Prognostic Factors in First-Episode Schizophrenia

Five-year Outcome of Symptoms, Function and Obesity

ROBERT BODÉN
Dissertation presented at Uppsala University to be publicly examined in Sal X, Universitetshuset, Övre Slottsgatan, Uppsala, Friday, March 26, 2010 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

**Abstract**


Our knowledge of prognostic factors and optimal treatment organisation in schizophrenia is incomplete. The disparity of outcome measures used has been a major obstacle for research. Increasing evidence has shown that schizophrenia is associated with increased cardiovascular mortality, development of obesity and autonomic nervous system imbalance. Assertive community treatment (ACT) has been suggested as a promising direction for organising treatment services for first-episode schizophrenia, but its long-term effect has not been evaluated.

One aim of the present thesis was to investigate prognostic factors for 5-year symptomatic and functional outcome and obesity development. A further aim was to evaluate a recently proposed definition of remission and examine the long-term effects of introducing a modified ACT programme (mACT). Thus, we performed a follow-up study of all consecutive first-episode psychosis patients in Uppsala County, Sweden during 1995-2000 (n=144).

In the first study we investigated the changes in a broad 5-year outcome of symptoms and function among patients presenting first time ever to psychiatric health care during 3 years before and during 3 years after the implementation of mACT. This change in the psychiatric service, however, was not followed by any long-term clinical benefits.

In the second study, we examined the association between remission of eight core schizophrenia symptoms and functional outcome. Remission was strongly associated with having good function and having a higher self-rated satisfaction with life.

In the third study, we explored a set of biochemical markers as predictors of weight gain and development of obesity. Haemoglobin, red blood cell count, hematocrit, γ-glutamyltransferase and creatinine were associated with the development of obesity in first-episode schizophrenia.

In the fourth and final study, we tested electrocardiographic measures of autonomic imbalance as predictors of symptomatic remission. Higher heart rate and high ST and T-wave amplitudes were related to symptomatic remission, indicating that cardiac autonomic imbalance at baseline may have a prognostic value in first-episode schizophrenia.

**Keywords:** First-episode, psychosis, schizophrenia, community mental health services, remission, functional outcome, biochemistry, obesity, weight-gain, prediction, autonomic balance, electrocardiography

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To all of you, everyday heroes,
struggling with this disease
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV Bodén R, Lindström L, Rautaharju P, Sundström J. Relations of electrocardiographic signs of autonomic dysregulation to five-year outcome in first-episode schizophrenia. *Submitted*

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Introduction

Schizophrenia is a chronic, episodic psychotic disease that affects a broad range of the patient’s life (1). Furthermore, it is one of the world’s top 10 leading causes of disease-related disability (2). Long-term maintenance treatment with antipsychotic medication is often needed to control the symptoms (3). Moreover, schizophrenia is a disease that affects not only the patient, but also family members and society (4, 5).

Epidemiology

The annual incidence of schizophrenia is between 8 and 40 per 100 000 inhabitants. Despite this wide interval of reported incidence throughout the world, the incidence has been regarded as relatively similar across continents (6-8). The point prevalence has been estimated to be about 0.5%, but with a considerable variation around the world (9).

Risk factors

Schizophrenia is a highly heritable disease. Twin studies have revealed that about 80% of the liability to schizophrenia is contributed to heritability factors (10). The genetic basis for schizophrenia is not yet fully understood. Nevertheless, there is evolving evidence that rare genetic aberrations with large effects each can increase the risk of schizophrenia, as well as polygenetic variations of many genes with small effects each (11, 12). Another intriguing observation is that older paternal age increases the risk of schizophrenia in the offspring (13). Moreover, there are strong indications that schizophrenia and bipolar disorder share a common genetic cause, with a considerable cross-over in heritability between the two disorders (12, 14).

Urbanicity and migration are associated with higher incidence rates (15-17). Other environmental risk-factors associated with small effect increases of the risk of schizophrenia are cannabis use (18), season of birth (19), prenatal infection and famine (20) and obstetric and perinatal complications (21).
Mortality

Patients suffering from schizophrenia have a 15 years shorter life expectancy compared with the general population (22). This increased mortality is mainly due to cardiovascular disease and suicide (22, 23); alarmingly, this excess mortality has been increasing in the past decades of the 20th century (24). For a long time, the suicide rate in schizophrenia has been cited to be 10% (25), but this notion has recently been challenged and instead a suicide rate of about half (i.e. 5%) has been estimated (26, 27).

History of the concept of schizophrenia

At the turn of the 19th century, the concept of dementia praecox, and a decade later, schizophrenia, was formed. In 1896, the German psychiatrist, Emil Kraepelin, formed the idea of a progressively dementing disease, dementia praecox, and thus defined the disease from its course (28). The Swiss psychiatrist, Eugen Bleuler, later developed the phenomenology further and opposed to defining dementia praecox from its course and instead proposed a new name, schizophrenia. In his textbook Dementia Praecox in 1911 Eugen Bleuler identified fundamental schizophrenic symptoms, which included thought disturbances, ambivalence, indifference and autism. The fundamental symptoms were, according to Bleuler, closely associated with the presumed underlying pathophysiology of schizophrenia. Hallucinations, delusions and catatonia were termed accessory symptoms and subordinate to the understanding of the causes of the disease. He also divided the patients with schizophrenia into different diagnostic subgroups (paranoid, hebephrenic and catatonic) and noted that the disease had a chronic, episodic course (29).

Fifty years later, Kurt Schneider proposed 10 “first-rank” symptoms supposedly discriminative of schizophrenia, which have been much debated since (30). These first-rank symptoms emphasise implausible delusion and hallucinations as especially important. In the early 1970s there was a big gap between European and American criteria regarding the diagnosis of schizophrenia: the American definition was far broader and included more of the affective and briefer psychoses compared with the more narrowly defined schizophrenia in Europe (31). These two ways of defining schizophrenia resulted in discrepancies in incidence and prevalence, making ecological comparisons difficult across the world.

In 1980, Tim Crow, a British psychiatrist, made an attempt to combine previous theories by postulating that schizophrenia may consist of two neuropathological processes: type 1, which impairs neurotransmitters balance (e.g., dopamine) with associated hallucinations and delusions responsive to antipsychotic treatment, and type 2, with loss of grey and white matter in the brain and associated with negative symptoms and treatment resistance and eventually leading to cognitive decline (32).
DSM-IV diagnostic criteria for schizophrenia

In the Diagnostic and Statistical Manual released in 1980 (DSM-III), a more narrow definition of schizophrenia was presented that was influenced by Kraepelin’s onset and course description, Bleuler’s fundamental symptoms and Schneider’s first-rank symptoms. This definition was widely accepted throughout the world (33). The criteria for schizophrenia in the most recent edition from 1994 (DSM-IV) are outlined in Table 1 (34).

Table 1. DSM-IV Diagnostic Criteria of Schizophrenia

A. Characteristic symptoms:
Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. delusions
2. hallucinations
3. disorganized speech (e.g., derailment or incoherence)
4. grossly disorganized or catatonic behaviour
5. negative symptoms, i.e., affective flattening, alogia, or avolition

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

B. Social/occupational dysfunction

C. Duration:
At least 6 months and must include at least 1 month of symptoms (or less if successfully treated) that meet criterion A

D. Schizoaffective and mood disorder exclusion

E. Substance/general medical condition exclusion:

F. Relationship to a pervasive developmental disorder:
Additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month
Longitudinal outcome studies

It is important to bear in mind the above described history of different diagnostic boundaries when considering outcome studies in schizophrenia. The outcome of a disease is of course dependent on which patients are included in the definition of the disease.

Mental hospital discharge samples

Throughout the 20th century, many long-term follow-up studies have been performed on patients discharged from mental hospitals. When trying to compare these studies over time, it seems as though the outcome of schizophrenia has improved between the 1920s and 1970s (35). This improvement is largely attributed to new treatments, especially antipsychotic medication.

Results from more recent mental hospital follow-up studies in the 1960s to 1980s, as reviewed by McGlashan, revealed consistently that the course of schizophrenia mostly is chronic but not progressive along the entire course, but tends to plateau 5-10 years after first admission to hospital (36). This meta-analysis also found that schizophrenia is associated with increased risk of physical illness and mortality. Moreover, the outcome of schizophrenia is not only worse than that of other major mental diseases but also heterogeneous, much of which can be linked to sample characteristics. The heterogeneity of the phase of the disease is regarded as the major obstacle when trying to compare these kinds of studies.

From Manfred Bleuler’s unique 20-year follow-up of a population of patients with schizophrenia (some of them treated by his father Eugene Bleuler), comes the often-cited prognostic distribution: 25% have severe chronic schizophrenia, 25% moderately severe, 30% mild and 20% recover (37).

Studies of the early phase of schizophrenia

To create homogenous samples of patients with schizophrenia regarding disease phase studies of the early phase have become the gold standard to investigate outcome and its predictors. Another reason for studying prognostic factors in first-episode samples is that information about prognosis is probably clinically most interesting in the beginning of the course of the disease.
Definition of baseline

A crucial issue when defining illness stage is how to define the time of onset of the disease (38). Schizophrenia often has an insidious onset of the psychotic symptoms and a long period of prodromal symptoms not specific to schizophrenia, such as withdrawal from social contacts, decline in job or school performance, pondering and sleep disturbances (39). To operationalise a fixed starting point many first-episode studies have set first admission to hospital as baseline, but as the number of inpatient beds has gradually decreased during the 1970s and thereafter, this threshold became more and more exclusive. This exclusivity was because a significant proportion of the patients were not admitted or because they had a prolonged period of outpatient treatment before first admission (40). Thus, in recent decades first contact with mental health care has more often been set as the baseline.

Included diagnoses

Another important question in first-episode studies is which diagnoses are included in the sample. There are different trajectories for a patient presenting for the first time to mental health care with psychotic symptoms. If there has been a short duration of the psychotic symptoms and they resolve completely within a month, this could be a brief psychosis; however, if there has been affective symptoms simultaneously, this could be an affective psychosis (manic or depressive) or perhaps a drug-induced psychosis if drug abuse is confirmed. However, if the symptoms persist and all the other criteria in Table 1 are met, this could be a development of first schizophreniform disorder (1 to 6 months) and finally schizophrenia (>6 months). The bottom line is that the earlier the mental health system gets in contact with a patient with psychosis, the more time is needed before a definitive diagnosis can be determined (41). Yet, to obtain baseline measures of all patients with first-episode schizophrenia, all patients with first-episode psychosis must be included, and then as time goes on sort out those with first-episode schizophrenia. Thus, there is generally a better outcome reported in first-episode psychosis samples than in first-episode schizophrenia samples because schizophrenia, in general, has a poorer prognosis than brief psychosis and affective psychoses (40).

Outcome measures

How good or poor outcome is defined is the next methodological issue that affects the results. Some authors have regarded being discharged from hospital or decreased delusional thinking a good outcome, whereas others have set the threshold higher to total absence of psychotic symptoms (42). Outcome can also be considered in other areas than symptoms: for example, function-
ing in daily life, work, social activities and quality of life (QoL) (43). In Manfred Bleuler’s 20-year follow-up the definition of a mild end state of schizophrenic illness included that the patients should be able to maintain a conversation about other topics than their delusions and hallucinations and performing some useful work and living outside the institution or on a quiet ward (37). The array of definitions of outcome has further decreased the opportunity of comparison between different settings and increased the heterogeneity in findings about the course of schizophrenia (44). Recently, however, a condensed and operational definition of symptomatic remission has been proposed after many years of consensus work, although its relation to functional outcome has not been established (42).

Rating scales of symptoms and remission

There are many available rating scales for symptoms in schizophrenia. The newly proposed definition of remission is based on eight core symptoms in schizophrenia and can be measured with several of the available scales (42). One of the most widely used rating scales in schizophrenia research is the Positive and Negative Syndrome Scale (PANSS) (45), consisting of 30 items that are rated on a seven-point scale ranging from absent to severe, and grouped into positive, negative and general psychopathology (Table 2).

Table 2. PANSS items and remission items

<table>
<thead>
<tr>
<th>Positive and negative items</th>
<th>General psychopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1 Delusions*</td>
<td>G1 Somatic concern</td>
</tr>
<tr>
<td>P2 Conceptual disorganization*</td>
<td>G2 Anxiety</td>
</tr>
<tr>
<td>P3 Hallucinatory behaviour *</td>
<td>G3 Guilt feelings</td>
</tr>
<tr>
<td>P4 Excitement</td>
<td>G4 Tension</td>
</tr>
<tr>
<td>P5 Grandiosity</td>
<td>G5 Mannerisms &amp; posturing*</td>
</tr>
<tr>
<td>P6 Suspiciousness/persecution</td>
<td>G6 Depression</td>
</tr>
<tr>
<td>P7 Hostility</td>
<td>G7 Motor retardation</td>
</tr>
<tr>
<td>N1 Blunted affect*</td>
<td>G8 Un cooperativeness</td>
</tr>
<tr>
<td>N2 Emotional withdrawal</td>
<td>G9 Unusual thought content*</td>
</tr>
<tr>
<td>N3 Poor rapport</td>
<td>G10 Disorientation</td>
</tr>
<tr>
<td>N4 Passive/apathetic social withdrawal*</td>
<td>G11 Poor attention</td>
</tr>
<tr>
<td>N5 Difficulty in abstract thinking</td>
<td>G12 Lack of judgment &amp; insight</td>
</tr>
<tr>
<td>N6 Lack of spontaneity &amp; flow of conversation*</td>
<td>G13 Disturbance of volition</td>
</tr>
<tr>
<td>N7 Stereotyped thinking</td>
<td>G14 Poor impulse control</td>
</tr>
</tbody>
</table>

*Included in the definition of remission
Predictors of outcome

The identification of predictors of outcome is important in establishing a prognosis to inform patients and peers, to tailor secondary preventive strategies and treatment and to enhance the understanding of the pathophysiology of the disease. In older studies of prevalent samples of patients with schizophrenia several predictors of schizophrenia outcome have been noted. These predictors comprise family history, schizoid personality, premorbid function in the social, work and cognitive domains, illness onset and symptom constellations (36). In a review of first-admission studies conducted in the late 1980s Ram et al concluded that duration of illness prior to first hospitalisation seemed to be an additional important predictor, although methodological differences in case definition, sampling and risk factors limited the possibility to identify definite prognostic variables (41). However, in the 1990s prospective first-episode studies with a more rigid methodology also emphasised duration of untreated psychosis (DUP) as an important predictor of outcome (46). DUP is the time from first psychotic symptom to the time of initiation of treatment.

The observation that a longer DUP was associated with poor outcome and the observation of the plateau effect of the progress of schizophrenia were the basis for the formulation of the “critical period hypothesis” and early intervention (47). This concept is based on the idea that the disease process is detrimental in some way and that the treatments we have can stop this process — the sooner the better (48). However, the empirical support for lasting effects of early intervention in clinical practice remains weak (49, 50).

First-episode cohorts

Although it is still inconclusive if early intervention can prevent the development of chronicity in schizophrenia, the rapidly growing number of longitudinal first-episode cohorts to study early intervention has become an Eldorado for the study of prognostic factors of schizophrenia. Some of the predictors of outcome that hitherto have been identified are presented in Table 3. The outcome measures predicted range from treatment response, relapse, to remission and global function. Although the predictors in Table 3 are numerous, the effects of each one are weak, with most odds ratios (ORs) ranging from 1.1 to 2.2, except for discontinuation of antipsychotics with a more substantial effect with ORs of about 5.
Table 3. **Predictors of outcome**

<table>
<thead>
<tr>
<th>Predictor category</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-morbid factors</strong></td>
<td></td>
</tr>
<tr>
<td>Obstetric complications (51)</td>
<td>response*</td>
</tr>
<tr>
<td>Sex (51-54)</td>
<td>response, remission, global function</td>
</tr>
<tr>
<td>Social function and marital status (52-57)</td>
<td>remission, social function, ADL</td>
</tr>
<tr>
<td>School/work function (52-54, 56)</td>
<td>remission, global function</td>
</tr>
<tr>
<td><strong>Onset, symptoms and co-morbidity</strong></td>
<td></td>
</tr>
<tr>
<td>Age of onset (52)</td>
<td>remission</td>
</tr>
<tr>
<td>Positive symptoms (51, 54)</td>
<td>response, global function</td>
</tr>
<tr>
<td>Negative symptoms (54, 58)</td>
<td>social &amp; global function</td>
</tr>
<tr>
<td>Cognitive dysfunction (51, 57, 58)</td>
<td>response, social &amp; global function</td>
</tr>
<tr>
<td>Insight (59)</td>
<td>readmission</td>
</tr>
<tr>
<td>Alcohol abuse or dependence (60, 61)</td>
<td>response, chronicity</td>
</tr>
<tr>
<td><strong>Neurobiological measurements</strong></td>
<td></td>
</tr>
<tr>
<td>Lateral ventricular enlargement (62, 63)</td>
<td>response</td>
</tr>
<tr>
<td>Enlarged pituitary (64)</td>
<td>response</td>
</tr>
<tr>
<td>Dysrythmic EEG (65)</td>
<td>remission</td>
</tr>
<tr>
<td>Neurological soft signs (55)</td>
<td>remission</td>
</tr>
<tr>
<td>Autonomic imbalance (hyperarousal) (66)</td>
<td>social function, work, negative symptoms</td>
</tr>
<tr>
<td><strong>Early treatment factors</strong></td>
<td></td>
</tr>
<tr>
<td>DUP (52, 55, 56, 67)</td>
<td>remission</td>
</tr>
<tr>
<td>Early treatment response (55, 67)</td>
<td>remission</td>
</tr>
<tr>
<td>Discontinuation antipsychotics (57, 68, 69)</td>
<td>readmission, social function, ADL</td>
</tr>
<tr>
<td>Drug-induced Parkinsonism (51)</td>
<td>response</td>
</tr>
</tbody>
</table>

*Response in this table= response to antipsychotic treatment
DUP= duration of untreated psychosis
ADL= activities of daily living

Some of the important more recent prospective first-episode cohorts are outlined in Table 4. Many of these projects are still running and adding to our knowledge of the early phase of schizophrenia. As can be seen, there is a drawback when attempting to include the acutely psychotic patients at baseline, mainly because this renders attrition already from the beginning, which, in combination with follow-up attrition, severely impairs the generalisability of the findings.
Table 4. Prospective first-episode cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>City, Country</th>
<th>Years</th>
<th>Diagnoses, baseline</th>
<th>N</th>
<th>Attrition baseline</th>
<th>Attrition follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suffolk (70, 71)</td>
<td>New York, USA</td>
<td>1989-1991</td>
<td>Schizophrenia 1(^{st})-admission</td>
<td>96</td>
<td>28%</td>
<td>25%, 4 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limitations: Non-representative sample (71), high doses (72)</td>
<td></td>
</tr>
<tr>
<td>PEPP (73, 74)</td>
<td>Ontario, Canada</td>
<td>1997-2003</td>
<td>Non-affective psychosis 1(^{st})-admission</td>
<td>159</td>
<td>Not reported</td>
<td>38%, 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limitations: No comparison group for treatment outcome</td>
<td></td>
</tr>
<tr>
<td>Opus (75-80)</td>
<td>Multicentre, Denmark</td>
<td>1997-1998</td>
<td>Non-affective psychosis 1(^{st})-contact</td>
<td>562</td>
<td>10-37%</td>
<td>45%, 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Strength: RCT</td>
<td></td>
</tr>
<tr>
<td>EPPIC (81)</td>
<td>Melbourne Australia</td>
<td>1995-1996</td>
<td>Non-affective psychosis 1(^{st})-admission</td>
<td>250</td>
<td>48%</td>
<td>25%, 1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limitations: different catchment areas, only English-speaking patients</td>
<td></td>
</tr>
<tr>
<td>LEO (82)</td>
<td>London, England</td>
<td>2000-2001</td>
<td>Non-affective psychosis 1(^{st})-contact</td>
<td>144</td>
<td>Not reported</td>
<td>9%; 18 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Strength: RCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limitations: Short follow-up</td>
<td></td>
</tr>
<tr>
<td>Nottingham (83)</td>
<td>England</td>
<td>1992-1994</td>
<td>Non-affective psychosis 1(^{st})-contact</td>
<td>112</td>
<td>1% (!)</td>
<td>19%, 3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limitations: Historical comparison</td>
<td></td>
</tr>
<tr>
<td>Hillside (68)</td>
<td>New York, USA</td>
<td>1987-1996</td>
<td>Schizophrenia 1(^{st})-admission</td>
<td>219</td>
<td>62%</td>
<td>12%, 1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limitations: Only English-speaking, no involuntary treated patients</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country/City</td>
<td>Time Period</td>
<td>Diagnosis</td>
<td>Setting 1st-Contact</td>
<td>First Episode</td>
<td>Follow-up</td>
</tr>
<tr>
<td>---------------------</td>
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<td>---------------</td>
<td>-----------</td>
<td>---------------------</td>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Cantabria (84)</td>
<td>Spain</td>
<td>1989-1990</td>
<td>Schizophrenia</td>
<td>1st-contact</td>
<td>86</td>
<td>0% (!)</td>
</tr>
<tr>
<td>Bordeaux (85)</td>
<td>France</td>
<td>2001-2002</td>
<td>Non-affective psychosis</td>
<td>1st-admission</td>
<td>65</td>
<td>11%</td>
</tr>
<tr>
<td>MAP (86)</td>
<td>Vancouver, Canada</td>
<td>1982-1984</td>
<td>Non-affective psychosis</td>
<td>1st-contact</td>
<td>318</td>
<td>45%</td>
</tr>
<tr>
<td>EPP (87)</td>
<td>Calgary, Canada</td>
<td>Since 1996</td>
<td>Non-affective psychosis</td>
<td>1st-contact</td>
<td>278</td>
<td>Not reported</td>
</tr>
<tr>
<td>Dublin (88)</td>
<td>Ireland</td>
<td>1995-1999</td>
<td>All psychoses</td>
<td></td>
<td>166</td>
<td>30%</td>
</tr>
<tr>
<td>TIPS (89)</td>
<td>Norway, Denmark</td>
<td>1997-2000</td>
<td>Non-affective psychosis</td>
<td>1st-admission</td>
<td>301</td>
<td>29%</td>
</tr>
<tr>
<td>The Parachute Project (53)</td>
<td>17 centra, Sweden</td>
<td>1996-1997</td>
<td>Schizophrenia</td>
<td>1st-contact</td>
<td>175</td>
<td>31%</td>
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Aetiological theories about schizophrenia

A descriptive diagnosis, such as schizophrenia, with no biomarkers connected to a causal explanation of the disease is predestined to be surrounded by a plethora of presumed aetiological theories. Moreover, the concept of schizophrenia probably includes several different diseases, making it difficult to even pose the question of the cause of schizophrenia (90). However, the following chapter will try to describe some of the important prevailing theories of the aetiology underlying this enigmatic disease.

Neurodevelopmental hypothesis

The neurodevelopmental hypothesis suggests that events during early life cause schizophrenia through an interaction between genetic and environmental factors during early periods of brain development. These disruptions in early life are clinically silent until after puberty when maturational events in the brain lead to a psychotic episode (91). Observations in patients with schizophrenia supporting this view are higher frequencies of minor physical abnormalities (92, 93), aberrant dermatoglyphics (94), neurological soft signs already in childhood (95) and delayed development in childhood, including motor abnormalities (96).

Neurodegenerative hypothesis

The Kraepelinean concept of dementia praecox as a progressive brain disease has been renewed by brain imaging studies exhibiting a progressive loss of grey and white matter in the brains of patients with schizophrenia (97). One argument against this view has been that no obvious cognitive decline has been observed in longitudinal studies (98). Thus, some people now argue for a synthesis of the two concepts: schizophrenia may be both a developmental and progressive brain disease (99, 100).
Dopamine and other neurotransmitters

Dopamine dysregulation has been identified as having a central role leading to the symptoms observed in schizophrenia. The evidence is based on the observation that stimulation of D₂ receptors in the brain produces psychotic symptoms and the dopamine-antagonising medications reduce these psychotic symptoms (101). Striatal excess and frontal lack of dopamine are thought to explain positive and negative symptoms in schizophrenia (102). Another neurotransmitter that is thought to play an important role in the causal pathway is glutamate and the corresponding N-methyl-D-aspartate (NMDA) receptor. In low doses NMDA receptor antagonists can induce negative and cognitive symptoms seen in schizophrenia. Furthermore, NMDA receptor activating agents may reduce negative symptoms when added to regular antidopaminergic treatment (103).

Autonomic dysregulation

Already in beginning of the 20th century, signs of autonomic dysregulation were observed in patients with schizophrenia with discrepancies between blood pressure and pulse frequency, oscillating body temperature and non-adaptive sweating (29, 104). Over the following century, there has been an abundance of reports of autonomic dysregulation from various bodily functions controlled by the autonomic nervous system, including pupil function (105, 106), sweat glands (107-109), vascular baroreceptors (105), heart rate control and repolarisation disturbances (110-114). Autonomic dysregulation has been hypothesised as one mediating factor that precipitates and leads to a psychotic episode and that contributes to the increased risk of cardiovascular disease in schizophrenia (107, 110, 115).

Despite the numerous reports of disturbances in various functions controlled by the autonomic nervous system, it is only electrodermal activity (sweat gland regulation) that so far has been evaluated as a prognostic tool in schizophrenia. The results are somewhat inconsistent: electrodermal non-responding to external stimuli in male patients with schizophrenia was associated with poor functional 2-year outcome (108), whereas female patients with electrodermal non-responding was associated with good functional 2-year outcome (109). However these samples were mixed regarding disease stage. Moreover, the samples were too small to differentiate the analyses between chronic and first-episode patients. In a recent study with a sample of only patients in their early phase of schizophrenia (after initial stabilisation of acute psychosis) both hyperarousal and hyperresponsiveness at baseline were associated with more negative symptoms and poor functional outcome 1 year later (66).
Heart rate variability studies suggest a lower parasympathetic activity in schizophrenia (110, 116), an activity that seems to be related to the degree of symptoms (112, 117, 118).

Moreover, autonomic cardiac dysregulation is evident in attenuated form in first-degree relatives (119), raising the question of whether autonomic dysregulation is perhaps both state and trait phenomena of schizophrenia. Despite the numerous reports of autonomic dysregulation in schizophrenia and the obvious advantages of electrocardiogram (ECG) measurements being cheap, easily obtained and widely used, there have not been any studies on ECG measures and their association with longitudinal outcome.
Treatment of schizophrenia

Antipsychotics

Before the introduction of antipsychotics in the 1950s, the majority of patients with schizophrenia were dwelling in mental hospitals. Because of the new pharmacological option to control psychotic symptoms, a dramatic change took place in psychiatric hospitals: some of the patients that had previously been in mental hospitals for years with severely disturbing and aggressive behaviour could now be discharged and live in the community (120). The dopamine-2 receptor antagonists, also called antipsychotics, are still the only effective therapeutic pharmacological agents currently available to treat psychotic symptoms (121). Clozapine is more effective for treatment-resistant positive symptoms and suicidality (122, 123). Olanzapine may also be somewhat more efficacious but otherwise there is similar efficacy on positive symptoms (hallucinations, delusion, and agitation) among the other available antipsychotics (124-126). Antipsychotics have a limited efficacy on negative and cognitive symptoms, but because high doses of dopamine-2 blockade can produce negative and cognitive symptoms; claims of efficacy for these symptoms should be evaluated with close scrutiny of the dosing of the comparator drug (127).

Assertive community treatment

As a response to the deinstitutionalisation in the early 1970s, a team-based approach called Assertive Community Treatment (ACT), a service-delivery model, was formed as a means of delivering care for severe mentally ill people living in the community. ACT has proven to be an evidence-based treatment in the sense of making the patients keep in contact with mental health services, reduce hospital admissions and improve accommodation status, employment and patient satisfaction. However, the effects of ACT on mental state and social functioning are still conflicting (128). In samples of patients with first-episode psychosis the large Danish OPUS study and two smaller randomised controlled trials found some support for the short-term efficacy of services with ACT (80, 129, 130). The long-term effectiveness of this treatment approach for first-episode psychosis in a naturalistic setting has not been established, however (81).
Psychotherapy

Some studies report benefits from family treatment and cognitive behaviour therapy for patients with schizophrenia as add on treatment (131, 132). However, Lynch et al observed no effect of cognitive behavioural therapy on symptoms or relapse in schizophrenia in a recent comprehensive meta-analysis (133).
Side effects of antipsychotic medication

While most patients with schizophrenia are relying on long-term maintenance antipsychotic medication to control their symptoms, it becomes utterly important monitoring both symptoms and side effects longitudinally and optimise treatment to maximise antipsychotic effects and minimise the burden of the side effects. Patients with first-episode schizophrenia are also more prone to experience side effects (134). The most common or serious side effects are extrapyramidal symptoms, metabolic, sedation, hyperprolactinemia, heart rhythm abnormalities and neuroleptic malignant syndrome.

Extrapyramidal side effects

The general concern with the older antipsychotics has been the extrapyramidal side effects (EPS): akathisia (inner restlessness), parkinsonism (rigidity, tremor, hypokinesia), dystonia (muscle cramps) and tardive dyskinesia (involuntary movements, often in facial muscles) (135). The newer antipsychotics were introduced with high expectations that they would not be associated with EPS. Nevertheless, in non-commercially funded, large quasi-experimental, long-term studies the newer antipsychotics have been found to be associated with considerable levels of EPS (125, 126). Moreover, parkinsonism and dyskinesia have been observed in populations of patients with schizophrenia that have never been exposed to antipsychotic medication, indicating that these motor symptoms partly are intrinsic aspects of the illness (136, 137).

Metabolic side effects and obesity

The introduction of the new antipsychotics with a different receptor binding profile has somewhat changed the focus of side effect concerns. With perhaps somewhat lower propensity for EPS, the newer antipsychotics have, on the other hand, been associated with considerably higher frequencies of metabolic side effects (125, 126). The metabolic side effects include weight gain, hyperlipidemia and impaired glucose tolerance (138, 139).

The weight gain observed with some commonly prescribed antipsychotics in the two landmark studies CATIE (patients with chronic schizophrenia in
the USA) and EUFEST (first-episode patients in Europe) are depicted in *Figure 1* and *Figure 2*, respectively (125, 126). In the CATIE study the mean age was 41 years and mean baseline body mass index (BMI) 30; in the EUFEST study the mean age was 26 years and the mean baseline BMI 22. As can be seen in the figures, a substantial proportion of the patients experienced a clinically significant weight gain. In addition, first-episode and leaner patients seem to have a greater risk of weight gain that is due to antipsychotic medication. However, there is also some evidence that the risk of developing obesity is an intrinsic feature of schizophrenia, regardless of antipsychotic medication and lifestyle factors (140).

*Figure 1.* Proportion of patients in the CATIE study with a 7% weight gain.

*Figure 2.* Proportion of patients in the EUFEST study with a 7% weight gain
Already in the beginning of the 20th century Eugene Bleuler observed that patients with schizophrenia with a rapid weight gain during acute psychosis had a poor prognosis. Moreover, he noted that many patients exhibited considerable weight gain after the psychotic episode, sometimes more than 25 kg, and that the weight gain was not parallel to food intake (29). This observation was also made by Emil Kraepelin a decade earlier in patients with dementia praecox (28).

First-episode patients seem to be more susceptible to gaining weight, even when treated with assumed weight-neutral antipsychotics such as ziprasidone (125, 141). These findings raise the question of whether the risk factors in developing obesity should be explored beyond the field of exposure to antipsychotics. Except for the different antipsychotics, known predictors associated with an increased risk of weight gain in first-episode samples include lower age, more negative symptoms and lower BMI at baseline (142, 143).

Obesity is a major risk factor for cardiovascular disease in the general population (144) and patients with schizophrenia have an increased risk of dying from cardiovascular disease (23). Other adverse effects of obesity in schizophrenia are poor QoL (145) and non-adherence to treatment leading to worse outcome (146). Thus, studies of early risk factors in the development of obesity in schizophrenia are urgently needed to enable more efficient tailoring of early preventive interventions (147).
Hypotheses and Aims

1. The overall aim of this study was to collect an epidemiologically representative semi-historical (archival assessments and investigations) cohort of first-episode non-affective psychosis patients and through a comprehensive 5-year follow-up explore a wide array of predictors of various aspects of long-term outcome.

2. The aim of the first study was to investigate all consecutive patients with a non-affective first-episode psychosis within the psychiatric services in Uppsala County, as well as to compare the two cohorts treated 3 years before and 3 years after the service change. Our hypothesis was that the implementation of a modified ACT programme would be followed by improvement in symptomatic and functional 5-year outcome.

3. In the second study the aim was to investigate the relations of symptom remission to a broad functional outcome, including subjective satisfaction with life in a 5-year follow-up of a subsample of the above cohort consisting of patients with first-episode schizophrenia spectrum disorder. We hypothesised that remission would be associated with better functional outcome and subjective satisfaction with life, and that other factors than the ones included in the definition of remission may be important predictors of functional outcome.

4. The aim of study III was to explore routine blood chemistry variables as predictors of developing obesity and weight gain over 5 years in first-episode schizophrenia.

5. The aim of study IV, the final study in this thesis, was to investigate whether routine ECG measures reflecting cardiac autonomic balance (such as altered heart rate, repolarisation and left ventricular hypertrophy early in the schizophrenic disease) can predict remission status 5 years later. Our hypothesis was that the degree of autonomic dysregulation is associated with the symptomatic outcome of first-episode schizophrenia.
Methods

Local background

Uppsala University Hospital has a long tradition of prospective first-episode schizophrenia studies (148, 149). In the early 1990s one ward at the University Hospital was assigned to admit and examine all patients with a first-episode psychosis according to a protocol that included clinical interviews with the patients and their parents, siblings, friends and spouse, a psychiatric evaluation (including DUP), social evaluation (educational level, occupational status and frequency of social activities), somatic assessment (somatic status, blood biochemistry, ECG, weight, height and electroencephalography) and neurocognitive testing. After this initial inpatient phase, the patients were referred to one of three sectorised clinics with eight community-based teams serving all psychiatric patients living in that part of the county, irrespective of diagnosis.

In 1998, the psychiatric treatment organisation was changed and a modified ACT (mACT) model was implemented, where seven multidisciplinary teams were established with specialisation in outpatient treatment of schizophrenia. The modifications of ACT according to the Dartmouth criteria were (150): no 24-h coverage by the teams and no specialist in substance abuse treatment within the teams. The goal was to have close co-operation with the vocational and residential help organisations in the community and to ensure optimal multidimensional rehabilitation. One of the seven teams was specialised in the treatment of young adults with early non-affective psychosis. However, the algorithm for the initial examination of the patients remained unchanged.

Study design

This study was designed as a semi-historical cohort study in order to maximise inclusion of all consecutive patients because asking actively psychotic patients about research participation at baseline can render severe attrition already from start. Thus, we used historical data (from patient charts such as ECGs, blood biochemistry, DUP) and then made a prospective follow-up.
Setting

The study was performed in a geographically defined area (Uppsala County in Sweden), which consists of a semi-rural and semi-urban region with 290,000 inhabitants. All patients with psychosis were treated within the same organisation of psychiatric care — care that is state financed in Sweden. Homelessness is rare in Sweden in the general population (151). Employment ratios and the proportion of high alcohol consumption in the general population were virtually stable during the study period (152, 153).

Case-finding process

To identify all patients with first-episode psychosis we searched the electronic psychiatric health care registers of Uppsala County with the period set to 1995-2000. These registers contain information on which health care facility has been attended, date and diagnosis of each outpatient visit to a psychiatrist, admissions and discharges from inpatient care. Forensic psychiatric patients are also found in these registers and, according to Swedish legislation, patients with psychotic disorders cannot be imprisoned. The set of search criteria used was all non-affective psychosis diagnoses with DSM-IV codes: 295.1-295.9, 297.1, 298.8 and 298.9 (i.e. schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychosis and psychotic disorders not otherwise specified). In 1998, the local register in Uppsala changed to ICD-10 and from this point we used the search criteria of the corresponding ICD-10 diagnoses with the codes F20-F29.

All medical records were then manually evaluated if the case in the register was a first episode of non-affective psychosis. Patients were included if they were between 16 and 59 years old. If organic causes or severe drug abuse was identified as a main cause of psychosis, the patient was excluded. We identified 167 patients in the register search. After a review of the medical records of the first year of illness, 13 patients were found to have an affective psychosis and 6 patients had a personality disorder (with no clear psychotic symptoms found in the psychiatric records). In addition, two patients had severe drug abuse and two had an organic cause of their psychosis. This yielded a final sample of 144 patients with a first episode of non-affective psychosis. Of these 144 patients, 124 had a schizophrenia spectrum disorder (schizophrenia, schizophreniform or schizoaffective disorder). Baseline was defined as the date of first contact with a mental health service with psychotic symptoms recorded in the patients’ medical record. A flow-chart of attrition in the different papers is displayed in Figure 3.
Review of the psychiatric records

The first year of illness was reviewed with a structured reassessment using a checklist composed of DSM-IV diagnostic criteria. Confirmation of the diagnosis and a baseline GAF rating, based on information in the medical records, were carried out by the principal author (RB) with consensus agreement by two of the co-authors of Paper I (EL and I-MW), who are both experienced psychiatrists. Baseline sociodemographic variables, DUP, weight and height measures, ECGs, blood chemistry data and treatment exposure during the first year were extracted from the psychiatric records.

Five-year follow-up interview

A follow-up interview was conducted 5 years after the patients’ first presentation to mental health care. Patients were traced by using their personal identification number to locate their current address. The patients were first sent a letter and then contacted by phone. The follow-up face-to-face interview was conducted in one or sometimes two sessions. The assessments consisted of the Positive and Negative Syndrome Scale (PANSS) (45), the Alcohol Use Disorders Identification Test (AUDIT) (154, 155), the Subjective Satisfaction
With Life (SSWL) scale (156), the Global Assessment of Functioning (GAF) scale (34) and a life-time re-diagnosis according to DSM-IV.

In addition, information was collected on education, employment status, accommodation, height, weight and current medication. If a patient declined being interviewed, but consented to participation, a phone interview or mail interview and/or review of the current psychiatric records was performed, including AUDIT, SSWL, education, employment status, accommodation and height and weight. The principal author (RB) conducted 80% of the interviews while five trained MDs conducted the remaining 20% of the interviews.

Investigated predictors and outcome measures

Psychiatric service changes and symptoms (Paper I)

First, we explored how the predictor of first presentation to mental health services and having initial treatment during 3 years before or during 3 years after the implementation of mACT in 1998 was associated with a broad array of outcome measures at the 5-year follow-up.

The two co-primary endpoints were poor outcome regarding positive and negative symptoms at the 5-year follow-up, defined as having a rating of >4 on any positive or negative subscale item. Secondary outcome measures were dichotomised and defined as poor according to the following: GAF <40, AUDIT >7, use of illicit drugs, any domain on SSWL <2, being homeless or living in a sheltered or supervised accommodation, not working or studying at all the previous year, or having committed suicide.

Symptomatic remission and function (Paper II)

Remission of core schizophrenia symptoms was the main predictor in the second paper. Other psychopathology factors were also tested and included excited, depression and anxiety factors, negative symptoms, lack of judgement and insight. Additionally, comorbid alcohol use or obesity and pretreatment factors, such as educational level, premorbid occupational function and DUP were investigated.

A composite outcome measure labelled “good function” was created and defined as: living independently (not sheltered living or homeless), in competitive work or studying at least 50% during the past year and meeting friends at least once a month. All three criteria had to be met to be rated as having good function.
Biochemistry and obesity (Paper III)

In the third paper the following routine biochemistry variables were explored as predictors: haemoglobin, red blood cell count, hematocrit, white blood cell count, platelet count, alkaline phosphatase, alanine aminotransferase, γ-glutamyltransferase, thyroid-stimulating hormone, albumin, calcium, sodium, potassium and creatinine.

The presence of obesity at the 5-year follow-up was the primary outcome measure. Obesity was defined as having a BMI ≥30, which is in accordance with the WHO definition (157). As a secondary outcome, Δ-BMI was considered, defined as the difference between the 5-year follow-up BMI and baseline BMI.

ECG measures and remission (Paper IV)

In the last paper 10 ECG variables were selected to reflect autonomic regulation: heart rate, repolarisation disturbances (various QT and T-wave measures) and left ventricular hypertrophy measures (Cornell and Sokolov-Lyon voltage).

The outcome measure was symptomatic remission at the 5-year follow-up. Remission was defined as a score of “3=mild” or less on all of the previously described eight items from the PANSS.

Statistical analyses

All continuous variables were tested for normality. Skewed variables were transformed with a natural logarithm to promote normality. If non-normally distributed variables contained values of zero, they were dichotomised with median as cut off to maximise power. Non-linear associations between the independent and dependent variables were investigated with multivariable regression-penalised spline.

In the first paper we analysed the dichotomised variables one by one in separate logistic regression models with exposure group (non-mACT and mACT) serving as the main independent variable. We considered one unadjusted model and one adjusted for a baseline propensity score (including all baseline variables) and use of antipsychotic medication at the 5-year follow-up.

In the second paper we also investigated the predictors one by one in separate analyses as independent variables in logistic regression models. In this paper good function was the dependent variable. C-statistics (area under the receiver-operating characteristics curves, ROC) was calculated from those models to analyse the discriminatory capacity of symptomatic remission for good function.
In Paper III logistic regression with obesity status as the dependent variable was used to investigate relations of the independent variables to the primary outcome variable. For the secondary outcome, linear regression models with ΔBMI as the dependent variable were used.

In the last paper logistic regression models were applied to investigate the relations of the 10 ECG variables to the dependent variable, i.e. non-remission. Data were analysed using the software packages SPSS 15.0-16.0 (SPSS Inc., Chicago, IL, USA) and Stata 10.0-10.1 (StataCorp; College Station, TX).

Ethical considerations

Asking patients with schizophrenia about participation in research can be a sensitive and difficult issue, not only because schizophrenia is often a disease with fluctuations in insight, suspiciousness and delusions but also because many patients with schizophrenia have been subjected to involuntary treatment. Additionally, all patients, whichever diagnosis, are in a subordinate position in relation to the healthcare system.

If the patients still had an ongoing treatment for the time of the follow-up assessment, they were first asked by their primary staff member if they allowed someone from the research team to contact them for information about the research programme. Then the patients were contacted by phone and received information about the nature of the research project and that their participation would consist of an interview that would last about 1-1.5 hours. The patients were also given written information about the project and at the time of the interview there was an initial reassurance that the patients had understood the information and that they consented to participation.
Summary of results

Paper I
In contrast to our hypothesis, patients in the mACT group had a borderline significant increased risk of having a poor 5-year outcome regarding positive psychotic symptoms (adjusted OR 3.21, 95% confidence interval [CI] 0.97 to 10.63). Concerning negative symptoms, there was no difference (adjusted OR 1.65, 95% CI 0.48 to 5.66), nor were there any differences in any of the secondary outcome measures: global assessment of functioning, hazardous alcohol use, use of illicit drugs, not working or in education, independent living, subjective satisfaction with life or suicide.

Results were similar in subgroup analyses, but in the subgroup of patients with a schizophrenia spectrum diagnosis the mACT group had a higher risk of having poor outcome on positive psychotic symptoms with an OR of 3.67 and a 95% CI of 1.07 to 12.56, adjusted for the baseline data propensity score and use of antipsychotics at the 5-year follow-up.

Paper II
The proportion of patients having good function was significantly higher among remitters than non-remitters in all domains (Figure 4). Subjective satisfaction with life was also rated higher among remitters (Figure 5). In comparison with non-remission, symptomatic remission was strongly associated with good function (OR 13.2, 95% CI 4.3 to 40.3). A DUP of 3 months or less as compared with a longer duration was associated with having good function at the 5-year follow-up independently of remission status. The discriminatory capacity of symptomatic remission for having good function vs. not was acceptable (c-statistic=0.78), which was significantly improved to an excellent discriminatory capacity by adding DUP less than 3 months vs. not adding DUP to the model (c-statistic=0.83, p=0.04).

Having insight was significantly associated with good function, but the association was attenuated after adjusting for remission status.
Figure 4. Functional outcomes among remitters and non-remitters. **=p<0.01, *=p<0.05

Figure 5. Subjective Satisfaction with Life (SSWL). Boxes represent the interquartile range, line in box represents the median and whiskers represent the range (2.5 - 97.5 percentile). **=p<0.01

Paper III

The proportion of obese patients was more than twice as high at the 5-year follow-up compared with baseline (Figure 6). The mean change of BMI over 5 years (Δ-BMI) was a 4.1 kg/m² increase (4.5 SD). The greatest BMI increase was observed among the patients who had a normal to low BMI at baseline; in contrast, the patients who were obese at baseline experienced a median BMI decrease (Figure 7).

Development of obesity among those who were not obese at baseline was predicted by baseline haemoglobin levels (odds ratio per standard deviation [OR/SD] 3.3, 95% CI 1.4 to 7.5), red blood cell count (OR/SD 2.6, 95% CI 1.2 to 5.5), hematocrit (OR/SD 2.8, 95% CI 1.3 to 5.9), γ-glutamyltransferase (OR/SD 2.8, 95% CI 1.2-6.3) and creatinine (OR/SD 3.1, 95% CI 1.2 to 8.0). Sodium level was borderline significantly associated with subsequent obesity (OR/SD 2.1, 95% CI 1.0-4.6). Adjusting for baseline BMI attenuated the associations for γ-glutamyltransferase and creatinine.
Higher heart rate at baseline was associated with a higher risk of being in non-remission 5 years later (OR 2.2, 95% CI 1.0-4.8, per SD). Among the ECG variables reflecting repolarisation, T-wave amplitudes above the median in leads V1 or V5 were associated with higher risks of non-remission, OR 4.8 (95% CI 1.2-19.1) and 5.2 (95% CI 1.2-21.6), respectively. An ST60 amplitude from lead V5 above the median was also associated with a higher risk of non-remission (OR 6.4, 95% CI 1.5-27.2). Adjusting models for heart rate did not materially change the results, except from T-axis and QRS-T axis that became borderline statistically significant.
Discussion

General strengths and limitations
The strengths of this study are that we included all patients in a defined catchment area and used a fairly long follow-up time. One limitation is that we used archival naturalistic data from the patients’ psychiatric records for the investigated predictors (e.g., height, weight, routine measures of blood biochemistry and routine ECG recordings). Thus, the external conditions were not strictly standardised and held constant: for instance, the same time of day, duration of fasting and resting time before recordings. On the other hand, these measures are cheap, easy to obtain, already widely used in clinical practice, and because this is a naturalistic study, it is a more fair reflection of clinical reality, not suffering from the initial baseline attrition as “traditional” cohort studies. Because the clinical investigation was formalised and held constant during the study period, the available baseline predictors were numerous. Unfortunately, we did not have comprehensive baseline symptom ratings, precluding the opportunity to explore the independent contribution of the predictors to the prognosis. Another limitation is the small sample sizes, which precludes controlling for a variety of different possible confounders.

Paper I
The main result in this paper was that we could not support our hypothesis that the implementation of mACT would be followed by a more beneficial 5-year outcome of first-episode psychosis. This result differs from other recent studies of ACT for first-episode psychosis (77, 78, 130). Because we designed this study as a before and after comparison, it is not possible to draw any definitive conclusions on causality of the findings. On the other hand, naturalistic studies can give more knowledge about the “real world” effectiveness of a certain intervention.

Contrary to our expectations, there was even a borderline significant increased risk of having poor outcome of positive psychotic symptoms after the implementation of mACT. Because antipsychotics are mainly known to have an effect on positive symptoms, these outcome differences may be due to a confounder co-varying with drug treatment adherence (158). A greater
proportion of the patients in the mACT group had hazardous alcohol use after 5 years, which may partly explain the results regarding positive symptoms. More patients in the mACT group were prescribed a second-generation antipsychotic as first antipsychotic and at the 5-year follow-up. There is no substantial difference in efficacy between first and second generation antipsychotics concerning positive psychotic symptoms, but there is some evidence for better short-term tolerability in the latter (134). Thus, this could not explain the present findings. One possibility is that the doses used have decreased over time (when using the second-generation antipsychotics) and hence it may be that too low doses have been used in recent years.

**Paper II**

Core symptoms of schizophrenia seem to have an important limiting effect on function and life satisfaction in the early course of the illness. This position is consistent with the results from studies on chronic samples (159, 160).

Our finding that there is no independent association between depressive and anxiety symptoms and good function concurs with a recent Dutch study on a chronic sample (161).

Insight was associated with both good function and remission in the present study. This finding is in accord with a Canadian study that reported correlations between insight and positive and negative symptoms at four consecutive measuring times during the first year of psychotic illness (162). Insight has previously been shown to predict good functioning, but this could be due to the relation to remission (163). Because lack of insight and judgement had a trend towards an independent association with good function in our study, we calculated c-statistics to evaluate the discriminatory capacity of good function for this single item. The c-statistics was 0.75, which can be compared to 0.78 for remission (severity criterion). Having insight vs. not having insight was also associated with a higher mean on the three subscales of the SSWL scale.

One of the limitations with this study is that the interviewers were not blinded to the patient’s functional outcome when rating the symptoms. This limitation could perhaps bias the results towards a stronger association between symptoms and function in that the interviewers might tend to rate symptoms lower if the patient had a good function. However, the SSWL is a self-report measure and not subject to this possible bias. Moreover, the SSWL had a concordant tendency in the results as the other functional measures.
Paper III

The pattern of biochemistry predictors of obesity may indicate that the more dehydrated the patient is at baseline, the higher the risk of developing obesity over a 5-year period. Previous studies have reported that patients with schizophrenia have lower fractions of body water compared with healthy controls, measured with bioelectrical impedance analysis (164, 165). Further, dehydration has been observed in a Japanese sample of patients with acute psychosis (166). Dehydration in the acute psychotic phase may be predictive of poor response to antipsychotics, which, in turn, eventually leads to treatment with clozapine, the most weight-gain prone antipsychotic (167).

Another possible mechanism is based on the notion that treatment-naïve patients with first-episode schizophrenia have been reported to have impaired glucose tolerance (168). In the general population haemoglobin and hematocrit have been proposed as surrogate markers for insulin resistance (169, 170), which, in turn, is predictive of the development of obesity (171). Furthermore, γ-glutamyltransferase has also been suggested as a predictor of metabolic syndrome and type II diabetes in the general population (172).

A third possible interpretation could be an altered autonomic tone, which has been associated with schizophrenia and with prediction of obesity in the general population (114, 173). Interestingly, both increased pituitary volumes (64, 174) and basal hypothalamic-pituitary–adrenal axis hyperactivity with increased ACTH and cortisol levels have recently been reported in patients with schizophrenia (175). Sympathetic dominance can cause both dehydration and insulin resistance and may be a possible link explaining the predictive capacity of these biochemical markers.

Paper IV

One possible explanation of our observations in the last paper is that autonomic dysregulation with sympathetic dominance at baseline is related to subsequent non-remission. How this altered balance in the autonomic nervous system is affecting the prognosis is not obvious; but if cardiac sympathetic dominance is a reflection of the same phenomenon as overarousal in EDA measures, then the recently observed association between overarousal and negative symptoms and subsequent poor outcome supports our hypothesis and observations (66). The lack of activation in medial prefrontal cortex observed in patients with schizophrenia might be the correlate in the central nervous system affecting the inhibitory control over autonomic function in amygdale (176).

A recent study of relatives of patients with schizophrenia found that autonomic cardiac dysfunction was also evident among the relatives, although with attenuated strength (119). Thus, autonomic dysregulation may be partly
a state and partly a trait phenomenon. The possible state part of the autonom-
ic dysregulation may, however, not be specific to schizophrenia alone, i.e. cardiac autonomic dysregulation has also been reported in several other mental diseases, such as major depression and panic disorder (177, 178).

Future research

Based on the results of these studies, some directions for future research can be proposed. First, because the findings of biochemical risk factors in the development of obesity in schizophrenia and that ECG measures of autonomic balance can predict remission are rather unique, the first step would to replicate the findings in other study populations and settings. Preferably, such a replication would be done in larger samples so that the differential effect of the studied risk factors can be clarified. Because most pharmaceutical trials include the biochemical measures used in paper III and the ECG recordings used in paper IV as part of the safety routines, it should be feasible to perform these analyses on existing datasets.

The observed biochemical risk factors would be of worth to associate with other measures of insulin resistance (insulin and glucose levels), dehydration (bioimpedance) and measures of autonomic tone (from, e.g., ECGs, EDA or cortisol curves). In addition, moderating effects of these predictors on the effect sizes of the weight-gaining effect of various antipsychotics should be investigated.

It would also be worthwhile to explore whether the observed ECG aberrations in our study are present even before onset (archival ECGs?) or in first-degree relatives or other mental illnesses.

The relation of ECG predictors to treatment response or tolerability and if there is a differential effect of different antipsychotics would be particularly important to study. Early biomarkers to guide treatment choices (both regarding side effects and effect) would be a significant improvement in the clinical management of schizophrenia.
Conclusions

1. The implementation of the mACT programme was not followed by any long-term clinical benefits and was even accompanied by worse outcome regarding positive symptoms for the subgroup of schizophrenia spectrum disorders.

2. The recently proposed definition of remission of schizophrenia has an acceptable discriminatory capacity for good function; moreover, when adding DUP of 3 months or less, the discriminatory capacity proved excellent. Remission is also related to higher subjective satisfaction with life. Thus, symptomatic remission could be a feasible intermediate treatment goal for patients with first-episode schizophrenia. Insight was also associated with good function, suggesting it should be investigated as a possible clinical predictor of functioning in future studies.

3. Easily available routine biochemistry markers can be useful in predicting development of obesity in first-episode schizophrenia. The mechanisms underlying the observed associations are unknown, but the predictors identified in this study may be consistent with dehydration, insulin resistance or dominance of the sympathetic nervous system.

4. Routine 12-lead ECG measures in the early phase of schizophrenia are related to subsequent symptomatic remission status. Our observations indicate that it is an altered cardiac autonomic regulation (with both the sympathetic and vagal systems involved) that may be associated with an increased risk of not being in remission 5 years later.
Sammanfattning på svenska

Bakgrund

Frågeställningar och målsättning
Resultat


Remission av kärnsymtomen vid schizofreni var starkt kopplat till god funktion och högre självskattad livstillsfredsställelse, men även sjukdomsin-sikt var lika starkt kopplat till god funktion. Symtomatisk remission av schizofreni ter sig således som ett kliniskt relevant delmål.

Viktuppgången under de första fem åren av schizofrenisjukdom var avsevärd med en BMI-ökning på 4,1 kg/m² i medeltal. Flera rutinbiokemiska blodprover (Hb, EPK, EVF, γ-GT och kreatinin) visade sig ha ett prognostiskt värde för fetmautveckling. Dessutom observerades att ju lägre BMI patienterna hade från början desto större risk för en stor viktuppgång.

EKG-mått vid första psykosinsjuknandet som tyder på obalans i autonoma nervsystemet såsom hög hjärtfrekvens, höga T-vågor och ST-sträckor kan delvis prognosticera symtomatisk remission av schizofrenisjukdomen fem år senare.
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