately predict which individuals with FEP are the highest risk for developing adverse metabolic changes. Future studies should examine clinically useful predictors for the development of abdominal obesity and other metabolic risks in FEP. Current findings in genetic risk factors for metabolic abnormalities have only a limited utility in identifying increased risk for metabolic abnormalities. In the future, constructing instruments with clinically significant predictive accuracy (e.g. genetic risk scores) would offer valuable tools to increase the identification of individuals with a high risk. Determining early thresholds for intervention to prevent further detrimental metabolic changes would be clinically useful. Further studies on early pharmacotherapy (e.g. metformin) to prevent antipsychotic-induced weight gain are needed.

Determining in detail the development of inflammatory processes in FEP with more refined measurements of immunological activity is warranted. Studies aiming to clarify the longitudinal course of immune activity in psychotic disorders by following individuals from high-risk states to full-blown psychotic disorders are needed. The effects of risk factors for psychosis, lifestyle factors and antipsychotics on inflammatory activity should be further differentiated. In this study, hs-CRP was strongly linked to waist circumference and therefore it is not a potential marker for the risk or progress of psychotic disorder. However, future studies should examine in

detail the effects of chronic inflammation on the mortality risk in psychotic disorders.

The mortality gap between people with SMI and the general population does not seem to be diminishing. Research is needed on the quality of treatment of physical disease in SMI. Future studies should address the questions of whether physical risk factors among people with SMI are identified and resolved with the timeliness and intensity required by guidelines of care, and what the reasons are underlying the probable lower quality of treatment of physical disease in people with SMI. Research on ways to facilitate the integration of care of chronic psychiatric and physical conditions is necessary in order to close the mortality gap.

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