Early detection and intervention in psychosis.

A long-term perspective.

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Scientific environment

The early Treatment and Intervention in Psychosis Study (TIPS) is a collaboration between Stavanger University Hospital, Oslo University Hospital Ullevaal, and Roskilde Amtsygehus, Denmark and with Yale Medical School (USA). The ten-year follow-up study also cooperates with the Thematic Psychosis Study (TOP), at Oslo University Hospital.

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Introduction

Over the last decades there has been a growing interest in early detection and intervention in first episode psychosis (FEP). Psychotic disorders are arguably among the most serious mental disorders and have been known to have a relatively poor prognosis. Human and societal costs are high. Psychotic disorders strike predominantly in early adulthood and interfere with career and partnerships choices. Unfortunately, mental health care often has seen patients in a late stage of the disorder. In spite of improved prognosis after the introduction of neuroleptics and a more humane treatment, many patients still suffer chronically from symptoms and poor functioning. Over the years the question rose whether detecting psychosis earlier could improve prognosis. Perhaps "applying existing schizophrenia treatments as soon as possible in the course of the disorder may slow or stop deterioration" (McGlashan and Johannessen,1996). That means, detecting and intervening in psychosis earlier. In this thesis, a long-term follow-up study of early detection of psychosis will be presented. First, after an introduction on psychosis in general, I will present a brief history of early detection in psychiatry. I will go on to provide an overview of long-term studies of outcome and recovery in psychosis in general and FEP in particular. Duration of Untreated Psychosis (DUP) will be described and discussed. An overview of early detection programmes, meant to reduce DUP, will be presented. I will then describe the methods and the content of the TIPS Early Detection programme, and present results from the study. Finally, results will be discussed, and some methodological and ethical considerations presented.

Sammendrag (summary in Norwegian)

Bakgrunn: Psykoselidelser er blant de alvorligste psykiske lidelsene og kjennetegnes av vrangforestillinger, forvirring og/eller hallusinasjoner (positive symptomer), tilbaketrekning og/eller apati (negative symptomer), og/eller kognitive funksjonsforstyrrelser. Mer enn 50% av pasienter har fremdeles symptomer etter ti år, og varierende grader av funksjonsnedsettelse hemmer opptil 90%. Studier har vist tid fra sykdomsstart til behandling henger sammen med prognose. Tidlig Intervensjon ved PSykose (TIPS)-prosjektet utviklet og implementerte et intensivt program for å forkorte varighet av ubehandlet psykose (VUP). TIPS består av intensive informasjonskampanjer rettet mot allmennbefolkning, skoler, helsepersonell og andre relevante parter, samt et lavterskel tidlig oppdagelsesteam. TIPS-prosjektet har kontinuert dette arbeidet i 13 år. En kvasi-eksperimentell studie som sammenliknet TIPS tidlig intervensjon ved psykose med vanlig oppdagelse ble gjennomført mellom 1997 og 2000. Tidlig Intervensjonssektor (TI-sektor) sektor var Rogaland, mens kontrollsektorer var Oslo (Oslo Univsersitetssykehus, Ullevål) og Roskilde i Danmark. I TI-sektor ble VUP redusert fra 26 til 4.5 uker, medianverdi. I kontrollsektor var VUP median 16 uker. Pasienter fra TI-sektor hadde lavere symptomnivå ved start av behandling, lavere nivå av negative symptomer etter ett og lavere nivå av negative, depressive og kognitive symptomer etter to og fem år. Lite er kjent om variasjon i VUP over tid og langtifdsforløp ved tidlig intervensjon ved psykose.

Målsetninger: Det første målet med studien var å undersøke variasjoner i VUP over en 18-årsperiode (1993-2010) med varierende TI-intensitet. Det andre målet var å undersøke om forskjellene mellom TI-kontrollsektor –forskjeller i symptomnivå holdt seg i et tiårsperspektiv. Forskjeller i rater av tilfriskning, som er en kombinasjon av symptomremisjon og funksjonsfriskhet, ble også undersøkt.

Som siste del av studien ble det undersøkt hvilke faktorer som bidrar til at en del pasienter ikke oppnår symptomremisjon på tross av tidlig intervensjon.

Metoder: En naturalistisk langtidsstudie ble brukt for å undersøke variasjon i VUP. VUP ble registrert på alle nye pasienter som møtte kriterier for første episode psykose (FEP) mellom 1993-1994 (pilotfase) og 1997-2010. Studien ble delt inn i TIPS1 (1997-2000; oppdagelsesteam pluss informasjonskampanjer), TIPS2 (2002-2004, kun oppdagelsesteam), TIPS2, TIPS3 (2005-2006; oppdagelsesteams pluss informasjonskampanjer) og TIPS4 (2007-2010; oppdagelsesteam pluss informasjonskampanjer, nå med fokus utvidet med rusinduserte psykoser). Alle pasienters (N=602) VUP-verdier ble inkludert i studien, uansett om pasientene ønsket å være med i en klinisk oppfølgingsstudie eller ikke. Dette ga et unikt representativt datagrunnlag. For sammenlikningen av TI-sektor med kontrollsektor ble N=281 pasienter, alder 18-65, inkludert mellom 1997 og 2000, med informert samtykke. Av disse ble 101 TI og 73 kontrollsektorpasienter undersøkt igjen etter ti år på klinisk og funksjonsmessig utfall. Til slutt ble pasienter i symptomremisjon sammenliknet med pasienter ikke i symptomremisjon på tidlig symptomstatus og behandling, og logistisk regresjon ble brukt for å identifisere variabler som kunne predikere ikke-remisjon.

Resultater: VUP-fordelingene indikerer at TI reduserte VUP ved å rekruttere flere pasienter svært tidlig. Den laveste VUP medianverdien ble registrert i TIPS1, og en tilsvarende lav verdi ble ikke oppnådd igjen før i 2009. Kortere VUP viste en generell sammenheng med informasjonskampanjer, men VUP økte da målgruppen for kampanjene i 2007 ble utvidet med rusinduserte psykoser. Sammenlikningen mellom TI og kontrollsektor viste at signifikant flere pasienter fra TI-sektor var fullt tilfrisknet etter ti år (31 vs 15%). TI mer enn fordoblet sjansene på tilfriskning (odds ratio 2.5; konfidensintervall 1.2-5.4), inklusive

stabil symptomremisjon og fulltids ordinært betalt arbeid. Dette funnet var robust på tross av at signifikant flere pasienter som hadde hatt høye symptomnivå ved tidligere målinger droppet ut i kontrollsektor. Full tilfriskning hang også sammen med nivå av negative symptomer helt i starten av behandling.

Med unntak av eksitatoriske (agitasjon m.m) symptomer, som hadde høyere verdier i TI-sektor, var det ingen forskjeller i gjennomsnittlig symptomnivå etter ti år, i motsetning til hva en fant ved ett, to og fem år.

Femtitre prosent av TI-pasienter og 48% av kontrollsektorpasienter var i symptomremisjon ved ti-års oppfølgingen. Ikke-remisjon ble predikert av varighet og nivå av positive symptomer, spesielt hallusinasjoner, i de to første årene etter behandlingsstart. Det var ingen forskjell i behandling mellom pasienter som hadde og ikke hadde vedvarende positive symptomer i disse årene.

Konklusjoner: TI forkortet VUP ved å rekruttere flere pasienter svært tidlig. Til tross for dette var VUP lang for en del av pasientene med dårlig prognose. Disse pasientene kan tenkes å ha vært motstandsdyktige mot TI-arbeidet. Det kan spekuleres at fornekting eller tvil rundt mindre iøyenfallende negative symptomer har spilt en rolle. Videre indikerer resultatene av TI bør ha et stabilt og vedvarende intenst fokus.

TI ser i et langtidsperspektiv ut til å øke sjansene for et mildere sykdomsforløp med mindre negative symptomer og bedre funksjon. Mekanismene bak dette er fremdeles ikke klare, men resultatene indikerer en sammenheng mellom timing av behandling og utfall. Symptomatisk ikke-remisjon på den andre siden viser sammenheng med tidlige positive symptomer. Det kan se ut som at negative og funksjonelle på den ene, og positive symptomer på den andre, følger ulike traseer. Siden symptomremisjon er en forutsetning for full tilfriskning indikerer disse

resultatene at en mer aktiv behandling av vedvarende positive symptomer i de første årene av behandling er nødvendig, uavhengig av om pasienter har blitt oppdaget tidlig eller ikke.

Abstract/Press release

Background: The Scandinavian early Treatment and Intervention in Psychosis Study (TIPS) engineered an early detection (ED) of psychosis programme that sought to reduce the duration of untreated psychosis (DUP) through early detection teams and extensive information campaigns. The ED programme was continued for over 13 years. A quasi-experimental study ran from 1997 through 2000, comparing an area practising ED (ED area) to an area with usual detection (NoED area). In the ED area DUP was reduced from 26 to 4.5 weeks, median value. DUP in the NoED area was 16 weeks. Patients from the ED area had significantly lower overall symptom levels at study inclusion, milder negative symptoms at one-year and milder negative and cognitive symptoms at two and five years follow-up. Little is known about long-term variation in DUP and long-term patient outcomes in ED of psychosis.

Aims: First, the objective was to track vicissitudes of DUP over an 18-year period (1993-2010) with differing ED efforts. The second objective of this study was to investigate ten-year ED-NoED differences in symptoms and recovery, which is a combination of symptomatic remission and good functional outcome. Third, factors explaining poor symptom outcome with and without ED were explored.

Methods: The DUP of all patients meeting criteria for first episode psychosis (FEP) was measured 1993-1994 (pilot phase) and from 1997 through 2010, in a naturalistic long-term study. The study was divided into TIPS1 (1997-2000; detection teams plus information campaigns), TIPS2 (2002-2004; detection teams only), TIPS3 (2005-2006; detection teams plus information campaigns) and TIPS4 (2007-2010; detection teams plus information campaigns, now also addressing substance induced psychosis). DUP values of all patients were

included (N=602), irrespective of patients' participation in the clinical follow-up study, yielding a highly representative sample. For the ten-year ED-NoED comparison, 281 (ED: 141, NoED: 140) patients aged 18-65 with a first episode of non-affective psychosis were included between 1997 and 2001. Of these, 101 ED and 73 NoED patients were followed up at 10 years and compared on symptom levels, remission and non-remission, and recovery. Finally, remitted and non-remitted patients were compared on early symptom progression, and logistic regression was applied to identify variables predicting non-remission.

Results: The distributions of DUP indicate that ED manages to reduce mid- and long-range DUP by recruiting more patients very early. However, the low median DUP that was achieved in 1997-2000 was not re-achieved until 2009. Shorter DUP was associated with the presence of information campaigns, however DUP increased when target population changed to include patients with substance-induced psychosis in 2007, though not statistically significant. In the second study, a significantly higher percentage of ED compared to NoED patients were recovered at ten years (31% vs. 15%), largely because of higher employment rates for patients in this group. This held true despite more severely ill patients dropping out of the study in the NoED area. Except for higher levels of excitative symptoms in the ED area, there were no mean symptom differences between the groups. Fifty-three per cent of ED and 48% of NoED patients were in symptomatic remission. Regardless of ED, symptomatic non-remission was predicted by positive symptoms at inclusion and persisting positive symptoms during the first year of treatment. Of individual symptoms only hallucinations were significantly predictive of ten-year non-remission. Early symptom differences were not reflected by differences in treatment.

Conclusions: First, the DUP curve as a whole has been moved towards the shorter (left) end of the continuum. However, ED seems to have failed in picking

up some of the poorer-prognosis long DUP patients. Perhaps denial and stigma, along with doubts as to the more insidious symptoms, need to be addressed more explicitly. Furthermore, it seems that ED information campaigns should have a stable target group, a stable focus and a high intensity level. Future research should further elucidate pathways to care in order to establish principal targets for information campaigns. Second, ED appears to increase the chance of milder deficit formations and superior functioning. The mechanisms by which this strategy improves the long-term prognosis of psychosis remain speculative. Nevertheless, our findings over ten years may indicate that a prognostic link exists between timing of intervention and outcome that deserves further study. Third, long-term symptomatic non-remission seems associated with early positive symptoms. It appears that functional and symptomatic development follow different, partly independent tracks, negative symptoms being more closely linked to functional outcome, while positive symptoms remain associated with symptom outcome. More assertive intervention may be needed in patients who do not respond robustly in the first year of treatment, whether or not they have been detected “early”.

List of publications (in order of appearance)

1. Hegelstad, W. Ten Velden; Larsen, TK., Auestad, B., Evensen, J.; Haahr, U.; Joa, I.; Johannesen, JO.; Langeveld, H.; Melle, I.; Opjordsmoen, S.; Rossberg, JI.; Rund, BR.; Simonsen, E.; Sundet, K.; Vaglum, P.; Friis, S.; , McGlashan, T. *Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome*. Am J Psychiatry; 2012; 169: p. 374-380.

2. Hegelstad, W. ten Velden; Larsen, TK., Auestad, B., Evensen, J.; Haahr, U.; Joa, I.; Johannesen, JO.; Langeveld, H.; Melle, I.; Opjordsmoen, S.; Rossberg, JI.; Rund, BR.; Simonsen, E.; Vaglum, P.; McGlashan, T.; Friis, S. *Early detection, early symptom progression and symptomatic remission status after ten years in a first episode of psychosis study.* Schizophr Res; 2013; 143; p. 337-343.

3. Hegelstad, W. ten Velden; Larsen, TK., Auestad, B., Evensen, J.; Haahr, U.; Joa, I.; Johannesen, JO.; Langeveld, H.; Melle, I.; Opjordsmoen, S.; Rossberg, JI.; Rund, BR.; Simonsen, E.; Vaglum, P.; McGlashan, T.; Friis, S. *Variation in Duration of Untreated Psychosis in an 18-year perspective,* Early Int in Psych; accepted.

Content

1. Background

1.1 Psychosis

Psychosis, according to the Oxford Dictionary, is defined as "a severe mental disorder in which thought and emotions are so impaired that contact is lost with external reality". Psychotic symptoms may arise without any known environmental or biological trigger, or following stress (Lataster et al.,2012), drug use (Arendt et al.,2005; McKetin et al.,2006; Satel and Edell,1991), certain medical conditions, trance states (Castillo,2003), or sleep deprivation (Boivin,2000; Gottesmann,2006). They include hallucinations, most often auditory hallucinations in the form of voice hearing, but visual, tactile, olfactory or taste hallucinations may occur. They also include thought disorganisation, to be observed as incoherent speech or disorganised behaviour, and delusions, bizarre or non-bizarre. These are all labelled positive symptoms. The more serious forms of psychoses give rise to negative symptoms, such as lack of motivation and initiative, psychomotor poverty, flat affect, apathy, and social withdrawal.

Psychotic symptoms do not occur within psychotic disorders only. They may be present within a wide range of diagnostic categories described in the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association (APA)(Association,2000), such as affective disorders, posttraumatic stress disorder (Read et al.,2005), dissociative disorders (Ross et al.,1992); borderline personality disorder (Yee et al.,2005), in schizotypal and schizoid personality disorders, and in Asperger's syndrome (Skokauskas and Gallagher,2010). Some findings even suggest that positive psychotic symptoms occur in 5-8% of the general population not presenting for treatment (van Os,2003).

Specific psychotic disorders include schizophrenia, delusional disorder, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder and psychosis not otherwise specified. Schizophrenia is the most severe form. Its point prevalence is approximately 4.5 per 1000, lifetime prevalence about 1%, and yearly incidence on average 15 per 100 000 of the population (Tandon et al.,2008). It is diagnosed on the basis of the number, severity and duration of psychotic symptoms. In schizophrenia psychotic symptoms often fluctuate in an episodic manner, with recurring psychotic episodes and intermitting periods of remission. In about 20-30% of patients, the course is chronic. Furthermore, schizophrenia is associated with heightened mortality (Ruschena et al.,1998). Rates of completed suicide have been found to range between 5 and 13%(Pompili et al.,2011). In a Danish study, 15-26% of patients had made one or more suicide attempts before their first contact with mental health care(Nordentoft et al.,2004). Loneliness and social alienation are important issues; compared to the general population, schizophrenia patients also have a 7-10 times higher risk of being single 10 years after first admission (Agerbo et al.,2004). In sum, the human cost is vast and often devastating.

1.2 A brief history of early intervention and psychosis

The concept of early intervention in psychiatry developed in the latest decennia of the 20th century within the framework of a mainly biological paradigm, tracing back to the 1910s and -20s, when psychiatry was something that was practised in mental asylums concerning very ill and deviant patients. The German psychiatrist Kraepelin strongly adhered to a medical model of mental disorders, organising clusters of symptoms into a classification of nosological disease entities. This became widely used by clinicians in the Western world. After World War II, the realisation of the impact that "stress", and trauma, could have on mental health

grew, especially in the USA. The existing psychiatric nosologies failed to capture that. Neurotic symptoms such as anxiety problems received increased interest. Intervening in these states was thought to possibly prevent more severe psychological symptoms; a precursor of today's early intervention in psychiatry. There was also a renewed interest in psychoanalytical thinking.
Mental illness came to be seen as a result of psychological conflict and environmental factors colliding (First and Wakefield,2010). In addition, sociology and anthropology gained influence because of the basic questions that rose about war and its causes and effects.

The growing influence of these scientific disciplines was also apparent within psychiatry. Social class, for instance, was through several studies established as a determinant of mental disorders (Klerman et al.,1985). The social and analytical ways of thinking were combined into a psychosocial model of mental disorder, which remained the prevailing paradigm in psychiatry until the mid-70s. The first Diagnostic and Statistical Manual for Mental Disorders DSM, published in the USA 1952, was a product of this paradigm. Psychological symptoms did not reflect disease entities, but rather fulfilled a function of disguising underlying conflict. In the field of psychosis, psychologists and psychiatrists looked for aetiological factors and explanations in adverse childhood experiences, particularly emotional experiences related to communication. Typically, psychoses were called "schizophrenic reactions", and "psychotic depressive reactions", and so forth. In the European and Scandinavian countries, however, psychiatry tended to maintain the Kraepelinian tradition, in which disease entities such as psychosis were believed to have specific biological causes. Hence, in the North American tradition at this time, mental illness was a much more unitary concept, where diagnostic groups were quantitatively, not qualitatively, different manifestations of the same, environmentally determined causes, whereas in the European tradition, different aetiologies still were thought to cause different diseases.

Because in the North American tradition boundaries between the well and the sick became diffuse, the anti-psychiatry movement gained terrain(Szasz,1974): The labelling of people as "mentally disordered" was a mechanism of societal control (Goffmann,1961; Scheff,1970), and compromised the legal and human rights of patients. Furthermore, in a model where mental disease as an entity did not exist, validity and reliability of diagnoses were vigorously disputed. As a reaction, the reliability of diagnoses was evaluated empirically (Robins and Guze,1970). To facilitate this work structured instruments to make diagnostic classifications were developed. Also, an increasing number of psychiatrists criticised anti-psychiatry, to defend their profession, which, as a result of social psychiatry and social activism, was on "the edge of extinction" according to the president of the American Psychiatric Association at that time (Wilson,1993). Furthermore, the argument was made that severely ill patients did not get the treatment they needed. This marked a return to the medical model of disease, a return that was fuelled by the growing use of medication like lithium and neuroleptics, introduced in the 1950s and 1960s. These improved the course of symptoms. During the 1970's the APA developed a new version of the DSM, which was finished in 1980. It would be a descriptive manual for the assessment of easily observable symptoms. It was important to call the listed diagnoses "disorders", "disease", "illness" or "syndromes", not only for ideological reasons listed above but also for economical reasons- insurance companies would not reimburse treatment of what was no disorder, disease, illness, or syndrome. A paradigm shift back to biology was now a fact, and the hope was that diseases with known, predominantly biological, aetiologies would with time and research replace the theory-neutral categorical and descriptive diagnoses in the DSM.

This course of history also influenced the understanding and treatment of the psychoses and the concept of early intervention. Over the decades the concept of

neurotic early symptoms as mild varieties of later severe psychopathology, as seen after World War II, joined with the biological paradigm. Early detection and intervention in psychosis was said to be "based on the conviction that current treatment modalities for schizophrenia are extracting diminishing returns because they do not address the basic neurobiological deterioration or deficit formations associated with the disorder" (McGlashan and Johannessen,1996). This notion presupposes some sort of degenerative process, with roots in the biological paradigm in psychology and psychiatry.

1.3 First episode psychosis (FEP)

While patients may experience one episode only, most do not. In a Dutch incidence study (part of the International Study of Schizophrenia (IsoS), 75% of first episode schizophrenia patients had at least one more episode by the 15-year follow-up. Of those who relapsed, 80% had more than two relapses. Hence, FEP is a predictor of future psychotic episodes (Wiersma et al., 1998). Research indicates that early illness phases and response to treatment during the first years after onset are relevant for future course (Birchwood et al.,1998; Crumlish et al.,2009). It has been hypothesized that a biologically driven deterioration operates within the window of neurodevelopment, and when this development stops, so does deterioration(McGlashan and Fenton,1993). For instance, symptomatology (Birchwood et al.,1998; Crumlish et al.,2009) shows a decline during the first 2-3 years of illness, but levels off and stabilizes, as does neuropsychological functioning (Bozikas and Andreou,2011; Rund et al.,2004). Delayed, or non-response to psychopharmacological treatment (Harrison et al.,2001; Perkins et al.,2004) resulting in more time in psychosis during the first two years of illness predict poorer outcome in terms of higher long-term symptom levels.

1.4 Course and Outcome

Most of the knowledge of outcome in psychosis stems from either chronic, treated incidence, or "first episode schizophrenia" samples, or a mixture of all these, often convenience samples from hospitals. This hampers comparability (Olesen and Mortensen,2002). These studies indicate that even though course and prognosis have improved after the introduction of antipsychotic medication (Jablensky,1997; Schwartz et al.,1993) and structured psychosocial treatments (Pilling et al.,2002), up to 80% of patients with the most severe forms of psychosis still suffer an outcome characterized by either relapsing symptoms, functional incapacity or both (Bottlender et al.,2003; Bottlender et al.,2010; Ganev et al.,1998; Harrison et al.,2001; Hopper and Wanderling,2000; Marneros et al.,1989; Modestin et al.,2003; Wiersma et al.,1998). **Table I of the appendix** shows outcomes, samples, and definitions of long-term studies (>10 years). Poor outcome is associated with male gender and young age/early age of onset (Altamura et al.,2007; Tandon et al.,2009; Wiersma et al.,1998), poor premorbid functioning (Larsen et al.,2004; Ucok et al.,2004), substance abuse(Green et al.,2004), and psychological trauma (Hodgins et al.,2009; Lysaker et al.,2009).

At least 50% of schizophrenia patients have been found to experience positive psychotic symptoms beyond 10 years after onset (Bromet et al.,2005; Stoll et al.,1993). Furthermore, approximately 15% display deficit pathology, i.e. syndromes characterized by chronic negative symptoms and poor outcome, rising to 25-30% in chronic populations (Kirkpatrick et al.,2001; Strauss et al.,2010). By the 1990's, it was considered an established fact that negative symptoms are among those that most adversely influence outcome (Keefe et al.,1987). Between 20-45% of schizophrenia patients are affected, depending on the follow-up time of the sample (Boonstra et al.,2012). They are associated with

impairments in independent living skills, social functioning, and quality of life (Alvarez-Jimenez et al.,2012; Browne et al.,2000; Kirkpatrick and Fischer,2006; Milev et al.,2005; Norman et al.,2000; Petersen et al.,2008; Ramsay et al.,2011; Schmitz et al.,2007; Turner et al.,2009). A link between negative symptoms and biological processes has been suggested. A recent meta-analysis showed that negative symptoms are linked to genetic susceptibility (Esterberg et al.,2010). Furthermore, cognitive dysfunctions (Bora et al.,2009), grey matter reductions (Bora et al.,2011), and other brain abnormalities are more common in the more severe cases of schizophrenia with negative symptoms (Ellison-Wright et al.,2008). These abnormalities seem related to total duration of illness. Few long-term studies, defined as >10 years, of FEP have been completed. Existing studies report about 60% poor outcome, with some variability in what constitutes "good outcome" (Henry et al.,2010; White et al.,2009) **(Table 1).**

1.5 Recovery

Recovery is the opposite of a poor outcome with lasting symptoms and functional impairment. It is closely linked to functional outcome. It has been of interest since Kraepelin addressed this at the beginning of the 20th century. Kraepelin was under the impression that some patients with schizophrenia recovered, while Eugene Bleuler had a much more pessimistic outlook on prognosis, stating that he had never seen a single patient becoming completely free of symptoms after an episode of schizophrenic psychosis. In 1962, a clinical study (N= "about" 200) on recovery in schizophrenia was published (Vaillant,1962), defining recovery as a combination of lack of positive and negative symptoms as well as a "return to the highest premorbid level of functioning". Fifteen per cent of patients in their sample fulfilled this criterion after a follow-up period of at least one year. One other older study (Helgason,1990) (patients recruited in 1966-67 and assessed in

Table 1. Long-term outcome in FEP studies

References	Location/study	N	Time span	Recovery/outcome definition	recovery; employment, outcome
(White et al.,2009)	Manchester, UK	N=109	10 years	*Poor mental health and no work, poor social functioning *working at time of assessment *work last year *working more than 5 of last 10 years	63% 19% 23% 44%
(Makinen et al.,2010)	Finland	N=46 FEP (1966 birth cohort)	10 years	Negative symptoms	39 %
(Henry et al.,2010)	Melbourne, Australia (EPPIC)	N=651	7 years	*GAF > 60 *Symptom remission *Social recovery: social, basic living tasks, and work, (any paid employment, or school > half time) *Remission+social recovery	42.1% 36.8% 30.5% 23.5%
(Hill et al.,2012)	Dublin, Ireland	N=123	12 years	*Remission *Independent living: *Employment (hours unspecified)	60.2% 40% 37%

1987) also reported on functional outcome. They conclude on 107 patients with schizophrenia, followed up over 20 years, that: “Over half of them never married, 32% of those who married had divorced and a similar number had lost the support of their families.”

Recovery as a concept gained momentum during the later 1980’s, and has been described as “a deeply personal, unique process of changing one’s attitudes, values, feelings, goals, skills and/or roles. It is a way of living a satisfying, hopeful, and contributing life even with limitations caused by the illness. Recovery involves the development of new meaning and purpose in one’s life as one grows beyond the catastrophic effects of mental illness"(Anthony,1993).

1.5.1 **Studies on recovery**

Recovery has been operationalized in differing ways. An overview is presented in the appendix **(table I).** In Germany, it has been assessed using the Mannheim Disability Assessment Schedule(Bottlender et al.,2010), a derivate of the WHO Disability Assessment Schedule (WHO-DAS) assessing, among others, work and social functioning last month (Jablensky et al.,1980; Janca et al.,1996). In that study, only 14% of schizophrenia patients (N=61) had “no social impairment” (Bottlender et al.,2003; Bottlender et al.,2010; Jager et al.,2004; Moller et al.,2010; Moller et al.,2010) after 15 years. A large study in the USA used a scale called Levenstein-Klein-Pollack scale (Levenstein, 1966) combined with the Strauss-Carpenter Scale(Strauss and Carpenter,1977), and defined recovery as one year of no symptoms, no admissions, no poor social functioning, living independently, and working half time or more (Harrow and Jobe,2005). About

20% of patients with schizophrenia or schizophreniform diagnoses at study inclusion, and 40% of patients with "other psychoses" including affective psychosis, fulfilled these criteria after 15 years. Out of the total group of assessed patients (N=274), 40% had had at least one period of recovery during the follow-up period. One major publication (Harrison et al.,2001) from the large, multi-site International Study of Schizophrenia (ISoS) reports recovery rates in industrialised countries of 15% after 15 years, based on the Bleuler Scale of Recovery (symptoms last month) (Bleuler,1978) and the WHO-DAS. This is in concordance with another publication from this study, looking at European countries only and using the same measurements, and finding 14% of patients recovered after 15 years (Wiersma et al.,2000). In a UK study, the Life Chart Schedule (Susser et al.,2000), measuring functioning and symptoms over the past two years, showed that 17% of a treated incidence cohort of schizophrenia patients were in "full recovery" after a mean follow-up time of 13 years (Mason et al.,1995). A more favourable outcome was found in Bulgaria, where 31% of "recent onset" (within two years prior to inclusion) schizophrenia patients at 16 years follow-up, for the past two years had had no psychotic symptoms, had held a job, had lived independently and were married or divorced (Ganev et al.,1998). Also, though using unstandardized assessments, the large Vermont-study in the USA had more favourable outcomes, as 26% (Maine) 47% (Vermont) of a chronic schizophrenia sample "worked in some capacity" after 30 years (DeSisto et al.,1995). In a sample of FEP recently studied in the UK, symptom outcome according to a "General Practitioner Questionnaire" was "poor" in 63% of cases after 10 years, while 23% had been employed (part- or full time) the last year (White et al.,2009). Another long-term FEP study rated 23.5% of patients as recovered, defined as having symptom remission and unimpaired social and vocational functioning after seven years (Henry et al.,2010). An Indian study used a recovery measure composite of "No hospitalisation last 2 years", GAF score > 80, Quality of Life Scale score > 80, 3 or higher (on a 3-5 scale) on scale for «social

functioning, independent living, education and social burden» and a «Clinical Global Impression Scale» and found that between 32% and 46% of the studied 101 schizophrenia patients fulfilled these criteria after 10 years (Shrivastava et al.,2010).

Employment is a part of most definitions of recovery. In a review, Marwaha and Johnson found that only 10-20% of patients with chronic schizophrenia, and 13-43% of first-episode of psychosis patients had any employment (Marwaha and Johnson,2004). Dickerson and colleagues found that 36% of patients hospitalized with psychotic symptoms, both affective and non-affective, had no work or school activity at all within two years of illness (Dickerson et al.,2007). The unemployment rate for FEP-patients in another study was 65% for the month prior to hospital admission (Ramsay et al.,2012).

Norway has low unemployment rates: 2.3% in 2012. The EU and USA figures for the same year are 10% (range 5% -26%) and 7%, respectively, and rising as a result of the financial crisis. In contrast, Norwegian disability pension rates are high; about 10%. In the UK, USA, Australia and the EU these rates are about 4-5%. In 2000, a Norwegian study published unemployment figures of a sample of 76 schizophrenia patients (Melle et al.,2000). Seven years after diagnosis admission to an acute unit, 94% had no employment and had a disability pension or other illness benefit. Similarly, a large register-based (N=4604) study reported "no income from employment" in 93% of schizophrenia patients (Helle and Gråwe,2007). In a FEP study using TIPS data, 59% at start of treatment and 62% at 2-year follow-up did not have employment-based income (Tandberg et al.,2011). This indicates that about 60% of FEP patients receive some form of disability pension already after two years, and this figure seems to increase during longer-term follow-up (Melle et al.,2000). Hence, one may conclude that rates of unemployment are very high among patients with psychosis, especially

compared to the general population, also in Norway where unemployment seems low.

1.6 Criteria of recovery

In most studies, recovery incorporates some version of symptomatic remission. Outcome research has been hampered by divergent remission criteria, and it has been shown how these differences yield different remission rates. One study tested this explicitly, using four different sets of remission criteria: With and without negative symptoms in addition to positive symptoms, and time spans of 3 and 6 months of stable remission. Using positive symptoms only and 3 months' stable remission, a rate of 94% was achieved in a sample of 141 FEP patients. For 6 months, this rate was 84%. Including negative symptoms as well, remission rates dropped to 70% and 56% for 3 and 6 months, respectively(Cassidy et al.,2010). Furthermore, not only symptoms included in criteria vary, so do assessment instruments used: GAF (Ganev et al.,1998; Harrison et al.,2001; Henry et al.,2010; Mason et al.,1995), PANSS (Moller,2002); SANS (Mason et al.,1996; Moller,2002), SADS (Marengo et al.,2000), and PSE (Ganev et al.,1998; Mason et al.,1996; Wiersma et al.,2000) being among the ones most frequently used. Furthermore, samples studied have been heterogeneous as well, consisting of a mix of chronic (DeSisto et al.,1995; Modestin et al.,2003), "recent" or first onset schizophrenia (Bottlender et al.,2003; Ganev et al.,1998; Harrison et al.,2001; Hopper and Wanderling,2000; Kua et al.,2003; Shrivastava et al.,2010), FEP (Henry et al.,2010; Makinen et al.,2010; White et al.,2009), non-affective only (Harrow et al.,2005; Moller,2002; Stephens et al.,1997; Wiersma et al.,1998; Wiersma et al.,2000); or mixed affective and non-affective (Marneros et al.,1992; Marneros et al.,1989; Moller et al.,2010; Racenstein et al.,2002)samples. Long-term follow-up in FEP, defined as > 10 years, is rare, only three studies are

reported in the literature (Hill et al.,2012; Makinen et al.,2010; White et al.,2009).

As an answer to the issues concerning lack of comparability and clarity of remission criteria an international work group led by Nancy Andreasen and supported by the WHO developed a set of criteria. The aim was that this be implemented in research internationally. Besides scientific usefulness, the workgroup also aimed for clinical improvement. They argued that the use of standardised criteria will "facilitate comparisons across treatments and populations, and provide the basis for more clearly formulated goals and expectations for patients, caregivers and families" (Andreasen et al.,2005). Furthermore, recognising the importance of negative symptoms on relation to outcome, the criteria include several negative items from the PANSS. The criteria are as follows: No score of 4 (moderate) or higher for the past 6 months on any of the following PANSS-items: P1 delusions, P2 disorganized thought, P3 hallucinatory behaviour, N1 Affective flattening, N4 Passive social withdrawal, N6 lack of spontaneity, G5 bizarre posture, or G9 unusual thought content (Andreasen et al.,2005). As such, outcome research has been provided with an assessment tool, a standard time criterion, and a fixed set of symptoms to be scored with a fixed cut-off score. This is a major improvement for the research field. However, the work group also pointed to the need of functional measures of outcome as well, to make a relevant and reliable measure of recovery, as a good outcome takes more than symptom control alone.

2. Duration of untreated psychosis and prevention strategies

2.1 Duration of Untreated Psychosis (DUP)

DUP consists of the emergence of psychotic symptoms and the start of treatment, and is usually defined as the time in weeks or months between these two. In 1962, a study was published introducing a concept called "length of onset of six months or less". It was associated with good outcome (Vaillant,1962). During the late 1970's, the 80's and the early 90's, several studies showed that a longer duration of illness before commencement of treatment was associated with poorer outcome (Crow et al.,1986; Helgason,1990; Lo and Lo,1977; Loebel et al.,1992; Moscarelli,1994; Rabiner et al.,1986). The idea emerged that perhaps intervening earlier could prevent severe psychopathology and chronicity from developing. This was later warranted by two meta-analyses on DUP and outcome, confirming the association between the two (Marshall et al.,2005; Perkins et al.,2005). Both have indicated that DUP is more strongly associated with level of negative, than positive symptoms. A recent meta-analysis showed the same (Boonstra et al.,2012). The authors argue that this is consistent with the notion that a biological deterioration, expressed as negative symptoms, may be ameliorated by early detection and treatment.

2.2 International DUP findings

The earliest studies discussing and explicitly reporting on DUP stem from the late 1970s. One of the first studies was conducted in China (Lo and Lo,1977),

poignantly as DUP has been a focus mostly in the Western world. Definitions and operationalizations differ between studies. In some studies, start of treatment equals time of first hospitalisation, in others it is more stringently defined in terms of medication and psychotherapy. In table II provided in the appendix, several known lengths of DUP are presented along with location, study, definition, and sample size (N). Using the search words *duration of untreated psychosis, treatment delay, schizophrenia, psychosis, timing of treatment,* and *schizophrenia onset* on PubMed, I found 42 studies reporting "natural" DUP, that is, DUP values unaffected by interventions meant to shorten it. Samples consisted of patients with diagnoses in the schizophrenia-spectrum: schizophrenia, schizophreniform disorder, or schizoaffective disorder if not otherwise reported, and ranged in size from 42 (Amminger et al.,2002) to 998 (Bottlender et al.,2000). Five of the 42 studies applied a standardised interview specifically addressing the timing of symptom onset; four used the IRAOS (Addington et al.,2004; Hafner et al.,1993; Ropcke and Eggers,2005; Townsend et al.,2002), and one used the SOS (Perkins et al.,2004). In the studies where no standardised instrument was used, DUP was estimated on the basis of all sources of information available, i.e. interviews with patients, interviews with relatives, partners of caregivers, and medical records. Mean values ranged from 14.5 to 130.5 weeks (excepting one study including patients in the pre-neuroleptic era and investigating extremely long DUPs (Scully et al.,1997)), and median values from 6 to 47 weeks; thus, the variation is substantial. Eastern countries (India, Singapore) in these studies tend on face value to have longer median DUPs, however, a clear geographical pattern is difficult to detect as both the USA and Germany also have samples with very long DUPs (Hafner et al.,1992; Ho et al.,2000; Rabiner et al.,1986). Close to Norway, the OPUS trial reported a median DUP of 45.5 weeks in a sample receiving specialised early psychosis treatment, and 53 weeks in a treatment as usual group (Petersen et al.,2005). The largest group of DUP-values lie between 10 and 30 weeks, and the shortest are 6 weeks

(Australia) (McGorry et al.,1996)and about 8 weeks median (UK, USA, Finland, Spain, Canada) (Beiser et al.,1993; Kalla et al.,2002; Perkins et al.,2004; White et al.,2009). The longest is found in India, with a median value of 47 weeks in one study and a median to be found between 6 and 15 years (median is not reported directly) in another (Shrivastava et al.,2010).

2.3 Programmes to reduce DUP: Early Detection

Early intervention can be viewed as having two distinguishable elements: Early, phase-specific treatment and early detection (Marshall and Rathbone,2011). Several treatment programmes around the world have specialised in the early phase-specific treatment, generally with optimistic results (Bertelsen et al.,2008; Craig et al.,2004; Jackson et al.,2008; Lenior et al.,2001). They are not to be confused with early detection programmes. These were recently reviewed by Lloyd-Evans et.al (Lloyd-Evans et al.,2011). They found eight programmes that fit the defined criteria of being "designed to enhance the identification and prompt treatment of people with first-episode psychosis": The BiRmingham Early Detection In untREated psyChosis Trial (REDIRECT) (Lester et al.,2009) and The Lambeth Early Onset in psychosis trial (LEO) (Power et al.,2007) in the United Kingdom, DETECT (Renwick et al.,2008) in Ireland, Early Psychosis Prevention and Intervention Centre (EPPIC) 1 and 2 (McGorry et al.,1996) (Yung et al.,2003) (Krstev et al.,2004) in Australia, Early Psychosis Intervention Programme (EPIP) in Singapore (Chong et al.,2005), Early Case Identification Program (ECIP) (Malla et al.,2005) in Canada, and the early Treatment and Intervention in PSychosis (TIPS) in Norway (Johannessen et al.,2001), from which this dissertation stems. REDIRECT, LEO and DETECT all provided information to general practitioners (GPs) only. EPPIC 1 undertook "unspecific networking and community education" and organised an early intervention team to help detect cases in the health care

system. EPPIC 2 was more extensive; in this project there were mobile assessment teams, educational sessions in schools, and information for and interaction with GPs. This approach Lloyd-Evans called “multi-focus”. The same multi-focus approach was used in ECIP and EPIP, as well as TIPS. In **table 2**, results of these programmes are displayed.

In REDIRECT, there was, despite of no significant reduction of overall DUP, a significant decrease of delay in time from seeking help to reaching early interventions services, or, health system delays. The same tendency was found in LEO CAT. Both this and REDIRECT were programmes for GP’s mainly. EPPIC 2 in Australia identified some patients with an extremely long DUP (>1000 days) and managed to reduce mid-range DUP. In ECIP, an increase of patients with a relatively short DUP (<12 weeks) could be observed, along with an increase of patients with a DUP > 1 year, as well. EPIP and TIPS were the most comprehensive programmes, and the ones yielding the most favourable results. In sum, reviewing the literature reveals variation between content and intensity of programmes, length of programmes, sample sizes, definitions and assessments of DUP, and DUP values. However, some factors seem to influence DUP across studies and countries.

Table 2. DUP-reduction programmes, mean and median DUP.

Programme /duration	DUP definition	N	Pre- or control DUP	Post- or experimental DUP	Statistical significance
LEO United Kingdom 27 months 2003-2005 Cluster randomized trial(Power et al.,2007)	"The time from the transition to psychosis' (unremitting psychotic symptoms for 1 week) to the commencement on antipsychotic medication (greater than 50% treatment adherence for a minimum of 1 month).	113	Mean 98.4 weeks (SD 230) Median: **not reported**	Mean: 50.2 weeks (SD147.7) Median: **10.1** weeks Range: 0 weeks – 24 years	N.S.
REDIRECT United Kingdom 30 months 2003-2006 Stratified cluster randomized trial(Lester et al.,2009)	"The time interval between the onset of psychotic symptoms and the initiation of treatment with neuroleptic medication, and calculated according to a stringent protocol adapted from criteria developed by Larsen *et al*." (Use of Beiser interview)	83	Mean: 232.2 days (SD 290.0) Median: 71.0 days (approx. **10** weeks)	Mean: 247.1 days (SD 454.2) Median: 56.6 days (approx. **8** weeks)	N.S.
EPPIC1 Australia 8 months 1993 Pre- post matched control quasi-experimental design (McGorry et al.,1996)/ Parallel comparison group (Yung et al.,2003)	"Time from onset of psychosis to hospital admission"	102 /53	Mean: 236.6 days (SD 702.2) Median: 30 days (approx. **4** weeks) Mean: 469 days (SD 953) Median: 92 days (approx. **13** weeks)	Mean: 191.4 days (SD 483.6) Median: 52 days (approx. **7** weeks)	N.S.
EPPIC2 Australia 12 months 1996-1997 Quasi-experimental parallel design(Krstev et al.,2004)	"The length of time between the onset of psychosis and the commencement of treatment."	98	Mean: 254.4 days (SD 379.7) Median: 104.5 days (approx. **15** weeks)	Mean: 313.8 (SD 558.6) Median: 59 days (approx. **8** weeks)	N.S.
ECIP Canada (Malla et al.,2005) 26 months	"The period between the time of onset of psychotic symptoms contiguous with the	188	Median: **21.9** weeks	Median: **24.3** weeks)	N.S.

2000-2002 Quasi-experimental historical control design	presenting episode, plus any previous episodes of psychotic symptoms, to the time of adequate treatment with antipsychotics." (Used IRAOS)				
EPIP Singapore 24 months 2001-2003(Chong et al.,2005)	"The time between the onset of psychotic symptoms (i.e. hallucinations, delusions, and/or thought disorder or disorganized behaviour) and the time when a definitive diagnosis and treatment were established."	384	Mean: 32 months (SD59.3) Median: 12 months (approx. **52** weeks) Range: 0.1-336 months	Mean: 13.3 months (SD 26) Median: 4 months (approx. **17** weeks) Range: 0- 240 months	p < .002
TIPS Norway 48 months 1997-2000 Quasi-experimental design with historical and parallel control (Melle et al.,2004)	"Time from score of 4 or higher on at least one PANSS positive subscale item, throughout the day for several days or several days a week to initiation of adequate treatment (defined)."	43/ 281	Mean: 114.2 weeks (SD 173.6) Median: **26** weeks Median: **16** weeks Range: 0-966 weeks	Median: **5** weeks Range: 0-1196 weeks	p <.003
[1]Where possible, median durations of DUP are reported in weeks and printed in bold, for readability and enhancement of a quick overview. Range and standard deviations are only reported when provided in the original paper.					

2.4 Factors influencing DUP

A long DUP indicates treatment delay, and several factors contributing have been suggested from study findings. A lack of insight into need for treatment on the hand of the patient; attitudes of families towards symptoms and mental health care; lack of skills recognising psychosis on the hand of health care both specialist and general, and social withdrawal and a poor social network have been reported in the TIPS-study of which this dissertation is part(Larsen et al.,1996).

In later years, the issue of delays in the so-called “pathways to care” have been studied increasingly intensively and systematically. A qualitative study of pathways to care in African American families found four main themes delaying help-seeking: (i) society's beliefs about mental illnesses; (ii) families' beliefs about mental illnesses; (iii) fear of the label of a mental illness; and (iv) a raised threshold for the initiation of treatment (Franz et al.,2010). It seems from other studies that the same mechanisms operate in ”white” cultures (Tanskanen et al.,2011). Perceived stigma about psychosis appears to play a role both regarding beliefs both about symptoms and mental health care. Sufferers may be afraid that they are ”crazy”, that they will be rejected by their peers, and avoid a feared confrontation with health care. Also, mental health care carries the stigma of ”injections and sections” (i.e. complusory detain), and patients being ”put away” for a long time causing hesitancy in seeking treatment. Families are likely to attribute positive symptoms and behavioural disturbances to ”adolescent rebellion” and to not recognise negative symptoms(Bergner et al.,2008).

Furthermore, poor premorbid adjustment and insidious onset also seem associated with long DUP. An obvious decline in functioning prompts help-seeking much more than a more trait-like failure to meet adjustment standards.

However, several studies point to a delayed response from health care also contributing to long DUP. O'Callaghan et.al found that there was an even split between "help-seeking delays" and "health system delays" (O'Callaghan et al.,2010). Compton et al neatly sum up previous findings regarding help-seeking delays: Level of family involvement in help-seeking, absence of family history of psychosis, lower levels of awareness and knowledge of mental illness, a tendency towards denial of mental illness as existing, a lower ability of tolerance and coping, and poorer family strengths all potentially may obstruct the pathways to care (Compton et al.,2004). On the side of health-system delays, a "wait and see"-attitude presented by a GP may delay treatment (Tanskanen et al.,2011). One study found an average of three first line health care consultations before first contact with mental health care (Steel et al.,2006). But then, unfortunately, reaching mental health care is also no guarantee for quick help. In a recent study by Marshall et al., it was concluded that receiving treatment in youth and adolescent mental health care was associated with long DUP (Marshall, personal communication, October 2012). Anderson et al present a review of 30 studies (Anderson et al.,2010) into (among other factors) health system delays. They found some differences between countries. In Europe and Canada, a first contact with a non-physician seemed to delay treatment for psychosis. Furthermore, private psychiatrists and psychologist were among the worst "treatment-delayers" both in Europe, Canada, and China. In the USA, however, general practitioners tended to postpone referrals or start of anti-psychotic treatments. In Singapore, it turned out a patient might as well go to a "healer" as to a health professional; treatment delays were equal- and substantial. Schaffner et al conclude that: "Since negative factors in pathways-to-care involve features on all relevant levels (patient, social environment and health-care system), an optimisation of pathways-to-care will require the integration of services and continuous awareness programmes targeting the general population and mental health-care professionals." (Schaffner et al.,2012).

In sum, the following factors prolonging DUP have been suggested: Lack of knowledge, stigma, social withdrawal, poor social network, poor premorbid functioning, and insidious onset, and delayed health system response. Finally, a recent paper presents data on DUP over time, indicating temporal stability (Jackson et al.,2008).

2.5 Prevention strategies in psychosis

2.5.1 **Primary prevention**

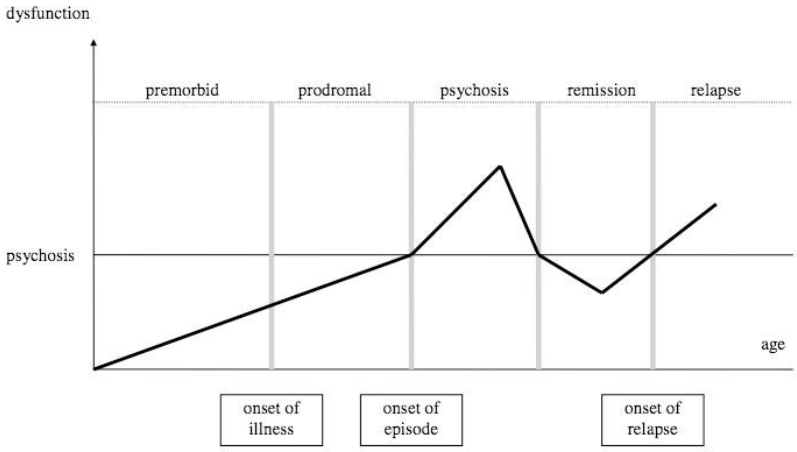
Primary prevention of any disease or illness (disease meaning organic dysfunction and illness referring to subjective complaint) is aimed at reducing incidence by eliminating risk. Despite some clues as to the biological and environmental factors contributing to psychosis, present time understanding of psychosis risk factors does not yet warrant primary prevention. Proposed biological factors so far include maternal influenza during pregnancy (Mednick et al.,1988), advanced parental age (Matheson et al.,2011), obstetric complications (Cannon et al.,2002), aberrant neurodevelopmental processes during puberty (McGlashan and Fenton,1993) resulting in diminished neural connectivity and total volume of grey matter in the brain (Cahn et al.,2002; Cahn et al.,2002; DeLisi,1999; Ellison-Wright and Bullmore,2009; Lim et al.,1996; Pantelis et al.,2003), and ventricular enlargement(Bora et al.,2011; Pantelis et al.,2005; Shenton et al.,2001; Sun et al.,2009; Ward et al.,1996; Woodruff et al.,1995). Environmental factors include living in dense urban environments (Lewis et al.,1992; Pedersen and Mortensen,2001; Spauwen and Van Os,2006; Vassos et al.,2012)migration (Cantor-Graae and Selten,2005), migration and belonging to a minority group (Veling et al.,2011), substance abuse (Callaghan et al.,2012),

psychological trauma (Schafer and Fisher,2011) or "early adversity" (Lataster et al.,2012). A stress-reactivity as a pathway to psychosis has been postulated (Myin-Germeys and van Os,2007). However, none of factors above have the specificity needed for the primary prevention of psychosis.

2.5.2 **Secondary prevention**

Secondary prevention is aimed at reducing prevalence by preventing chronicity. Early detection and intervention in psychosis is in part a form of secondary prevention, which is best understood when viewed within the framework of any disease, or illness, developing in stages.

Figure 1: The phases of development of psychosis (Larsen et al.,1998)



First, there is a premorbid phase (**figure 1)**. Functional deterioration expressed as deteriorating premorbid functioning in this phase is associated with poor outcome, and thus is probably related to some illness process already at play.

Second, there is illness onset, marked by the emergence of non-specific psychological problems and psychiatric signs and symptoms. In psychosis, this phase is often labelled “the prodromal phase”. These two phases would be the targets for primary prevention. Third comes the onset of psychotic symptoms. This phase is the target of secondary prevention and is aimed at providing treatment as effectively and early as possible, to arrest a disease process and negative consequences for remission and recovery.

2.5.3 **Tertiary prevention**

Subsequent phases concern outcome in terms of permanent damage and functional handicaps. Preventive efforts here are aimed at harm reduction and are called tertiary prevention, and are not the focus of this study.

2.5.4 **Universal, selective, and indicated prevention**

How secondary prevention may be achieved can be described within another conceptual framework. This framework classifies preventive approaches by target population. They are as follows: 1) the general population: Universal prevention, 2) at-risk population: Selective prevention, and 3) populations with minimal levels of symptoms: Indicated prevention (Gordon,1987). In universal prevention, a whole population is offered information and skills needed to prevent a certain disease or illness. In selective prevention, populations whose risk is elevated are addressed, on the basis of known risk factors involving, for instance, age, gender, or environment. Indicated prevention involves screening for early signs of disease or illness.

2.6 Reducing DUP: Combining different levels of prevention

Early detection of psychosis could be viewed combining universal, selective as well as indicated prevention on the one and secondary prevention on the other hand. Information about psychosis, meant to prompt quick help seeking in the general population, is a universal approach. Information provided to senior high school and college students and teachers is selective prevention, because it is aimed at a certain population based on age, a choice in turn based on the fact that psychosis incidence peaks at this age. Assessing signs and symptoms, and relaying treatment, at an earlier time than he- or herself would have sought help is indicated prevention.

3. Objectives, hypotheses and methods

3.1 Objectives and research questions

The early Treatment and Intervention in PSychosis (TIPS) study applies an Early Detection (ED) programme to reduce DUP and study effects on patient outcomes. The ED-programme, consisting of early detection teams and extensive information campaigns, was first active in the time period of 1997-2000. DUP was reduced from 26 to 4.5 weeks median. It conferred advantages for negative, cognitive and depressive symptoms at 1, 2 and 5 years follow-up. The programme was continued beyond the initial project in modified forms for over 13 years. A two-year period without information campaigns led to an increase of DUP (Joa et al.,2008). Longitudinal effects of the programme, on DUP and on patient outcomes, are however still unknown. In this study, the vicissitudes of DUP were tracked over a total of 18 years (1993-2010) with differing ED efforts. Second, differences in symptom levels and recovery at 10 years between an area with (ED area), and an area without ED (NoED area) are investigated. Recovery is a central concept because of its real-life relevance and human and societal benefits. Results may clarify to what extent ED can decrease chances of poor long-term outcome. Third, notwithstanding a possible ED-effect, there will be a need for enhanced knowledge of specific patient groups at risk for poor symptom outcome even within an ED-programme, as well as a need for knowledge of specific targets for early treatment after having detected patients early. Such knowledge may also help improve long- term outcome.

3.2 Hypotheses

- DUP remains at a stable low level during periods with full ED-programme
- DUP is associated with information campaigns
- ED symptom advantages from inclusion, one, two, and five year follow-up are maintained at the ten-year follow-up
- The ED-area has higher rates of recovery at ten-year follow-up
- Ten-year non-remission is predicted by:

    a. Poorer premorbid function
    b. Longer DUP
    c. Higher symptom levels at inclusion
    d. Longer time in psychosis during initial years of treatment

In addition, single symptoms were investigated for significant predictive value of poor outcome, and differences in treatment contributing to duration of psychosis after study inclusion in the ED and NoED-area examined.

3.3 Methods

3.3.1 **Design**

Longitudinal DUP study

To investigate DUP over time, a naturalistic long-term design over 18 years was applied, studying the ED area only. Information campaigns were introduced (TIPS1), terminated (TIPS2) and re-introduced (TIPS3 and TIPS4) during the study period. Except for 1993-1994 (pilot phase), detection teams were operational throughout the whole study. To facilitate comparability, all study phases were divided into equal two-year periods, except TIPS2, which started in

2002 and stretched into the first six months of 2004, adding up to 2,5 years.

Ten-year ED-NoED comparison

Investigating ED-NoED outcome differences, we used a quasi-experimental design. Four Scandinavian health care sectors participated. Two sectors in Rogaland County, Norway, made up the ED area (population approximately 370 000). Ullevaal Health Care Sector in Oslo County, Norway, and Roskilde County, Denmark, the NoED area (combined population approximately 295 000). The areas were similar in terms of sociodemographical characteristics (urbanicity, mean educational and income level) and opportunities for employment (Melle et al.,2008). In all sites health care services were catchment area based and publicly funded. The Regional Committee for Research Ethics Health Region East, Norway (#1.2007.2177), the Regional Committee for Science Ethics Region Zealand, Denmark (#1-01-83-0002-07), and the Regional Committee for Research Ethics Health Region West, Norway (#S-08010b) approved this study.

Ten-year prediction of non-remission

For the identification of patient characteristics associated with high risk of poor outcome in terms of non-remission in spite of ED, a naturalistic prospective design was employed. The sample studied was identical with the ED-NoED comparison sample. ED was investigated as one of other possible predictive factors.

3.3.2 **Participants**

The sample for the longitudinal DUP-study was recruited in the ED-area only (N=602). Because no clinical data except DUP and diagnostic category were

collected, it included patients that did not give informed consent to participate in the comparison study. TIPS4 marked a transition from excluding to including substance-induced psychosis. This implied a slight expansion of focus in the information campaigns. However, the patients with a diagnosis of substance-induced psychosis were not included in the data presented here, in order to secure comparability across time periods.

Table 3 outlines study periods TIPS1 through TIPS4, samples sizes, and estimates of treated incidence per 10 000 for the DUP study.

Table 3. Sample sizes and treated incidence, pilot phase through TIPS4.

Phase	Years	N	Yearly treated incidence, mean pr.10 000	Early detection effort
Pilot phase	1993-1994	44	-	None
TIPS1	1997-1998	86	1.9	Information campaigns plus detection team
TIPS1	1999-2000	60	1.3	Information campaigns plus detection team
TIPS2	2002- june2004	115	1.9	Detection team only
TIPS3	2005-2006	95	1.9	Information campaigns plus detection team
TIPS4	2007-2008	108	2.1	Information campaigns plus detection team; now including substance induced psychosis in campaigns
TIPS4	2009-2010	94	1.8	Information campaigns plus detection team

The sample for the ten-year ED –NoED comparison (N=281) was recruited from 1997 through 2000. The inclusion criteria were first episode schizophrenia, schizophreniform disorder or schizoaffective disorder, delusional disorder, mood disorder with mood incongruent psychotic features, brief psychotic disorder or psychosis NOS; living in one of the participating sites, being of age 18-65; and perform intellectually within the normal range of functioning according to a WAIS-R based estimate (IQ estimate >70). Participants must be actively psychotic, as measured by a PANSS score of 4 (moderate) or more on at least one of positive subscale items P1 delusions, P3 hallucinatory behaviour, P5 grandiosity, P6 suspiciousness, or G9 unusual thought content for at least 7 days; not having received previous adequate treatment for psychosis (defined as antipsychotic medication of > 3,5 haloperidol equivalents for > 12 weeks or until remission of the psychotic symptoms). They could have no neurological or endocrine disorders with relationship to the psychosis; no contraindications to antipsychotic medication and had to understand and speak a Scandinavian language. All study participants in the quasi-experimental ED-NoED comparison study gave informed consent. Of eligible participants, 23% refused. Those who refused participation had a longer DUP (32 vs. 10 weeks; $p < .00$), and were slightly older (30.4 vs. 28.1 years; $p= .05$). There was no significant difference in number of refusers or their DUP between the ED and NoED areas. This minimized the risk of biased comparison. An original sample of 281 (141 ED, 140 NoED) patients entered the study.

T**able 4** shows the characteristics at inclusion of patients with and without 10-year follow-up. **Figure 2** provides the number of subjects lost, dead, or followed-up at 1, 2, 5, and 10 years.

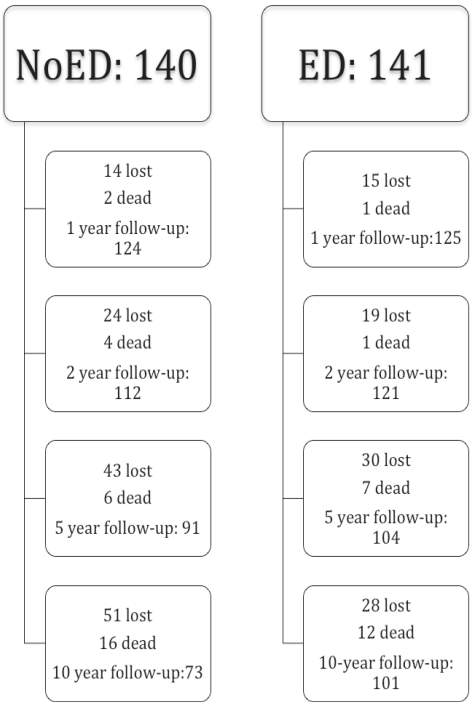
Table 4. Characteristics at inclusion of patients with and without 10-year follow-up

	NoED				ED			
Measure	Follow-up at 10 years (N=73)		No follow-up at 10 years (N=67)		Follow-up at 10 years (N=101)		No follow-up at 10 years (N=40)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	31.2	10.3	30.9	10.7	26.3	7.8	25.8	7.3
GAF Symptom	27.1	7.6	27.1	6.1	30.5	6.3	32.1	6.5
GAF Function	29.1	10.6	28.4	8.8	33.3	10.3	34.5	9.2
PANSS components								
Positive	16.3	3.8	16.4	4.4	14.4	4.4	14.2	3.7
Negative	21.9	8.9	22.6	10.6	18.9	7.1	18.0	6.3
Cognitive	7.9	3.3	7.9	3.3	6.8	3.3	6.4	2.8
Depressive	13.3	4.2	13.5	4.1	11.0	3.7	11.1	3.8
Excitative	10.6	4.9	11.1	4.8	8.7	3.9	8.6	3.1
	N	%	N	%	N	%	N	%
Gender (male)*	41	56	38	56	56	55	31	77
Alcohol abuse	9	12	15	22	13	13	8	20
Drug abuse	9	12	15	22	30	30	11	28
Core schizophrenia	41	56	42	63	65	64	27	68
	Median	Range	Median	Range	Median	Range	Median	Range
DUP**	13	0-520	22	0-966	4	0-416	18	0-1196

ED followed up group < ED no follow-up group, p <0.05
ED followed up group < ED no follow-up group, p <0.01

Between patients followed up at 10 years and patients lost to follow-up, there were no differences at inclusion in age or GAF, or on diagnostic distribution or substance abuse. In the ED area, there were fewer males in the followed-up group than in the group lost to 10-year follow-up (odds ratio: .4; 95% CI: .2-.8; p= .026), and patients lost to follow-up in both areas (unable to trace or get in contact with) had a significantly longer median duration of untreated psychosis (p= .006). Twelve patients in the ED and 16 in the NoED area had died. These were included in the "lost" group as there were no significant differences at inclusion on any of the variables between dead patients and patients surviving but lost to follow-up.

Figure 2. Overview of patients through ED- NoED study.



3.4 The Early Detection intervention

3.4.1 **The TIPS information campaigns**

The TIPS information campaigns were aimed at reducing DUP through raising awareness about signs and symptoms of psychosis, improving help-seeking behaviour of the general population, and improving referral to specialist treatment by GPs through enhancing knowledge about psychosis. How to contact the TIPS detection teams was an important part of all campaigns. Thus, the information campaigns had two main elements: examples of psychotic symptoms, and the phone number of the Detection Team. For instance: "If you are worried because someone you know hears voices, acts strangely, or seems confused, call TIPS at 51515959". The simple telephone number was chosen deliberately. But also negative symptoms were addressed in the campaigns, so that the detection team themselves could assess whether there were signs of psychosis: "If someone you know suddenly turns silent…they usually have something to say". Newspaper advertisements, intensively used, have been the most important message carrier. In addition there were brochures, posters, infomercials at cinema and on local TV and radio stations. Some examples can be viewed in **figure 3.**

Figure 3: Example of postcard logos, bus advertisement and information poster.

A web page was designed primarily as a service to health professionals and as an information base about the project. In addition to this, 80% (N = 300) of the county's GPs underwent an educational programme (4 hours) about psychosis. In 1997, the slogan: ''Seek help as early as possible and you have the best chance to recover.'' In January 1997, a brochure was distributed to all households in the county. This contained a presentation of all the topics from the advertisements, with emphasis on symptoms, available treatment, and the importance of seeking help at an early stage. A small brochure, the size of a business card, was

distributed to GPs, health workers, schools, and other places where it was natural to hand them out. In the autumn of 1997, we launched a school campaign. The main objective of this campaign was to provide knowledge about psychosis to teachers in the high schools. This has mainly been done through courses and lectures supported with advertisements and other material. The county's 45 high schools (approximately 1000 teachers) have all been visited on an annual basis and offered an educational programme consisting of lectures and videos. A brochure and posters were made for distribution to schools. The brochure contained a list of symptoms and comparison of warning signs to passing problems typical for adolescence. Other public relation strategies such as free postcards in restaurants, flyers, car stickers, t-shirts, and other brochures were made available to all thinkable audience. Social workers, local community psychiatric nurses, and GPs were all offered a yearly seminar, either in their own locations or at the hospital with focus on early intervention and information about the project status.

All in all, the programme was what Lloyd-Evans et al in their review called "multi-focal" (Lloyd-Evans et al.,2011) in that they were designed for multiple target audiences: the general population, schools –both teachers, social workers, and students- GPs and other health professionals in primary and community health care.

TIPS information campaigns have gone through several developmental phases. **Table 5** displays the campaigns as they have been used through these phases. All along a professional public relations company has aided in designing them. The information campaigns cost one million NOK (133 000 EUR) per year, from 1997-2000.

In addition to this specific TIPS programme, the annual Schizophrenia Days organised in Stavanger, Norway since 1989 should be mentioned. This conference has become the largest conference on mental health in Scandinavia and offers free lectures about mental health issues open to the general public. Information about TIPS and early detection of psychosis is amply available at these venues. They also work towards a de-stigmatisation of mental illness and mental health care, something that could contribute to a lower threshold towards seeking help. GPs are also invited to a seminar on these issues at the conference. GPs and other health care professionals were reached mainly through education programmes including a 3-4 hour training seminar. Along the same lines, trainings were provided for mental health care professionals. Schools were mainly reached by providing lessons for students and trainings for teachers and other personnel. Each year, high school graduate students are invited to a separate seminar at the Schizophrenia Days, as well. Nearly 2000 students participate.

Table 5. Content of information campaign across TIPS1 through TIPS4				
	TIPS 1	TIP S2	TIPS 3	TIPS 4
Educational programme for GPs about psychosis, early warning signs, and detection team	x		x	x
Distribution to GPs of a checklist for symptoms based on the DSM prodromal symptoms and a rating manual for core PANSS symptoms			x	x
Twice yearly news letter to GPs	x	x	x	x
Full-page advertisements in the largest newspapers in Norway (December 1996 and January 1997).	x			
7 yearly full-page local newspaper advertisements	x			
4 yearly full-page local newspaper advertisements			x	x
Two 12-page brochures about psychosis, early warning signs, and the TIPS project distributed to all households	x			
Frequent (approximately weekly) smaller newspaper advertisements	x	x	x	x
Active use of website (tips-info.com); Facebook page, youtube (film), Twitter			x	x
Flash-advertisements on the local newspapers' internet editions			x	x
Educational programmes for high school teachers and students (courses, lectures including a CD with 300 slides on the subject to choose from, and a textbook, information material)	x		x	x
Two local buses carrying large advertisements covering the back of the bus				x
Free postcards and small brochures with information, distributed at meeting places for young people, such as schools, university, cafés, restaurants, bus stations, etc.	x		x	x
Films and audio recorded advertisements for local cinemas, radio and television (some in collaboration with one of the country's most popular comedians)	x		x	x
Flyers, car-stickers, coffee mugs, pens and post-its distributed to all relevant parties	x	x	x	x
Brochures, newspaper ads, and education about substance abuse and psychosis				x

3.4.2 **Detection teams**

Detection Teams (one in each of the two sectors making up the ED area) consisted of three psychiatric nurses with additional training in screening for and assessment of psychosis. It also consisted of a clinical psychologist and two psychiatric residents carrying out further assessments and diagnostics. All cases were discussed within the team every week. The team was available by telephone every workday between 8am and 3pm, and the phone was open to all sources, including health professionals, social services, teachers, and the general public. Outside office hours there was a voicemail service ensuring that callers would be contacted on the following workday. The teams performed a telephone screening for psychosis for the person in question. In case of a positive screen, appointments were made and assessment by the PANSS carried out within 24 hours, or the next workday in case of weekend or holiday.

The teams' phone numbers were assertively advertised in the information campaign. If the assessment concluded with the presence of psychosis, a psychologist or psychiatrist within the TIPS team conducted a clinical interview for diagnostic purposes. Finally, it is important to note that no referral was needed to these teams, and they could refer to specialist treatments where needed, directly. This is important because, as Lloyd-Evans et al conclude in their review, service configuration seems to be necessary besides information, when aiming to reduce DUP. Persons with psychosis-like symptoms seeking help from the specialized psychiatric services underwent screening by the study's assessment team (36/100 000 per year). Costs of information campaigns plus detection teams were about 2 million NOK per year, covering a population of about 400 000.

3.4.3 **Treatment protocol**

To minimise differences in treatment influencing results, patients from both areas were treated according to a 2-year standard treatment protocol. It included antipsychotic medication, supportive psychotherapy twice weekly for at least two years, and multi-family psycho-education meetings every fortnight for two years. After some initial adaptations (Opjordsmoen et al.,2009) the medication protocol was as follows:

1st choice: Olanzapine, starting dose 10 mg, maximum dose 20 mg. If non-response, [defined as a persisting score of 4 (moderate) or more on any of the Positive and Negative Syndrome Scale (PANSS) (Kay et al.,1987) symptoms: Delusions (P1), hallucinatory behaviour (P3), grandiosity (P5), suspiciousness/persecution (P6), or unusual thought content (G9)), or intolerable side-effects] during a maximum observational period of 8 weeks then switch to Risperidone 2-4 mg, maximum dose of 10 mg. If non-response defined as above or intolerable side effects during a maximum observational period of 8 weeks, switch to Perfenazine, maximum dose 16 mg. If still no remission after an observational period 6 weeks, switch to Clozapine, augumenting up to 600 mg.

3.5 Assessments

Trained mental health personnel (clinical psychologist, psychiatrist, or psychiatric resident) carried out assessments at inclusion, 3 months, and one, two, five, and ten years (mean time to ten-year follow-up: 10,4 years; sd: 0.9 years). The structured clinical interview for the DSM-IV (SCID) was used for diagnostic purposes (Spitzer et al.,1992). Level of functioning was assessed using the Global Assessment of Functioning Scale (GAF) (Endicott et al.,1976). GAF

scores were split into symptom (GAFs) and function scores (GAFf) (Pedersen et al.,2007). DUP was estimated using all available information including interview, patient files and information from family when possible. It was defined as the time, in weeks, from the emergence of positive symptoms (PANSS score of four or more -moderate- on positive scale items P1 delusions, P3 hallucinatory behaviour, P5 grandiosity, P6 suspiciousness, or general scale item G9 unusual thought content) throughout the day for several days or several days a week to initiation of adequate treatment (the start of structured treatment with antipsychotic medications or the start of hospitalization in highly staffed psychiatric wards organized to manage disturbing psychotic symptoms). A few non-hospitalized patients started outpatient psychotherapy for psychosis, but did not want medication from the beginning. For these patients start of psychotherapy was regarded as start of adequate treatment. Duration of psychosis was the time during first year of treatment, measured in weeks, with a score of four or higher on these same PANSS items. Premorbid functioning was measured by the Premorbid Assessment of Functioning Scale (PAS) (Cannon-Spoor et al.,1982), which describes four premorbid periods in life: Childhood (up to 11 years), Early adolescence (12–15 years), Late adolescence (16–18 years), and Adulthood (19 years and beyond). The rating was based on interviews with the patient and/or with family members.

A previous analysis identified two premorbid dimensions: a social dimension consisting of PAS items social isolation and peer relationships and an academic dimension which contains school performance and school adaptation. For details about this modification, see previous publication (Larsen et al.,2004). PAS change scores were calculated as the difference between childhood score and the last score available (Haahr et al.,2008). A score of 6 on the PAS indicates the lowest level of functioning, whereas a score of 0 indicates an optimal level.

Symptom levels were measured by the PANSS. The scale scored five symptom domains: positive (delusions, hallucinations, grandiosity, unusual thought content, and lack of judgment and insight), negative (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, mannerisms and posturing, motor retardation, poor attention, disturbance of volition, active social avoidance), cognitive (conceptual disorganization, difficulty in abstract thinking, disorientation), depressive (somatic concern, anxiety, guilt feelings, depression, preoccupation), and excitement (hyperactivity, hostility, tension, uncooperativeness, poor impulse control) symptoms (Bentsen,1996). At 10 years follow-up, symptom remission was defined in accordance with the new international standardized criteria (Andreasen et al.,2005): No score of 4 or higher for the past 6 months on any of the following PANSS-items: P1 delusions, P2 disorganized thought, P3 hallucinatory behaviour, N1 affective flattening, N4 passive social withdrawal, N6 lack of spontaneity, G5 bizarre posture, or G9 unusual thought content.
Recovery was operationalized as a combination of symptom remission and adequate functioning in 3 functional dimensions based on the Strauss-Carpenter Level of Function Scale (Strauss and Carpenter,1977) continuously for the last 12 months:

1. Day-to-day living (independent living)
2. Role functioning (work, academic, or full-time home-making)
3. Social Interaction

A score of 0 indicated very poor and 4 adequate functioning. Patients in recovery had to have been in symptom remission according to the symptom remission criteria items listed above. Additionally, they had to have scored the maximum score of 4 on all 3 of the functional dimensions.

Alcohol and Drug use was assessed using the Alcohol Use Disorder Identification Test (Saunders et al.,1993) and the Drug Use Disorder Identification Test (Berman et al.,2005). These instruments were added at ten-year follow-up to the original assessment battery that used only the Clinician Alcohol/Drug Use Rating Scale (Drake et al.,2006).

Treatment characteristics were operationalized in the following way: Psychotherapy: number of weeks per year of at least one session of supportive psychotherapy per week. Medication: number of weeks per year of treatment with anti-psychotic medication. Defined daily dosage (DDD): DDD at the time of each assessment. Hospitalisation: Number of weeks in hospital per year.

3.5.1 **Reliability**

Reliability assessments have been carried out throughout the study and published in previous papers. When baseline data collection was finished, we drew a stratified random sample of 30 cases, comprising all sites. The site coordinators produced vignettes for cases from their own site, describing symptoms and development of the illness. Two experts, who were blind to the site ratings, scored the vignettes. The first eight vignettes were used for calibration and training. The following 22 vignettes were used for reliability testing (Friis et al.,2003). For analyses, diagnoses were dichotomized into core schizophrenia spectrum diagnoses (schizophrenia, schizophreniform disorder, and schizoaffective disorder) and other psychotic disorders. For diagnosis we found Kappa= 0.81, for the other measures: Intra Class Correlation Coefficients (one-way random effects model) were: GAF function: 0.86, and GAF symptoms: 0.91.

At 10 years, the raters were calibrated through trainings using video taped interviews and vignettes, and cases were discussed regularly to avoid drift. Twenty-eight patients gave informed consent for video recording of PANSS interviews, but due to technical problems only 26 were usable. Patients videotaped were not significantly different on PANSS or GAF scores from those who were not videotaped. The videos were rated by an experienced psychologist not involved in the project and blind to all ratings, however due to differences in dialects between sites full blinding was not possible. The ICC two-way mixed model was used with the consistency option, because we wished to determine the consistency of ratings between an independent rater and study ratings across sites. ICCs (95% confidence intervals) of the PANSS components were: Positive .65 (.20 – .93); Negative: .82 (.48 – .97); Cognitive: .76 (.34 – .96); Depressive: .67 (.18 – .94); and Excitative .61 (.16 – .92). The median value was .67. Whilst this is below a recommendation for health research of .75 or higher (Streiner and Norman,1995), it is well within the borders of what in the much cited article by Fleiss (Fleiss,1986) is called "fair to good": .40-.75.

3.6 Statistical analyses

The statistical analyses were conducted using PASW 18.0 and 19.0 (SPSS,2010) and R 2.10.0 (R,2009). In the longitudinal DUP study, ANOVA was used to compare means across phases and diagnostic groups, and Bonferroni post-hoc tests were carried out for multiple comparisons. We also tested for trends by using contrasts. DUP over time and the association with the presence of information campaigns were further examined using linear regression analyses with DUP as the dependent variable. Covariates entered were age, gender, and diagnostic category, in a stepwise procedure yielding R square change, indicating effect size and amount of explained variance.

In the ED/NoED comparison, there may have been selective attrition at 10-year follow-up, which had to be considered in data analysis. Firstly, ANOVA was applied to investigate the possibility of an interaction between type of symptoms at last follow up and ED/NoED dropout. Secondly, data from continuous outcome variables (PANSS, GAF) were analysed using linear mixed-effects models. We used symptom scores as dependent, and ED/NoED and time with their interaction as independent variables, exploring illness courses in ED and NoED areas and differences between them. Estimates were corrected for possible effects of the covariates gender, age, and DUP, the latter being log transformed to approach normal distribution. Data on clinical measures at inclusion induced a clear non-linearity and were excluded. In addition to the linear mixed effect analyses, group differences were estimated using independent samples t-tests for continuous, and odds ratios for categorical variables. Investigating the associations between outcome variables at ten years and categorical variables, odds ratios with 95% confidence intervals and the Pearson Chi Square test statistic were calculated.

Nonparametric analyses (Mann-Whitney U test for pairwise, and Kruskall Wallis Chi Square test for multiple comparisons) were applied for comparison of skewed data. All tests were two-tailed. Fourteen comparisons were made on outcome measures. As the Bonferroni correction is very conservative, we used a strict confidence level (beneath 2%) on outcome measures in order to minimize the risk of type I error. Finally, logistic regression analysis was applied to study which factors predicted recovery and non-remission. A stepwise variable selection routine was employed. For recovery: PANSS component scores at inclusion, age, gender, DUP and ED/NoED as candidate predictor variables. For non-remission: Age, gender, ED/NoED, and having a core schizophrenia spectrum disorder; weeks of psychosis during the first year. Only predictors showing

significant differences between ten-year remitted and non-remitted patients at inclusion were eventually selected. Because of a conceptual overlap and a statistically significant correlation between number of relapses and weeks of psychosis during the first year (Pearson correlation .3; $p < .000$), number of relapses was omitted. For the examination of the individual symptoms' contribution to the prediction of ten-year non-remission, we conducted a second binary logistic regression analysis, entering baseline scores on the individual remission criterion symptoms as independent variables (step 2) along with covariates age, gender, ED, having a core schizophrenia disorder and DUP (step one) and duration of psychosis during first year of treatment (step three).

4. Short summary of papers

4.1 Variation in Duration of Untreated Psychosis in an 18-year perspective

Background: The Scandinavian TIPS project engineered an early detection of psychosis program that sought to reduce the duration of untreated psychosis (DUP) through early detection teams and extensive information campaigns since 1997. In 1997-2000, DUP was reduced from 26 to 5 weeks median. The program was continued beyond the initial project in modified forms for over 13 years.

Objective: To track the vicissitudes of DUP over a 18 year period (1993-2010) in a defined catchment area, across phases varying in early detection intensity.

Method: The DUP of all patients meeting criteria for first episode psychosis was measured 1993-1994 and from 1997 through 2010 in a naturalistic long-term study. This time period was divided into four phases (TIPS phases), based on content and intensity of early detection efforts, following a pilot phase (1993-1994) with no early detection. DUP values of all patients were assessed and included in the study, irrespective of patients' participation in a clinical follow-up study, yielding a highly representative sample.

Results: DUP varied across phases with differing information campaign intensity and content.
There was a significant decrease from the pilot phase to the first TIPS phase. Furthermore, there was an association between the presence of information campaigns and DUP throughout the study period. However, changes in message

and an expansion of target group to including substance induced psychosis were followed by an increase of DUP, although this was not a statistically significant association. Also, having affective or brief psychosis was associated with shorter DUP.

Conclusions: The importance of information campaigns in reducing DUP was confirmed. Early detection campaigns seem to need a stable focus and high intensity level in order to be effective. Future research should elucidate pathways to care in order to establish principal targets for information campaigns.

4.2 Long-Term Follow-up of the TIPS Early Detection in Psychosis Study: Effects on Ten-Year Outcome

*Objective***:** Early detection in first episode psychosis confers advantages for negative, cognitive and depressive symptoms at 1, 2 and 5 years follow-up. Longitudinal effects are unknown. The objective of this study has been to investigate differences in symptoms and recovery at 10 years between an area with, and an area without early detection.

Methods: 281 (early detection: 141, no-early detection: 140) patients aged 18-65 with a first episode of non-affective psychosis were included between 1997 and 2001. Of these, 101 early detection and 73 no-early detection patients were followed up at 10 years and compared on symptom levels (PANSS) and recovery. Recovery combined standardized remission criteria and functional outcome.

Results: A significantly higher percentage of early detection patients compared to no-early detection patients were recovered at 10 years. This held true despite more severely ill patients dropping out of the study in the no-early detection area.

Except for higher levels of excitative symptoms in the early detection area, there were no symptom differences between the groups. Early detection recovery rates were higher largely because of higher employment rates for patients in this group.

Conclusions: Early detection of first episode psychosis appears to increase the chance of milder deficit formations and superior functioning. The mechanisms by which this strategy improves the long-term prognosis of psychosis remain speculative. Nevertheless, our findings over ten years may indicate that a mutative link exists between timing of intervention and outcome that deserves further study.

4.3 Early Detection, early symptom progression and symptomatic remission after ten years in a first episode of psychosis study

Background: Poor symptom outcome remains a challenge in psychosis: At least 50% of first-episode patients continue to have positive and/or negative symptoms after ten years.

Objective: To investigate rates, early predictors and early symptom progression of long-term non-remitted psychosis in an early detection study.

Methods: Symptomatic remission according to new international criteria was assessed in 174 patients at ten-year follow-up. Remitted and non-remitted patients were compared on early symptom progression, and logistic regression was applied to predict non-remission.

Results: At ten years, 50% of patients were in symptomatic remission. Non-remission was predicted by positive symptoms at inclusion and during the first year of treatment. Of individual symptoms only hallucinations were significantly predictive of ten-year non-remission. Early symptom differences were not reflected by differences in treatment.

Conclusions: Long-term symptomatic non-remission is associated with early positive symptoms. More assertive intervention may be needed in patients who do not respond robustly in the first year of treatment, whether or not they have been detected “early”.

5. Results

5.1 Longitudinal DUP-study

5.1.1 **Sample characteristics across TIPS phases**

There were differences in diagnostic distribution between TIPS-phases, displayed in **Table 6.**

Table 6. Sample characteristics TIPS1-TIPS4.

	Pilot (N=44)	TIPS1 (N=146)	TIPS2 (N=115)	TIPS3 (N=95)	TIPS4 (N=202)	Analysis	
Gender/ Diagnosis N (%)						**Chi²**	**p**
Female	16(36.4)	59(40.4)	45(39.1)	41 (43.2)	90 (44.6)	1.6	.65
Schizophrenia/ schizophreniform disorder	37 (84.1)	76(52.1)	48(41.7)	24(25.3)	65(32.2)	57.1	.000*
Delusional disorder	4(9.1)	6 (4.1)	10 (10.4)	12(12.6)	21(10.4)	6.5	.17
Brief psychotic disorder	1(2.3)	14(9.6)	13(11.3)	14(14.7)	18(8.9)	5.8	.21
Schizoaffective disorder	2(4.5)	22(15.1)	15(13.0)	9(9.5)	13(6.4)	9.6	.048**
Mood incongruent affective psychosis	0(0)	14(9.6)	15(13.0)	15(15.8)	24(11.9)	8.4	.08
Psychosis NOS	0(0)	14(9.6)	12(10.4)	21(22.1)	61(30.2)	42.7	.000#
						ANOVA	
						F	**p**
Age	28.4 (8.3)	25.0 (7.8)	26.7 (11.6)	28.2 (10.8)	27.2 (11.3)	1.8	.12

*Pilot phase > TIPS1, TIPS2, TIPS3, TIPS4

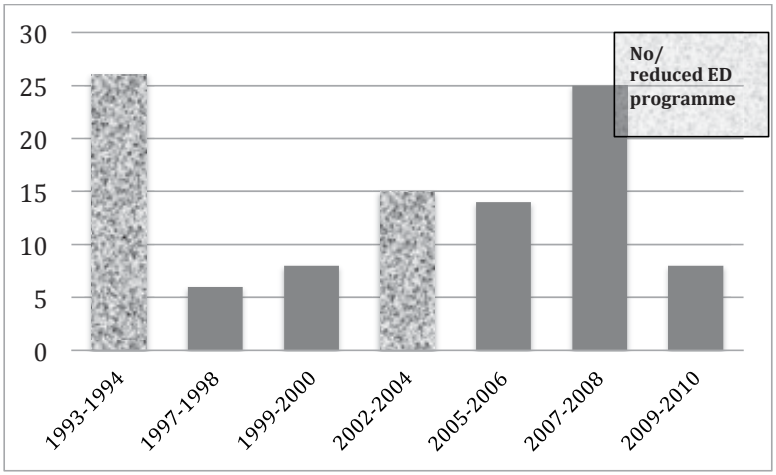
** Pilot phase < TIPS1, TIPS2, TIPS3, TIPS4

#Pilot phase < TIPS1 < TIPS2, TIPS3 < TIPS4

5.1.2 **DUP did not remain at stable low levels during periods with the full ED-programme.**

Data did not support the first hypothesis. On the contrary, there was substantial variation over the years (**figure 4**).

Figure 4. Median DUP values over time and across ED-programme phases.



1993-1994 pilot phase: Median: 26 weeks; range 0-936 weeks

1997-1998 TIPS 1: Median: 6 weeks; range 0-416 weeks

1999-2000 TIPS 1: Median: 8 weeks; range 0-364 weeks

2002-2004 TIPS 2, No information campaigns: Median: 15 weeks; range 0-2080 weeks

2005-2006 TIPS 3, Full ED programme: Median: 14 weeks; range 0-520 weeks

2007-2008 TIPS 4 Full ED programme: Median: 25 weeks; range 0-1530 weeks

2009-2010 TIPS 4 Full ED programme: Median: 8 weeks; range 0-1300 weeks

The low level that was achieved during TIPS1 was not stably sustained. As expected, there was a significant decrease from the pilot phase to TIPS1 (Z: - 3.4; $p < .001$; r= -0.3; medium effect size), and an increase from TIPS1 to TIPS2 (Z: 2.5; $p < .014$; r= 0.15; small effect size). However, DUP remained at the same median level upon re-implementation of the information campaigns in 2005. Then, 2007-2008 saw an increase, however statistically not significant (Z: -1.7; $p < .093$; r= -0.12). The low median DUP from TIPS1 was not re-achieved until 2009.

5.1.3 **DUP was associated with the presence of information campaigns**

Data supported an overall association between the presence and absence of information campaigns, and DUP (t: 3.4; df: 549; $p < .001$).

5.2 Ten-year ED-NoED comparison

An overview of ED-NoED comparisons is presented in **table 7.**

5.2.1 **ED Symptom advantages from inclusion, one, two, and five year follow-up were not maintained at the ten-year follow-up**

A statistical null hypothesis of no differences could not be rejected. Advantages in negative, cognitive and depressive symptoms from 1, 2 and 5 years were not maintained at ten years. There were no differences in GAF scores. The ED area had significantly higher excitative symptom levels than the NoED area. The ED area also had higher positive, negative, and cognitive symptom levels but these differences were not statistically significant. Furthermore, a significantly higher

Table 7. Symptom outcome, recovery, and treatment						
	NoED (N=73)		ED (N=101)		Analysis	
Measure	Mean	SD	Mean	SD	t	df
GAF symptom	8.95	3.8	10.04	5.8	.99	171.77
GAF Function	51.37	12.9	51.25	18.0	.05	171.99
PANSS positive component	8.95	3.8	10.04	5.8	-1.49	170.75
PANSS Negative component	15.66	6.2	17.17	8.2	-1.39	171.68
PANSS Cognitive component	4.58	2.1	4.92	2.7	-.90	170.88
PANSS Depressive component	9.62	3.8	9.27	3.8	.61	172
PANSS Excitative component*	6.79	2.2	8.41	3.9	-3.46	163.62
	N	%	N	%	Odds Ratio	95% CI
Remission	35	47.9	53	52.5	1.20	.66-2.2
Recovery♯	11	15.1	31	30.7	2.8	1.16-5.38
Still in psychotherapy	38	52.1	38	37.1	.56	.3-1.0
Still on antipsychotic medication	54	74	67	66.3	.69	.4-1.4
Not hospitalised last year	60	82.2	77	76.2	1.44	.68-3.1
Continuous positive symptoms**	2	2.7	23	22.8	10.5	2.4-46.0
No positive symptoms*	6	8.2	30	29.7	4.7	1.8-12.1

* ED > NoED, $p < .001$
** ED > NoED, $p < 0.0005$
♯ ED>NoED, $p < .027$

percentage of patients in ED had continuous positive symptoms last year. There was no difference in percentage of patients still in psychotherapy and/or using anti-psychotic medication to account for this finding. There was also no difference in number of patients hospitalised last year. Furthermore, there were no ED-NoED differences at study inclusion on sociodemographical variables or diagnostic distribution (**table 8**).

Selective attrition

At the ten-year follow-up, the ED area recruited significantly more (78.3%) of surviving patients (N= 129) than the NoED area (58.9 %) (N=124) (odds ratio: 2.5; 95% CI: 1.5-4.4; p = .001). **Table 9** displays the mean symptom scores at the five-year follow up of ten-year dropouts in ED and NoED. ANOVA showed significant interaction effects between dropping out and NoED for the negative (p= .016) and cognitive (p= .031) components. This indicates that the patients dropping out at ten years in the NoED area had higher negative and cognitive symptom levels than dropouts in the ED area. These are symptoms that characterise poor prognosis.

Table 8. Diagnostic distribution at study inclusion.				
	NoED		ED	
Diagnosis	**N**	**%**	**N**	**%**
Schizophrenia	41	29.3%	39	27.7%
Schizophreniform	30	21.4%	31	22.0%
Schizoaffective	12	8.6%	22	15.6%
Affective incongruent	21	15.0%	19	13.5%
Delusional	9	6.4%	6	4.3%
Brief	6	4.3%	13	9.2%
Other psychosis	21	15.0%	11	7.8%

Pearson chi^2: 9,5; $p < .15$

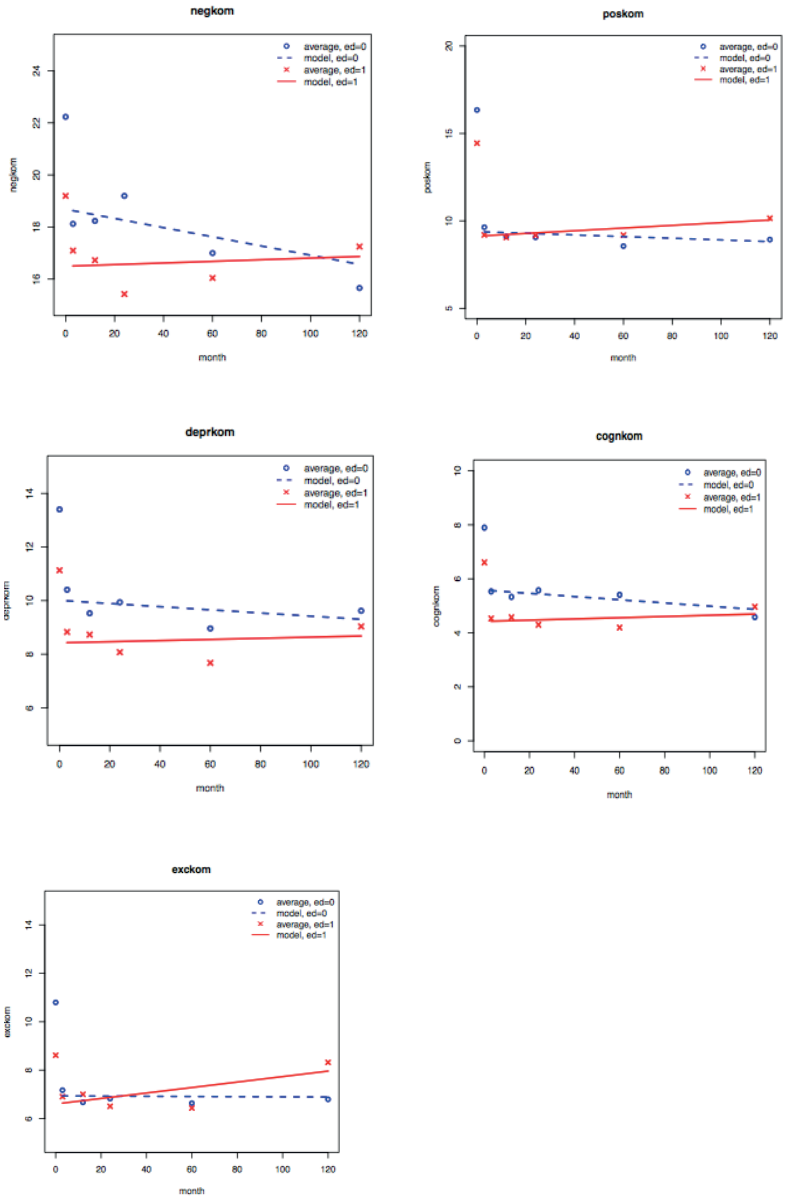
Table 9: PANSS component scores at 5 years for patients with and without 10-year follow-up.				
	Patients with 5 but no 10-year follow-up		Patients with 5 and 10 year follow-up	
Mean PANSS component score (SD)	NoED (N=21)	ED (N=12)	NoED (N=67)	ED (N=86)
Positive	9.7(5.9)	9.8(5.2)	8.2(3.7)	8.1(2.7)
Negative*	19.3(9.3)	13.1(5.3)	16.3(6.5)	16.4(7.5)
Cognitive**	6.1(2.9)	3.6(1.1)	5.2(2.3)	4.3(2.0)
Depressive	9.1(3.9)	7.7(2.5)	8.9(3.1)	7.8(3.3)
Excitative	7.0(3.2)	6.1(1.5)	6.5(2.1)	6.6(3.5)

Significant interactions between ED/NoED X completing/dropping out at 10-year follow-up:
*F=5,92; df=1;188; p=0.016
**F=4,69; df=1;188; p=0.031

Longitudinal symptom patterns

In an attempt to correct for the attrition, we fitted linear mixed effect models, which are statistical models combining fixed and random effects, and a way of handling dependencies of longitudinal data. They are displayed in **figure 5.** In the model estimating negative symptoms, NoED patients had a higher mean score at study inclusion, declining to ED levels at about 8.5 years. The same non-parallel tendency was seen for the other PANSS components, but only mean excitative symptoms were estimated to be significantly higher in ED at ten years ($p < .02$; other PANSS components ED/NoED difference at ten years: n.s.). The models could not, however, fully account for the non-randomness of the study sample attrition.

Figure 5. Linear mixed effect models of symptoms over ten years.

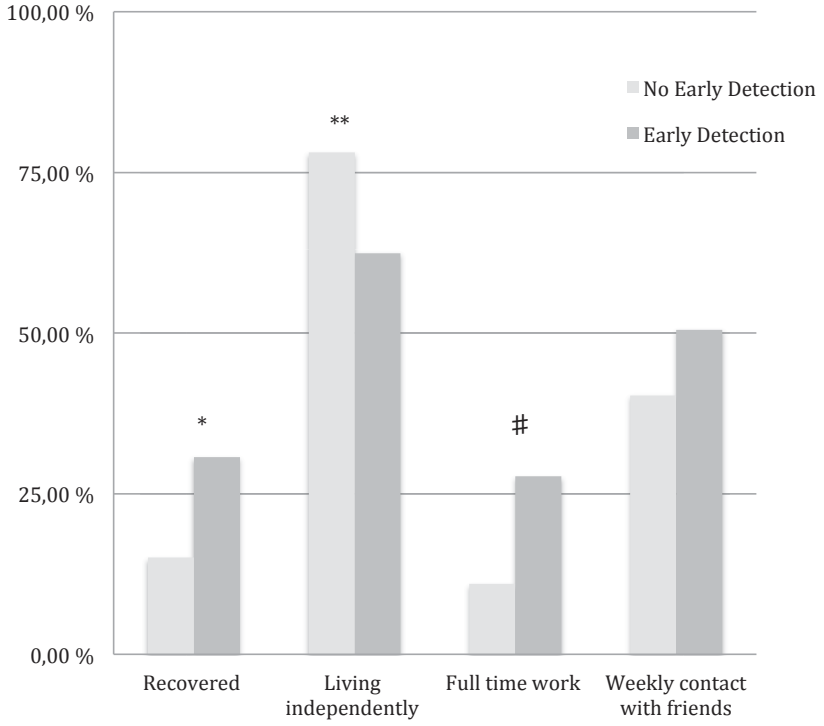


5.2.2 **The ED-area has higher rates of recovery at ten-year follow-up.**

The ED area had a significantly higher percentage of patients scoring as "recovered" (**figure 6)**. That is, 31% of ED patients had had stable symptoms remission for at least six months (in fact, all the recovered patients had had stable remission for one year or more), were living independently (not with family of origin), were seeing friends at least once a week, and had full time competitive employment (not on sick leave, but attending work) or studies, compared to 15% of NoED patients. There was no relation between recovery and schizophrenia spectrum disorder (odds ratio = .7; 95% CI= .2-2.9). Sixty-two per cent of ED patients lived independently, while in the NoED area this percentage was 78%. This difference was statistically significant.

In a logistic regression model, ED (p= .019) and negative symptoms at inclusion (p= .005) were predictors of recovery. DUP was not a statistically significant predictor of recovery in the regression model. Recovered NoED patients had a higher median DUP than non-recovered patients (median: 19; range 0-520; vs. 12 range 1-102 weeks), while in ED, recovered patients had lower DUP (median 5; range 0-364; vs. 4 range 0-416 weeks). An ANOVA analysing the natural logarithm of DUP across recovered/non-recovered and ED-NoED groups showed that this interaction was statistically significant (F=3.8; df: 1; p=.05).

Figure 6. Recovery and functional outcome



* Odds ratio ED vs. no ED= 2.5, 95% CI= 1.2 - 5.4, p= 0.017
**Odds ratio ED vs. no ED = .5, 95% CI= .2-.9, p= 0.027 (corrected α = (0.017)
Odds ratio ED vs. no ED = 3.1, 95% CI=1.3-7.3 p=0.007 (corrected α = 0.017)

5.3 Ten-year prediction of non-remission

Remission rates did not differ significantly between ED and NoED areas (NoED: 46.6%; ED: 52.5%; odds ratio= 1.3; 95% CI: .69-2.3). DUP, along with higher levels and longer periods of positive symptoms were associated with non-remission at ten-year follow-up (**table 10)**. However, DUP became clearly non-significant when duration of psychosis during the first year of treatment was entered into a logistic regression model. These were significantly correlated (correlation coefficient .411; $p < .00$). Furthermore, sixteen ED patients who had a short (<4 weeks) DUP still suffered a poor ten-year outcome with recurring relapses. These patients were characterised by higher symptom levels (for positive symptoms: $p< .03$) already from the start of treatment.

Statistically significant predictors of 10-year non-remission, hence, were level and duration of positive symptoms after inclusion and start of treatment, and of the positive symptoms, hallucinations were. Of the negative symptoms, affective flattening stood out as a symptom with higher scores at start of treatment in ten-year non-remitted patients, however it did not add to the statistical prediction of non-remission.

Table 10. Baseline characteristics of ten-year non-remitted and remitted patients.

	Symptomatic non-remission (N=87)	Symptomatic remission (N=87)	Analysis			
	N (%)	N (%)	OR	95% CI	Chi2	p
Being from ED area	48(55)	53 (61)	.83	.46-1.52	.35	.56
Male gender	54 (62)	43 (49)	1.92	.92-3.97	2.82	.09
Core schizophrenia	56 (64)	50 (58)	1.29	.7-2.37	.66	.42
Drug abuse	24 (28)	15(17)	1.92	.92-3.97	3.1	.08
	Mean (SD)	Mean (SD)	T	Df	p	
Age	28.0 (9.4)	28.7 (9.1)	-0.51	172	.61	
PAS score						
Childhood social	1.1(1.2)	0.8 (1.0)	1.57	169	.12	
Social change	0.7(1.5)	0.8 (1.4)	-0.73	169	.47	
Childhood academic	1.8 (1.3)	1.6 (1.0)	1.48	169	.14	
Academic change	0.5(1.3)	0.7 (1.3)	-1.07	169	.29	
PANSS component						
Positive	16.2(4.2)	14.2 (4.1)	3.12	172	.002	
Negative	21.2 (8.7)	19.1 (7.2)	1.73	172	.09	
Cognitive	7.3(3.3)	7.2 (3.4)	0.26	172	.80	
Depressive	11.4 (3.8)	12.5 (4.2)	-1.91	172	.06	
Excitative	9.3 (4.5)	9.6 (4.3)	-0.33	172	.75	
GAF symptom	28.6 (7.5)	29.7 (6.5)	-1.04	172	.30	
GAF function	31.0 (10.8)	32.0 (10.5)	-.61	172	.55	
Weeks in psychosis, total, first year	27.4 (19.8)	17.1 (16.4)	3.73	166	.000	
Weeks in psychosis, total, second year	21.6 (23.9)	7.3 (16.7)	4.56	154	.000	
Weeks in psychotherapy, first year	44.8 (13.5)	44.2 (13.8)	0.27	172	.79	
Weeks in psychotherapy, second year	46.7 (13.9)	39.3 (19.5)	2.84	168	.005	
Weeks on antipsychotics, first year	39.8 (16.1)	38.5 (17.0)	0.49	172	.63	
Weeks on antipsychotics, second year	39.5 (19.4)	30.2 (22.8)	2.89	171	.004	
Weeks as inpatient first year	17.2 (18.2)	14.6 (14.4)	1.03	172	.31	
Weeks as inpatient second year	13.1 (19.2)	7.3 (15.2)	2.19	171	.03	
	N (%)	N (%)	OR	95% CI	Chi2	p
One relapse or more first year	32 (37)	15 (17)	4.3	2.0-9.2	15.4	.000
Continuously psychotic first year	25 (29)	12 (13.8)	2.5	1.2-5.4	5.8	.016
	Median (Range)	Median (Range)	Mann-Whitney U	Z	p	
DUP (weeks)	8 (0-520)	4 (0-416)	3009.5	-2.3	.02	
Weeks to first remission	13 (1- >520)	9 (1-401)	3289.5	-1.5	.14	

6. Dicussion

6.1 Variation in DUP

6.1.1 **Decreasing salience of psychiatric information**

DUP was clearly prolonged when the information campaigns stopped in 2002-2004. However, upon re-introduction, there was no DUP shortening reduction from 2005, at least not until 2009. This may suggest a certain degree of saturation in the "market" of psychological and psychiatric awareness and information. In 1997, when TIPS started, there was very little information available through general media. Fifteen years later, however, such information is readily available, and perhaps denied, or overlooked, or ignored. Information campaigns may have lost some of their salience. More information about psychological and psychiatric illness may have led to habituation on the part of the public. This could have had an impact on information response and help seeking behaviour. Also, a certain amount of desensitisation and habituation may have affected mental health workers within a treatment system that had known TIPS for almost two decades. Experienced clinicians supervising novices may have lost some of the initial enthusiasm and hence, the early detection of psychosis and TIPS might have become less emphasised.

6.1.2 **Expanded focus of information campaigns may have led to expanded population**

Another line of reasoning concerns the content of the information campaigns through the different TIPS phases. The year 2007 was characterized by longer

median DUP but also an expansion of the information campaigns' focus to including substance-induced psychosis. Perhaps a slightly broader and partly different population was reached. A higher treated incidence for that year points in that direction (**table 3**). Whereas earlier information campaigns had more information about positive symptoms (i.e. "If someone you know becomes excessively interested in religion or philosophy, or his or hers talk starts to become incomprehensible, it could be a sign of developing psychosis"), there was now somewhat more focus on symptoms associated with substance abuse ("If someone you know suddenly starts withdrawing from social company, or becomes indifferent about their appearance."). This may have influenced results, even if patients with substance-induced psychosis were excluded from the analysis. Perhaps these campaigns may have missed some of the positive symptom, acute, short DUP patients.

6.2 Information campaigns were associated with DUP

The finding that DUP was associated with the presence of information campaigns is in line with previous findings. Information campaigns, when focussed on relatively clear positive symptoms, prompt very quick help seeking in patients with acute onset and/or prominent positive symptoms. The result is a shortening of median DUP. Results overall seem to indicate that it is important to keep a clear, steady focus.

6.2.1 **Help-seeking delays and health-system delays**

Patients can be referred to TIPS either via the detection teams, or directly from health care workers. We have previously shown that the detection teams tend to recruit young, male patients with insidious illness onsets (Johannessen et

al.,2007). This type of onset may be difficult to detect for family and even health professionals, and confers a delay in correct diagnosis and adequate treatment. These patients, their families or carers, or their health professionals, may have waited for longer before they decide to seek advice. Furthermore, some of them may even have received treatment in specialist mental health care services, without receiving a diagnosis and treatment for psychosis. Viewed in this way, detection teams may shorten health-system delays, while information campaigns to a larger extent shorten help-seeking delays. Perhaps in future work, negative signs and symptoms should still be addressed, but more focus should perhaps be placed on a message saying: "If in doubt, call us for advice".

6.3 No symptom differences at ten years

6.3.1 **Selective attrition**

Findings regarding symptom levels were contrary to expectations and previous findings. Some of this may be explained by the selective attrition. As shown, ED managed to keep a higher number of poor-prognosis patients with high levels of symptoms in the study while on the other hand, ED also had a lower mean negative, depressive and cognitive symptoms score during the first five years (Larsen et al.,2011; Larsen et al.,2007; Melle et al.,2008; Melle et al.,2004). It seems that ED outcomes were more polarized than NoED; a higher percentage of patients with very good, and a higher percentage patients with very poor symptom outcome. It may be the case that ED prevented symptom development in a subgroup of patients, but also kept high-symptom patients in the study, whereas in NoED, a larger part of the patients had symptoms decreasing through the follow-up period, partly due to loss of high-symptom patients.

6.3.2 **Relatively short NoED DUP**

The median DUP of 16 weeks in the NoED area was shorter than in most other studies (table II appendix). This may have raised the threshold for demonstrating differences in symptom severity between the areas. The NoED area did not have an ED-programme, but there was a team of researchers recruiting patients for the study. In some ways, this team may have acted like an attenuated version of a detection team. However, the relatively short NoED DUP, combined with outcome disadvantages in the first five follow-up years, may also suggest that active psychosis in its early phase may be more rapidly progressive than is realised.

6.4 Higher recovery rates in ED

The higher recovery rates in ED show that intervening early may pre-empt some of the long-term social damage so often implied by psychosis. It shows that significantly more ED patients had favourable outcomes in spite of four out of five mean symptom levels being equal, and one being higher. Moreover, it might be that sustained lower levels of negative symptoms over the first five years of the follow-up period have prevented some of the biologically mediated decline and its consequences for level of functioning. Twenty-seven per cent of ED patients had full-time employment or studies, compared to 10% in the NoED area. This is a high percentage in comparison with other studies (Marwaha and Johnson,2004; Melle et al.,2000), especially considering that the sample consisted of 65% patients with a core schizophrenia spectrum diagnosis (about 30% schizophrenia only, see **table 7**).

6.4.1 Criticism of interpretation of results

Some points of criticism have been raised regarding the interpretation of findings. For instance, more patients in the NoED area lived independently in comparison to the ED area. This fact has been put forward as a negative result for ED (Amos,2012). However, in ED 48.4%, as opposed to 17,9% in NoED, of these patients were also recovered. Thus, more NoED patients were living independently in spite of symptoms and functional impairment compared to ED patients. As such, living independently in itself cannot be a valid indicator of outcome.

Some additional criticism has been raised regarding the presentation of these results (Amos,2012). One point concerns hospitalisation. It was reported as significantly higher in ED than in NoED at the five-year follow-up, and omitted altogether in the presentation of the ten-year comparison. The question whether hospitalisation could be a confounding variable influencing recovery rates was raised. However, only non-remitted and thereby, non-recovered patients have higher rates of hospitalisation. It was not reported separately since none of the hospitalised patients were counted as having a favourable outcome. They all had had symptoms during the last year, and were neither remitted nor recovered.

Another point concerns employment status. There was no ED/NoED difference at the five-year follow-up (Larsen et al.,2011), but a significant ED advantage at ten years, and the results presentation is criticized for not providing further information. However, the measure employed at five years was work > 20 hours a week. At ten years, there was also no difference on this measure (ED: 32.7%; NoED: 27.4%; odds ratio: 1.3; 95% confidence interval 0.7-2.5). The stricter measure of full-time employment used at the ten-year follow-up showed a

significant ED advantage (**figure 6**). The criticism and our response are displayed in the appendix.

6.5 Prediction of non-remission

6.5.1 **Negative and positive illness trajectories**

The results from this study suggest that clinicians should be alert facing treatment non-response of positive, and especially hallucinatory, symptoms. Perhaps more stringent monitoring of patients' symptom levels and scrutinising of treatment should be introduced in our mental health care system.

It has been shown in a previous publication from our group that flat affect over the ten-year follow-up span was associated with both non-remission and non-recovery (Evensen et al.,2012). However, neither the PANSS negative symptom component nor affective flattening at start of treatment statistically predicted ten-year non-remission. This finding may be in line with findings from previous research (Emsley,2009; Suarez and Haro,2008), indicating that negative symptoms and function on the one hand, and positive symptoms on the other hand, follow different trajectories. It seems that in the first years after study inclusion, DUP, ED, negative, depressive and cognitive symptoms follow similar trajectories. In the ten-year perspective, this is the case for ED, negative symptoms and functioning on the one hand, and positive symptoms and remission on the other hand. Perhaps the intensity of an underlying aberrant biological process, giving rise to negative and cognitive (deficit) symptoms, is mutually associated with the resilience of positive symptoms. The more aberrant the underlying illness process is, the more resistant also the positive symptoms. As there is no treatment today effective for deficit symptoms, the way to arrest this process is to make positive symptoms remit. Where this is not possible, it

might indicate a more severe underlying process. As most patients do go into remission within the first years of treatment, chances to arrest that underlying process increases, in turn increasing chances of recovery. If patients do not remit, the chances to arrest the illness progression, i.e. negative symptoms, diminishes. This would be in line with findings from other research suggesting that early treatment response predicts remission and recovery (Emsley,2009). All in all, findings suggest that there is a negative-functional dimension and a positive dimension, moving along different but interdependent axes.

6.5.2 **Non-compliance**

Another issue concerns non-compliance. Some patients with hallucinations may have positive attitudes towards them, and this may result in treatment non-compliance (Moritz et al.,2012), again leading to worse outcome (Malla et al.,2006). In clinical work one can also observe patients who are afraid to get rid of omnipotent and threatening voices, fearing repercussions. We did not have data on reasons for non-compliance either regarding pharmacological or psychological treatment. We did however have data on "non-compliance" on the hand of psychiatrists and psychologists treating the patients. In spite of early and persisting symptoms, ten-year non-remitters did not receive more treatment during the first year, neither in terms of psychotherapy nor medication. Data indicate that patients with relapsing and remitting psychosis were particularly "prone" to interruption of medication, especially in ED. Furthermore, clozapine was not tried during the first year of treatment except for in four patients, even though the medication algorithm recommended doing so after six-months of non-response to treatment.

6.6 ED, DUP, symptoms, and outcome

The relationship between ED, DUP, symptoms and outcome appears to be complex.

First, the ED patients display more severe excitative symptoms, but at the same time they have higher recovery rates. Some of this inconsistency may be explained by the fact that the higher excitative symptom levels were found among the non-recovered patients only, i.e. controlling for recovery, the difference is eliminated.

Second, lower negative symptoms and ED independently predicted long-term recovery, but DUP did not. One explaining factor may be that ED lowered the symptom threshold for referral; hence that ED had an effect besides reducing DUP. Furthermore, from these results it appears that there is an association between ED and recovery, mediated by negative symptoms. From the linear mixed effects models, one could speculate that ED prevented symptom development, while in NoED, higher symptom levels diminished over time. ED negative symptom levels were significantly lower all through the first years of the follow-up period. It is possible that the lower symptom levels over time facilitated a more favourable functional outcome.

Third, ED patients presenting to treatment with a long DUP and higher symptom levels could be more likely to be resistant to the ED information campaigns: To lack insight, to either themselves or their families be more in denial, to have poor social networks not intervening, to have insidious negative onsets, or all of the above. These are all poor prognostic factors. A long DUP in ED is a more extreme event than a long DUP in NoED, because it occurs in spite of the massive ED efforts. The fact that in ED, non-recovered patients had longer DUP, while in NoED, this was not the case, supports this notion.

A long DUP in NoED may have meant long-standing mild, more benign symptoms, while in ED, it may more often have meant poor-prognosis type symptoms.

In sum, ED led to lower symptoms levels at presentation. This may have set out a more favourable trajectory from the beginning for the ten-year recovered patients, with less negative symptoms, and prevailing into the ten-year follow-up. For those with high symptom levels in spite of ED, prognosis was poor.

7. Methodological considerations

7.1 Measurement challenges in the DUP study

Measurement of DUP presupposes a starting point, usually to do with the emergence of psychotic symptoms, as well as an endpoint, usually the start of some treatment. What symptoms define the starting point of psychosis and subsequent treatment can be viewed as an issue of construct validity. It represents several challenges.

First, research has shown that patients developing psychosis undergo deterioration of social functioning well before the emergence of overt psychotic symptoms (Larsen et al.,2004). Furthermore, signs and symptoms such as anxiety, dissociation-like symptoms or ”basic symptoms” (Hafner et al.,1992), schizoid personality traits (Miller et al.,2002), depression, problems concentrating, perceptual abnormalities, and overvalued ideas (Yung et al.,2008) have been put forward as possible early stages of psychosis. Also, in about 70% of patients with psychosis, negative and cognitive symptoms were the first to emerge (Hafner et al.,1992). These signs and symptoms lack the specificity needed to include them in a definition of DUP. Therefore, DUP is defined disregarding any deteriorative illness processes leading to psychosis, focussing on specific symptoms like hallucinations, delusions, bizarre thought and/or behaviour, and disorganisation, in spite of the probable high importance of pre-psychotic deterioration.

Second, patients may have had brief, intermittent psychotic episodes. Few studies specify whether the reported DUP is cumulative, adding such episodes to “last” DUP.

Third, few studies specify frequency, severity and number of symptoms. Hence, patients with similar DUPs may have been exposed to very different "doses" of psychosis (Compton et al.,2011).

Similar variability has been observed for the DUP endpoint. The most widely used criteria are hospital admission or start of treatment with anti-psychotics. Trouble arises when patients have received some treatment earlier during DUP, but not "adequately", also an often times vaguely defined tem. Furthermore, the authors state, it remains a question whether it is not true that staying psychotic despite "adequate" treatment is as detrimental to mental health as untreated psychosis. de Haan et al. (de Haan et al.,2003) introduced including treated non-remitting psychosis into a widened concept of DUP as a possible solution. All in all, there are almost as many definitions of DUP as there are studies (table II).

Methods of assessment also vary from study to study. It seems legitimate to ask why a standardised measure has not been chosen and implemented. Some instruments have been developed. These include the Beiser scale (Beiser et al.,1993), the Symptoms Onset in Schizophrenia inventory (SOS) (Perkins et al.,2000), the Interview for the retrospective Assessment of Schizophrenia (IRAOS) (Hafner et al.,1992) and the Nottingham Onset Schedule (NOS) (Singh et al.,2005). All of these are semi-structured interviews. Surprisingly however, there is no standardised measure in use across studies and countries, like there is for symptoms assessment (like for instance the PANSS which is widely used) and since recently, remission criteria (Andreasen et al.,2005). Furthermore, reliability assessments of DUP are missing in most studies. In TIPS, DUP was measured using "all available sources of information", vignettes were scored, and consensus reached. Reliability was estimated, and was very high (icc 0.99), probably due to a large spread in the distribution. However, there were no standardised instruments available in Norwegian when TIPS started measuring in 1993.

Another measurement issue concerns study populations and their DUP distributions. Large et al.(Large et al.,2008) conducted a DUP meta-analysis on 7 studies providing individual patient data, and discovered how skewed distributions of DUP influenced not only mean values, but also median values reported. A large proportion on patients (312 out of 503) presented to treatment with a DUP of one week or less. He observed that after a DUP of one week or less, when there is a "bulk" of patients presenting, a logarithmic DUP variable showed a linear relationship to number of patients admitted, with a few outliers with very long DUP. Another challenge is that many of the studies reporting DUP include different diagnostic groups.

A final point of concern is the analysis of the DUP variable. Other research indicates there might be a critical DUP beyond which prognosis worsens (Boonstra et al.,2012), a threshold phenomenon which would not be captured by a linear DUP variable. In future research, outcome should perhaps be investigated in relation to such a critical value, and exploring its relation to other prognostic factors.

Furthermore, duration of negative symptoms may emerge as an important variable, considering its probable relation to DUP and the importance of negative symptoms for recovery.

7.2 Cohort effects

There are some problems concerning comparability across the different phases of the TIPS study. First, the pilot phase had significantly more patients with schizophrenia or schizophreniform disorder and less with schizoaffective disorder, compared to subsequent phases. Also, this sample consisted of

hospitalised patients only, and cannot pass as an epidemiological sample. Second, the diagnostic category psychosis NOS was used for significantly more patients in TIPS 3 and 4 compared to TIPS1 and the pilot phase (**table 6**). Third, a study covering a time-span of 18 years cover a range of societal and cultural changes not included as variables. For instance, during the time period 1993-2010, the internet was introduced to "everyone" and grew to become a main mass medium and means of communication. Mobile telephones and texting also changed how people relate and communicate. Furthermore, immigration increased and the ED area became more international; between 2000 and 2010, the percentage of first- and second-generation immigrants and foreign citizens rose from about 16 to 26% (www.ssb.no). Incomes rose dramatically; between 2004 and 2010 alone, median income per household increased by 27% after tax. All in all, new cohorts brought new generations of patients and families, who came to age in an in many ways different environment than their predecessors. Hence, there are many factors other than changing information campaigns that may have influenced results. We can only speculate about these. In any case, comparisons should be handled with caution.

7.3 Internal and external validity in the ED-NoED comparison

Internal validity is the extent to which a conclusion of a study is warranted. A confounder, or confounding variable, is a variable not defined and studied in the experimental model, but nevertheless influencing the dependent and/or the independent variable. Confounders can be seen as alternative explanations for an observed effect in an experiment, and thereby threaten internal validity.

External validity refers to the generalisability of results from an experiment to other populations, other situations and other times than the ones in the experiment itself. Generalisability in turn depends on representativity and is optimised by random selection of subjects, or randomisation to experimental conditions. Sampling bias can cause subject related factors to influence results in an unintended way and thereby threaten both internal and external validity. The same holds for other forms of methodological bias. Non-response bias, for instance, is when some subjects recruited for an experiment or a study are unwilling to participate. Selective dropout, meaning that certain subjects with certain characteristics don't complete the experiment, is another form of bias. Response bias occurs when questions or tests or outcome variables are operationalized in such a way as to elicit certain responses more than others.

Both confounders and biases can form alternative explanations to an observed effect on a dependent variable in an experiment.

The TIPS study employed a quasi-experimental design for the comparison of ED versus NoED. The quasi-experimental design is a derivation of the "true" experimental design (Shadish et al.,2001). An experimental design is a roadmap to data collection, analysis and interpretation. In the experimental design the effect of a manipulated independent variable on a dependent variable is investigated. The independent variable is the variable manipulated by the experimenter, for instance a treatment or stimulus of which the experimenter wants to know the effect. The dependent variable is the factor on which the experimental (independent) variable is thought to have an effect. In the experiment, there is at least one experimental condition in which subjects are exposed to the experimental treatment or stimulus, and at least one control condition in which subjects are not. Comparison between the groups gives information about the causal effect of the experimental factor. The aim is to

explain and to predict. To be able to achieve explanation and prediction, one needs to establish exclusive causality and therefore to rule out all other possible explanatory factors than the one being investigated. This is often referred to as internal validity. Campbell & Stanley (Shadish et al.,2001) in their standard book on research design suggest several sources of alternative explanations, or confounders and biases.

7.4 Circumstances

7.4.1 **Spin-off effects of ED: confounders or moderators?**

One possible confounder concerns differing circumstances in the ED versus NoED areas. Is the higher rate of recovery in ED an effect of the narrowly defined ED programme, or could it be something else, perhaps a "Stavanger Effect" (Stavanger is the main city in the ED area), a version of the confounding Hawthorne effect? Stavanger has built a reputation of expertise in the treatment of psychosis, both because of TIPS and for other reasons. Stavanger has for the last 20 years organised a major psychiatric conference called the Schizophrenia days. It is open to mental health professionals, workers in other relevant sectors (for instance police, school workers, social workers) and the general public. The conference also has an extensive cultural programme with arts, literature and music, and offers open lectures and exhibitions for the general public. This may have had an anti-stigmatising effect. It is also in Stavanger that the Psychiatric Educational Fund (PsykOpp) has been initiated, an organisation working with psycho-education for all kinds of target groups and the general public. It is also a publisher of literature and information booklets on the subject of mental health. It has its own shop, and offices, right in the middle of the town centre. The branding of the Schizophrenia Days, PsykOpp and TIPS may have been effective.

One could perhaps say that Stavanger might be a particularly "psychosis friendly" environment, where particularly many people both in and out of mental health care know particularly much about psychosis and its treatment. In other words, if there is a "Stavanger-Effect", it could make patients more likely to have lower symptom levels from other reasons than ED alone. On the other hand, the above factors may be viewed as part and parcel of ED, or a kind of a spin-off effect. In that case, it is more of a moderator. A confounder is a methodological problem, while a moderator is of interest as it pinpoints the condition under which an effect of ED is optimized. Furthermore, ED is likely to have an independent effect in and by itself. If an "ED-spin-off" or "Stavanger-effect" had been influencing how quickly patients came into treatment and how ill they were, one would have seen shorter DUP and perhaps even lower symptom levels already in the historical control group than in comparison groups. This is not the case.

7.4.2 **Degree of urbanicity**

There might be systematic differences between the NoED and ED area having to do with different degrees of urbanicity. Degree of urbanicity is known to correlate with incidence and symptom levels of psychosis. NoED sites Oslo and Roskilde - close to Copenhagen- both probably are more highly urbanised environments than Stavanger and neighbouring towns. We found no good way around this.

7.4.3 **Selection bias**

Sociodemographic differences at inclusion

Selection bias occurs when subjects in the experimental and control conditions differ from each other in ways that influence the dependent variable. Bias literally

means prejudice in favour of one thing over another, so here: Favouring one outcome over another, in a way that has nothing to do with the experimental factor. Biases can cause confounders and compromise internal validity, but are also a threat to external validity. To rule out sampling bias, subjects were compared at inclusion on variables such as age, sex and education, and on clinical variables. For age, there was a significant difference with the ED-subjects being younger than in both the comparison sites and the historical control group (Melle et al.,2004). ED patients also were less often married, more often had a Scandinavian ethnic background, more often had a diagnosis in the schizophrenic spectrum, and more often abused alcohol or drugs. None of the factors mentioned however removed the association of ED with DUP or outcome. Moreover, the differences at inclusion would all but ethnicity indicate a poorer prognosis for ED patients, i.e. younger age of onset, single status, more schizophrenia spectrum diagnoses and more substance abuse.

Refusers

One particular instance of selection bias concerns the patients identified as study appropriate, but who refuse to participate. In TIPS the overall refusal rate was 23%, about the same as or slightly lower than in other, comparable studies. The refusers did not differ from participants on background variables (sociodemographic, clinical, functional) but they did have significantly longer DUP. This could pose a threat to both validity and generalisability. Furthermore, the refusers represent loss of valuable information. However, refusers and their DUP lengths were distributed evenly across experimental and control sites. The comparison between ED and NoED may still be seen as valid in this respect. However, generalisability of results to the whole population of FEP is weakened. The refusers make up a substantial group of patients whom we know little about. This hampers generalisation. Also, the study of any mediating effect of DUP on

clinical and functional outcome parameters will be more difficult to detect, camouflaged by missing long-DUP and possibly poor outcome patients. A remark worth making here is that we are not aware of any studies that discuss the problem with loss of long-DUP patients. Most studies not even mention this problem of representativity in studies on first episode patients.

Bias on symptom levels

TIPS did not have pre- and post-experiment outcome measurements on the same group; this is impossible in this design. As soon as patients in the experimental site enter the study they have already been exposed to the experimental factor, which is ED. There is no good solution to this problem.

Another issue concerning bias on symptom measurements is the possibility of scoring bias across the areas and has consequences for internal validity. One wants to rule out the possibility that a difference between experimental and comparison sites just are artefacts of different scoring practises. One way to deal with this would be to have raters blind to site. This is impossible because of differences in language between Oslo, Stavanger, and Roskilde. Videotaping interviews and having them scored by an independent rater did not entirely solve this problem. In addition, videotapes from all sites were scored by the raters at all sites and compared afterwards in order to compute reliability coefficients. Results from this were satisfactory.

7.4.4 **Autonomous change within the subjects over time**

Between two measurements subjects may change on the dependent variable due to factors that have nothing to do with the experiment. There is a possibility that

even if symptom levels were lower in the ED area, this could have to do with naturally occurring change from before to after the experiment. ED patients might for some reason have been less ill even before the experiment took place. Because there are no representative pre-experimental symptom scores (the pilot sample was different from the ED and NoED samples), this could not be controlled for. However, diagnostic distribution across ED and NoED was similar (**table 4)**. Furthermore, if we presuppose that ED has a long-term effect, one might investigate the patterns of long-term symptom development, and compare them across sites. Parallel illness courses would indicate changes over time independent of ED. Results did however indicate that ED symptom levels were stably lower than NoED levels the first five years, while NoED symptom levels improved in the longer run.

7.4.5 **Retest-effect**

The measurements undertaken at one time point may influence the results on measurements on the same variable at the next (also known as learning effect). However, in this study, there are no tests vulnerable to learning. All measures are clinical evaluations and observations. We consider retest-effect problems to not be a threat in the ED-NoED comparison.

7.4.6 **Measurements at one time point may differ from measurements on the next**

Throughout the TIPS study all instruments have been held constant. Only at the ten-year follow up, some instruments have been added, and in the neuropsychological battery, one instrument has been updated with a newer, but

parallel, version. The measurements of symptom levels have remained the same. Therefore, one can be confident that this source of error does not come into play.

7.4.7 Statistical regression

This occurs when subjects are recruited to an experiment on the basis of their extreme score on some measurement in that experiment. Statistically, extreme scores always tend to be less extreme at a second measurement, independently of any experimental factor. ED symptom levels at inclusion were low compared to NoED. If this can be considered to be an extreme outcome, one would expect measurements on the next time points to be less extreme, i.e. higher, or closer to NoED scores. For the negative symptoms at three months, this is true (Melle et al.,2004). But after this, scores continue the pattern of ED scores being lower. Furthermore, ED symptom scores remained stable and showed no sign of regression towards the mean. The tendency for the initially more severe symptom levels in the NoED group to improve over time could be an effect of statistical regression. However, this cannot explain symptom levels in the ED group remaining stable.

7.4.8 Dropout.

Most experiments end with fewer subjects than with which they started, and this can distort the results of the experiment. If the dropouts are subjects with extreme scores on the dependent variable, a difference between scores at the start and the end of the experiment may unjustly be attributed to the experimental factor. The skewed loss of patients at the ten-year assessment was observed in spite of identical retention procedures in both areas. It may have influenced results, as recovery findings may have been stronger without this loss.

The greater ten-year follow-up participation of ED subjects may have been related to the ED program with its focus over many years on recognizing psychotic illnesses coupled with easier access to care. Perhaps easy access to mental health care also meant improved relations between patient and health care, in turn facilitating recruitment to follow-up assessments. My own clinical impression certainly supports this, as many patients gave positive experiences with their treatment as a reason to come. Furthermore, it has been proposed previously that longer DUP can negatively influence recruitment to studies (McGlashan,1999). In our study, this treatment delay was longer for refusers at inclusion and at the ten-year follow-up than for consenters.

8. Ethical considerations

Early detection of disease or illness in general, and psychosis in particular, raises ethical questions (Larsen and Opjordsmoen,1996). Some of the main ones will be outlined in the following.

8.1 False positives

A false positive occurs when a person does not fulfil criteria for a condition while a screening procedure indicated that he or she did. This may occur when screening criteria lack specificity. In psychosis however, positive symptoms like hallucinations, delusions, unusual thought content or disorganised speech are specific by definition. Early detection of psychosis is not about detecting patients at risk for developing psychosis, but patients who already have it. Rather, the opposite is true: some symptoms of serious psychosis, like schizophrenia, are more difficult to detect and are similar in presentation to other, nonspecific symptoms. The risk of false negatives may be greater than the risk of false positives.

8.2 Stigmatisation

Another issue in early detection of psychosis concerns stigmatisation. Could early detection lead to unwanted and unwarranted stigmatisation? It is a fact well established that serious mental illness such as psychosis is draped in myths of "madness" and frightening institutions a la the famous film "One flew over the cuckoo's nest" (Tarrier et al.,2007). One can easily imagine what stress a

diagnosis of "possibly developing psychosis" could do to the self-image of a youth, and to the worry of any parent. In both research and treatment, therefore, concise and accurate information is important, to combat these myths, placing the appropriate focus on the mental health issues the person in question presents with for him or herself. One should never "diagnose" anyone with the possibility of developing anything that the person doesn't already experience. Rather, one should address the health complaints of the person who has come to the attention of health care providers, and monitor symptoms in such a way that appropriate treatment is offered for which ever symptom emerges.

A second point to make when discussing stigmatisation is that fear of stigmatisation can in itself nourish social prejudice (van Leeuwen,2001). The information campaigns employed in the TIPS project are aimed at reducing prejudice and stigmatisation. Results from research, showing clear benefits of early treatment also helps de-stigmatise the conditions. In this perspective, not addressing and talking about psychosis heightens, and not lowers, social stigma.

8.3 Informed consent

Informed consent demands full understanding of what is requested and explained about a study, and this is turn demands absence of gross reality distortion. Reality distortion, however, is one of the hallmarks of positive symptoms in psychosis. So, how valid are the informed consent forms gathered? This ethical dilemma is readily recognised in the field (Lehrman and Sharav,1997). It is solved by waiting to request participation in a research project until the patient is in remission of positive symptoms. In the TIPS project, informed consent was asked at assessment, or whenever positive symptoms recede.

8.4 It's unethical not to intervene

The other side of the discussion is short, however relevant. With the indications from research that a prolonged DUP has an adverse effect on the outcome in the most serious of mental illnesses (Marshall et al.,2005; Perkins et al.,2005), not acting to shorten it seems clearly unethical.

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10. Appendices

10.1 Table I. Long-term outcome studies in psychosis.

References	N, sample	Time span	Recovery/ outcome measure	recovery; employment outcome
(Bottlender et al., 2003; Bottlender, Strauss, & Moller, 2010; Jager, Bottlender, Strauss, & Moller, 2004; H. J. Moller, Bottlender, Wegner, Wittmann, & Strauss, 2000)	177; first episode of sz (N=61), sa (N=58), or aff.psychoses (N=58) (ICD-19, DSM-III; ICD-10, DSM-IV)	15 years	Mannheim Disability Assessment Schedule (version of WHO-DAS), including «work role behaviour»	**20%** of sz and **60%** of sa «no impairment in work role behaviour». 14% of sz no social disability at all.
(H. J. Moller, Bottlender, R., Gross, A., 2Pre002)	N=114 (sz: 76; sa: 38) + 32 controls	15 years	ADMP; a German psychopathology inventory PANSS SANS -> negative symptoms: GAS(similar to GAF)	sz: 74% sa: 47% sz GAS > 50: 66% sz GAS < 51: 34% sa GAS > 50: 74% sa GAS < 51: 26%
(Harrow, Grossman, Jobe, & Herbener, 2005)	N=274	15 years	Levenstein-Klein-Pollack scale; Strauss-Carpenter Scale: 1 year of no symptoms, no admissions, no poor social functioning, living independently, and working half time or more «Having had periods of recovery», all psychoses, during the last 15 years	SZ: **19%** SZform:**25%** Other psychoses: 43% 40%

References	N, sample	Time span	Recovery/ outcome measure	recovery; employment outcome
(Harrow et al., 2004)	N=149 sz and non-sz delusional *out*patients recruited at index hospitalisation	11,5 years	Strauss-Carpenter; work scale	**57%** of nondelusional sz-patients worked more than half time; **9%** of «very delusional» did
(Harrow & Jobe, 2010)	N=200 (sz-spectrum only: N=53)	20 years	Strauss-Carpenter: 1 year of no symptoms, no admissions, no poor social functioning, living independently, and working half time or more	**11%** of delusional and **57%** of nondelusional sz-patients had had one or more periods of recovery over the past 18 years
(Racenstein et al., 2002)	N=173 «early course psychosis»; sz: N=70	10 years	Strauss-Carpenter; work scale	**33%** of whole sample (including affective psychosis) more than half time work
(Harrow, Grossman, Herbener, & Davies, 2000)	N=106 RDC sz+sa (+104 controls)	10 years	Levenstein-Klein-Pollack scale (including 1 years absence of symptoms and functioning); Strauss-Carpenter Scale, 1 year: work	SA: **< 40%** recovered 40-52% of sz poor outcome (symptoms+poor functioning) SZ recovery rate not reported (!)
(Marengo, Harrow, Herbener, & Sands, 2000	N=71 early, non-chronic cohort; sz+sa	10 years	Symptom outcomes (SADS, Psychiatric Assessment Interview)	59% no delusions 69% no hallucinations 65% no flat affect 59% no depressed mood

References	N, sample	Time span	Recovery/ outcome measure	recovery; employment outcome
(Harrison et al., 2001)	N=1171; 14 treated incidence cohorts; sz, and «other psychoses»	15 and 20 years	Bleuler scale of recovery, last 12 months; WHO-DAS Bleuler recovered 1 month: Bleuler recovered 1 month + GAF>60 Bleuler recovered+GAF>60+no episode of treatment last 2 years No psychosis last 2 years GAF>60 WHO-DAS excellent/good (symptoms and social incl work role) Paid work (full time at least part of the time»)	15% in developed countries 37% in developing countries Other psychoses 71% sz: 48% Other psychoses: 55% SZ: 38% Other psychoses: 36% Sz: 16% All psychoses: 50% sz: 42% All psychoses: 50.7% sz: 40% All psychoses: 40% Sz: 33% SZ: 37%
(Wiersma et al., 2000)	N=500 non-affective psychosis, «recent» (within 2 years prior to inclusion) onset	15 years	Present State Examination WHO-DAS Life Chart Schedule (symptoms, treatment, residency, employment) Work: *a combination of actually working and undertaking steps to get working*	No social disability, including full-time work: **14%**

References	N, sample	Time span	Recovery/ outcome measure	recovery; employment outcome
(Mason, Harrison, Glazebrook, Medley, & Croudace, 1996; Mason et al., 1995)	N=67, incidence cohort sz (ICD-9)	13 years	PSE, SANS Life Chart Schedule last 2 years (symptoms, treatment, residency, employment) Bleuler recovery past month GAF DAS (which later became WHO-DAS), last month	34% continuously psychotic (2 years) 56% Bleuler recovered (1 month) 49% GAFs > 60 50% GAFf > 60 97% living independently most of last 2 years 32% full-time employment at some point the last 2 years 43% no dysfunction in social roles 17% complete recovery over «longer term»: no symptoms, no disability, no treatment 18% never relapsed after 1st episode
(Wiersma, Nienhuis, Slooff, & Giel, 1998)	N=82 incidence cohort non-affective psychosis	15 years	Complete remission: symptom free and showing their usual personality, 1 month, PLUS unimpaired WHO-DAS functioning	27 %

References	N, sample	Time span	Recovery/ outcome measure	recovery; employment outcome
(Ganev, Onchev, & Ivanov, 1998)	60 «recent onset» (within 2 years prior to inclusion)	16 years	Last 2 years of work and social/work functioning PSE symptoms GAF Good outcome: job, no psychosis last 2 years, living independently, married or divorced	21% full-time work 38% no psychotic symptoms 46% continuously psychotic 31% GAF > 60 31%
(Marneros, Deister, & Rohde, 1990)	N=402 (Sz+SA: N= 249)	25 years	GAS (similar to GAF) Full symptom remission (unclear time criterion) German WHO-DAS, last month excellent adjustment very good adjustment: Excellent or good: Good, very good or excellent adjustment:	sz: 31% GAS>70 sa: 79% GAS >70 sz: 7% sa: 50% sz: 7% sa: 54% sz: 9% sa: 16% sz: 16% sa: 70% sz: 36% sa: 90%
(DeSisto, Harding, McCormick, Ashikaga, & Brooks, 1995)	N=269 Chronic sample	30 years	GAS Community Assessment Scale Mini mental state	47% «working in some capacity» in Vermont; 26% in Maine
(Hopper & Wanderling, 2000)	N=809 incidence cohort sz and other non-aff. psychoses	13 years	WHO-DAS last month	24% excellent or good (western countries)

References	N, sample	Time span	Recovery/ outcome measure	recovery; employment outcome
(Modestin, Huber, Satirli, Malti, & Hell, 2003)	N=208 (of whom 70% DSM-IV sz). Mixed chronic and incidence sample.	23 years	Recovery= no psychotic symptoms (some mild residues allowed), full time work, and unimpaired social funcitoning	22 %
(Kua, Wong, Kua, & Tsoi, 2003)	N=402 sz; ICD-9 confirmed diagnosis, first time hospitalised	10	Working and treatment status last 6 months GAS 8-9 (very high) Good: not in treatment, well, working Fair: not in treatment, not working; or out-patient and working Poor: in treatment (or hospitalised) and not working Full time work	43.5% at 20 years 32% 33% 35% 40.3%
(Strauss, Harrow, Grossman, & Rosen, 2010)	n=39	20 years	Strauss-Carpenter: 1 year of no symptoms, no admissions, no poor social functioning, living independently, and working half time or more	deficit patients: 13 % non-deficit patients: 63%
(Stephens, Richard, & McHugh, 1997)	n=484, of whom 476 sz-spectrum; first admission, also first treatment episode	5-29 years ; mean 13.8 years	Symptom course and levels: recovered= no residual symptoms, no minor exacerbations, no further hospitalisation	13 % (sz only: 7%)
(White et al., 2009)	N=109 FEP	10 years	WHO Life Chart Schedule; last 24 months: months of independent living, months of work; Poor outcome according to General Practitioner Questionnaire: poor mental health, no work, poor social functioning working at time of assessment work last year working more than 5 of last 10 years	 63% not-poor: 37% 19% 23% 44%

References	N, sample	Time span	Recovery/ outcome measure	recovery; employment outcome
(Makinen et al., 2010)	n=46 FEP (1966 birth cohort)	10 years	Negative symptoms	39 %
(Shrivastava et al., 2010)	N=101 sz (original sample N= 200)	10 years	No hospitalisation last 2 years, GAF> 80, QoLI >80, 3 or higher (on a 3-5 scale) on scale for «social fucntioning, independent living, education, social burden»; «Clinical Global Impression Scale» Employed Good social func. Indep.living Recovered	 20%-30% 23%-32% 50% 32%-46%
(Henry et al., 2010)	N=651 (original sample N= 723) FEP	7 years	GAF > 60 Remission: Andeasen work group-criteria minus the 6 months time-criterion Social recovery: 3 QLS items: social, basic living tasks, and work, (any paid employment, or school > half time) Employed full-time	42.1% 36.8% 30.5% 22%

10.2 Table II. Definitions and lengths of DUP across the world

Reference	Location, N	Definition	DUP length
(Lo and Lo,1977)	China N=82	"Duration of illness before seeking psychiatric attention; <1year, 1-3 years, or > 3 years.	<1 year: 64% 1-3 years: 20% > 3 years: 16%
(Johnstone et al.,1986)	United Kingdom N= 253	"Interval between onset and admission"	(<1 year: 52%) < 2 months: 28% 2-6 months: 24,5% 6-12 months: 26% >1 year: 26% >Unknown: 12%
(Rabiner et al.,1986)	USA N= 64	"Time from first sign of behavioural changes to baseline interview"	Mean: 14.5 months (approx. 62 weeks)
(Birchwood et al.,1992)	United Kingdom N=137	"Duration of onset, i.e. duration of illness before treatment". Treatment= hospital admission.	Mean: 30.3 weeks
(Haas and Sweeney,1992)	USA N=71	"Time from onset of first positive (SAPS, Andreasen et al, 1984b) symptom to first hospitalization"	< 1 year: 43.8% > 1 year: 56.2%
(Loebel et al.,1992)	USA N=70	"Time from onset of psychotic symptoms (and behaviour/personality change) to study inclusion"	Mean: 51.9 weeks (SD 82.3)
(Beiser et al.,1993)	Canada N=71[1]	"Treatment lag= interval between emergence of acute psychotic symptoms and initiation of treatment seeking"	Mean: 56.1 weeks Median: **8.2** weeks
(Hafner et al.,1993)	Germany N= 165	"Time from onset of first-rank symptom assessed by standardised instrument (IRAOS), to first hospitalisation"	Mean: 2.1 years (approx. 109 weeks)
(Larsen et al.,1996)	Norway N=43	"Time from score of 4 or higher on at least one PANSS positive subscale item, throughout the day for several days or several days a week to initiation of adequate treatment (defined)."	Mean: 114.2 weeks (SD 173.6) Median: **26** weeks
(McGorry et al.,1996)	Australia N=200	"Time from onset of psychosis to hospital admission"	Mean: 193.7 days (28 weeks) (SD 615.6) Median: 25 days (approx. **4** weeks)
(Scully et al.,1997)	Ireland N=48[2]	"The interval between age at onset of illness and age at initiation of neuroleptic treatment"	Mean: 13.9 years (SD 11.9)
(Wiersma et	The Netherlands	"Time from onset of positive	40%: average of 3

[1] Excluding affective psychoses
[2] Patients became ill before neuroleptic treatment was introduced; hence DUP is very long

al.,1998)	N=82	symptoms to initiation of mental health treatment"	months; 54%: "immediate" treatment
(Barnes et al.,2000)	United Kingdom N=53	"Time from onset of positive symptoms (behaviour/personality change and positive symptoms) to first treatment with anti-psychotic"	Mean: 59 weeks (SD 93) Median: **26** weeks
(Bottlender et al.,2000)	Germany N=998	"Time from first ADMP[3] psychotic symptoms to first hospitalisation"	% of patients: <1 week: 15.3 1-4 weeks: 22.9 1-3 months: 15.8 3-6 months: 11.2 6-12 months: 8.4 1-2 years: 13.5 2-3 years: 3.6 >3 years: 9.1 (< 1 year: 73.6)
(Browne et al.,2000)	Ireland N=53	"Time from emergence of psychotic symptoms as measured on the SCID, to first hospitalisation"	Mean: 22.7 weeks[4] (SD 36.8) Median: **6** weeks Range: 1-240 weeks
(Craig et al.,2000)	USA N=155 (schizophrenia and schizoaffective)	"Time from first psychotic symptoms according to SCID and other available information, to first hospitalisation"	Median: 98 days (**14** weeks)
(Drake et al.,2000)	United Kingdom N=248	"First onset of delusions, hallucinations to study inclusion"	Median: **12** weeks Range: 4- 624 weeks > 2 years: 6.5%
(Ho et al.,2000)	USA N=74	"1) The time period from the onset of the first symptom to the initiation of neuroleptic treatment 2) The time period from the onset of a full positive syndrome to the initiation of neuroleptic treatment.	1) Mean 130.5 weeks (SD 204) Median 53.5 weeks 2) Mean 60.8 weeks (SD 130.5) Median: **13.5** weeks
(Hoff et al.,2000)	USA N=50	"Duration (in months) of delusions, hallucinations, or formal thought disorder before treatment."	Mean: 11.4 months (approx. 48 weeks) (SD 16.2) Range: 1- 72 months
(Wiersma et al.,2000)	Europe N= 195	"Time between the (estimated) onset of psychotic symptoms and the first contact with a mental health professional"	Mean: 2.4 months (approx. 10 weeks) Range: 0-23 months >3 months: 20%
(Altamura et al.,2001)	Italy N=67	"The interval between the onset of the illness and the implementation of the first antipsychotic treatment."	Single episode patients: Mean: 7 months (approx. 30 weeks) (SD 4.3) Multi-episode patients: Mean: 23.6

[3] ADMP: Association for methodology and Documentation in Psychiatry; a rating scale
[4] There was a discrepancy between self-reported DUP and DUP as reported by relatives; relatives' scores had a mean of 15.9 weeks (sd 34.5); median 3 weeks, range 0-240 weeks.

			months (approx. 101 weeks) (SD 15.1)
(Norman et al.,2001)	Canada N=113	"The period from initial onset of psychosis to treatment is referred to as DUP(onset); and the estimated cumulative period of active psychosis as DUP(active)."	DUP(onset) Mean: 14.6 months (approx. 63 weeks) Median: 5.7 months (approx. **24** weeks) Range: 0.3-124.8 months DUP(active) Mean: 10. 3 months (approx. 44 weeks) Median: 4.9 months (approx. 21 weeks) Range: 0.3-78.2 months
(Verdoux et al.,2001)	France N=65[5]	"Time from onset of first psychotic symptoms to admission"	Mean: 22.7 months (approx. 97 weeks) (SD 59.3) Median: 3 months (approx. **13** weeks) Inter quartile range: 0.5-13
(Amminger et al.,2002)	Australia N=42	"DUP was defined as the period of time between the first experience of delusions or hallucinations and admission to EPPIC which was usually when neuroleptic treatment was commenced."	Mean: 246.3 days (35 weeks) (SD 525.2) Median: 76.5 days (**11** weeks)
(Bottlender et al.,2002)	Germany N=196	"The period between the onset of psychotic symptoms and the first psychiatric admission"	<6 months: 51% 6-12 months: 14.8% > 1 year: 34.2%
(Kalla et al.,2002)	Finland and Spain N=86	"DUP was defined as the time interval between the first manifestation of psychotic symptoms (hallucinations, thought disorder or inappropriate/bizarre behaviour, throughout the day for several days or several times a week, not limited to brief moments) and admission for treatment."	Finland (N=49): Mean: 4 months (approx.17 weeks) (SD 6) Median: 2 months (**8.5** weeks) Range: 0-25 Spain (N=37): Mean: 9.9 months (approx. 42 weeks) (SD 18.4) Median: 2 months (**8.5** weeks) Range: 0-72
(Malla et al.,2002)	Canada N=114	"Length of illness: Time of onset of any psychotic symptom (SANS/SAPS) and the time of the CT-scan"	Mean: 2.2 years (approx. 115 weeks) (SD 3.5)
(Malla et al.,2002)	Canada N=88	"The time of onset of first psychotic symptoms	Mean: 44.6 weeks (SD 66.6) Median:

[5] 22 of these had received antipsychotic mediaction previously

		contiguous with the presenting episode to the time of having received antipsychotic therapy for a period of 2 months unless significant response to medication was achieved earlier."	**22.5** weeks Mean value lower 50% of sample: 9.2 weeks (SD 6.13) Highest 50% of sample: 80.1 weeks (SD 69.5)
(Malla et al.,2002)	Canada N=66	"The time of onset of psychotic symptoms contiguous with the present episode, to the time of initiation of adequate antipsychotic treatment" (SAPA/SANS)	Mean: 55.1 weeks (SD 23.1) Median: **23.1** weeks
(Townsend et al.,2002)	Canada N=83	"The time of the onset of the first psychotic symptoms until either 1 month of treatment with antipsychotic medication or significant symptom reduction (defined clinically through interview with program staff) had been obtained, whichever occurred earlier." (Assessed with modified IRAOS)	Median: **24** weeks
(de Haan et al.,2003)	The Netherlands N=88	1. "Time from onset of delusions, hallucinations, and/or disorganised behaviour, to initiation of antipsychotic treatment" 2."Time from onset of delusions, hallucinations, and/or disorganised behaviour, to initiation of intensive psychosocial treatment"	1.Mean: 8.6 months (approx. 37 weeks) (SD11.4) Median: 3 months (approx. **13** weeks) 2. Mean: 19 months (approx. 81 weeks) (SD 19)
(Ho et al.,2003)	USA N=156[6]	"Time period from the onset of the full positive syndrome to the initiation of antipsychotic treatment. "Full psychotic syndrome" was defined as the presence of any one of five positive symptoms (i.e., delusions, hallucinations, bizarre [disorganized] behaviors, positive formal thought disorder, and catatonic motor behavior) rated at a severity level of moderate or worse."	Mean: 74.3 weeks (SD 145.1) Median: **13** weeks Inter quartile range: 52 weeks
(Keshavan et al.,2003)	USA N=104	"The time interval (in weeks) between onset of psychotic symptoms (hallucinations, delu- sions, or disorganization of thinking; bizarre or catatonic	Mean: 95.7 weeks (SD163.4) Median: **34.4** weeks Range: 0.3-1171

[6] Approximately 20% were not neuroleptic naive, but none of the patients had received antipsychotic treatment for longer than 3 months

		behavior) and index admission into this study."	
(Kua et al.,2003)	Singapore N=402	"Time of emergence of psychotic symptoms (both positive and negative) to the time of first admission"	< 1 month: 15.9% > 6 months: approx. 50%
(Addington et al.,2004)	Canada N=200	"The point at (from) which the first positive symptom was present and then (to) the length of time in weeks until the first effective treatment was initiated" Positive symptoms rated at least 4 on the PANSS. The symptom(s) must have lasted throughout the day for several days or several times a week, not being limited to a few brief moments." Use of IRAOS.	Mean: 84.2 weeks (SD 139) Median: **28** weeks Range: 1-780
(Perkins et al.,2004)	USA N=191[7]	"Onset of first psychotic symptom to onset of treatment (as defined in study)". Use of SOS.	Mean: 15.1 weeks (SD 20.4) Median: **8** weeks
(Tirupati et al.,2004)	India N=49	"The continuous period between onset of psychosis (delusions, hallucinations, disorganised behaviour, formal thought disorder first noted by the caregiver) and the time of initiation of treatment after case identification"	< 2 years: 6 (12%) 2-5 years: 13 (27%) 6-15 years: 12 (24%) >15 years: 18 (37%)
(Ucok et al.,2004)	Turkey N=79	"Time of onset of first psychotic symptom to the first hospitalisation"	Mean: 8.6 months (approx. 37 weeks) Median: 6 months (approx. **26** weeks)
(Ropcke and Eggers,2005)	Germany N=55 (Early onset sample, mean age 16 years)	"The period from the onset of first psychotic symptoms until the beginning of the first anti-psychotic treatment." Use of IRAOS.	Mean: 276 days (approx. 42 weeks) Range: 0-1002 days
(White et al.,2009)	United Kingdom N=109	"The time between onset of first positive symptoms (SAPS) and index admission".	Mean: 29 weeks (SD 42.1) Median: **8** weeks
(Shrivastava et al.,2010)	India N= 101	Time from onset of symptoms (positive and/or negative) to study inclusion.	Mean: 12.7 months (approx. 54 weeks) (SD 7.3) Median: 11 months (approx. **47** weeks) <6 months: 19.8% 6-11 months: 33.7% 1-2 years: 39.6% <2 years: 6.9%

[7] 62% of patients had received previous antipsychotic treatment, with a mean duration of 34.3 days/median 17 days.

(Penttila et al.,2010)	Finland N=89	The period between the onset of first psychotic symptoms and the commencement of treatment	Mean: 225 days (approx. 32 weeks) (SD 329) Median: 121 days (approx. **17 weeks)**

10.3 Letter by Dr. Amos to the editor of the American Journal of Psychiatry and response by TIPS group

develops enhanced colonic inflammatory responses in adulthood (3). This would set the stage so that when the perinatally BPA-exposed female rat becomes pregnant, the pregnancy may be marked by enhanced inflammation. Paradoxically, estrogenic exposure may have anti-inflammatory effects in the exposed adult, but inappropriate estrogen exposure may have pro-inflammatory effects in the perinatally exposed offspring. These effects were observed at levels of BPA exposure previously believed to be too low for observed adverse effects in humans (3).

I have proposed elsewhere an estrogenic endocrine disruption theory of schizophrenia, in which inappropriate dosage, timing, or duration of prenatal estrogen exposure causes schizophrenia (4, 5). Within this theoretical framework, inappropriate estrogen exposure occurring in the brain could also be occurring in the colon so that an association of celiac disease or some other inflammation and schizophrenia may be observable not from a genetic link per se but rather a transgenerational effect of prenatal estrogen exposure.

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Alternative Interpretation for the Early Detection of Psychosis Study

To the Editor: In the April issue, the Treatment and Intervention in Psychosis (TIPS) early-detection study reports 10-year results in a manner that overstates the impact of reducing the duration of untreated psychosis (1). The authors dismissed a 50% increase in hospitalization in the treatment group after 5 years as the result of regional policy differences. They did not describe the policy differences or analyze the effects of this impressive confound on the small difference in symptoms, instead claiming to have demonstrated "positive effects on clinical and functional status" (2, 3). They omit hospitalization results altogether at 10 years, despite this being by far the most impressive result at 5 years (1).

Perhaps because at 5 years the researchers reported a nonsignificant advantage in remission for the control group (2), at 10 years they introduce a new recovery metric, based largely on work function, which showed a significant advantage for the treatment group (1). Although they acknowledge a significant attrition bias by 10 years, they do not report that at 5 years there was no difference in work function, or suggest how reducing the duration of untreated psychosis at baseline would not improve work function at 5 years but double work function at 10 years.

The authors reported that the control group achieved independent living significantly more often at the 10-year mark, but dismiss this evidence of worse function in the treatment group, suggesting that independent living is not evidence of recovery because it is not included in the new metric. They do not analyze the possibility that failure to achieve independent living is evidence of poor function (1).

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Response to Amos Letter

To the Editor: Dr. Amos raises several points of criticism regarding the TIPS study and our interpretation of the data, as he did previously (1) in response to abstracts from our group. We thank the *Journal* for the opportunity to respond.

First, Dr. Amos points out that patients from the health care area practicing early detection had significantly higher rates of hospitalization at the 5-year follow-up, and he is critical of the fact that we did not thoroughly investigate this possible confounder. This is a valid concern; however, he seems to miss the point that it is the group of patients *not* in symptom remission (a prerequisite of recovery) who received more inpatient care in the early-detection area. For recovered patients, there was no difference between early and usual detection. Knowing that more hospital time did not lead to better recovery, hospitalization cannot be a confounder.

Second, Dr. Amos questions the finding that while there apparently were no differences in work function at the 5-year follow-up, the early-detection patients had double the chance of full-time employment at 10 years. He goes on to imply that we might have chosen a new measure of "recovery" out of convenience, having made sure that this measure would yield us more favorable results. At 5 years, we used "working at least

20 hours per week" as the employment outcome (2). At the 10-year follow-up, using a new measure of recovery chosen before data collection and on the basis of recent developments in the field, we looked only at full-time employment. This is a stricter measure and was significantly higher for early detection patients. However, nonrecovered patients had poor working capacity both in early and usual-detection areas, both at 5 and 10 years.

Third, Dr. Amos addresses the finding that more patients from the usual-detection area were living independently. However, living independently is a necessary but not sufficient element in recovery. In fact, as reported in our 10-year follow-up in the April issue, only 17.9% of the patients living independently in the usual-detection area were fully recovered with both symptom remission and full-time employment, compared with 48.4% for early-detection patients. This seems to indicate that living independently does not automatically imply better health and function.

All in all, as we have noted elsewhere (3), we agree that early detection cannot and should not be presented as a "cure for all." Nevertheless, our data show that early detection does seem to have long-standing positive associations with outcome measures for a large group of patients, and it improves the chances of recovery. However, for a considerable group of patients, we were not able to demonstrate a long-term effect.

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Bilateral Pallidal Necrosis and Cardiac Toxicity in a Patient With Venlafaxine and Bupropion Overdose

TO THE EDITOR: The new generation of antidepressants is generally thought to be safer than traditional antidepressants. Although combining antidepressants is recommended for the treatment of refractory depression, the toxicity of drug overdose from more than one antidepressant is seldom addressed.

Case Report

A 30-year-old woman was sent to the emergency department 1 hour after ingesting venlafaxine and bupropion in a suicide attempt. The exact dose was uncertain, but according to the metabolites of venlafaxine, bupropion, and benzodiazepine found in her urine, it is probable that she consumed a 1-month prescription of 150 mg venlafaxine, 300 mg bupropion, and 3 mg lorazepam that was prescribed 3 days earlier.

She had clear consciousness initially, but generalized myoclonus soon occurred. A fever (40.6°C) and tachycardia (100–170 bpm) developed with normal blood pressure (122/91 mmHg), respiratory rate (16/min), and O_2 saturation (SpO_2=95%). An ECG demonstrated prolonged QRS complex with a deep, slurred S wave on lead I and an R wave on lead aVR. Sodium bicarbonate was then administrated.

One hour later, the patient became drowsy and confused and she suffered respiratory distress. Her blood pressure decreased (94/36 mmHg), tachycardia increased (200 bpm), and SpO_2 decreased (49%). Endotracheal intubation was performed within 5 minutes, and her SpO_2 and blood pressure returned to normal. After sodium bicarbonate treatment, the patient recovered from the changes seen on the ECG. However, leukocytosis (10.27×10^9/L), elevated creatine kinase (520 U/L) and creatinin (1.5 mg/dL) levels, and changes in vital signs suggested serotonin syndrome. Cyprohepadine was provided with supportive treatment; intravenous lorazepam was also given continuously for agitated behavior. Fever and disturbed consciousness ameliorated within 2 days, but creatine kinase and alanine transaminase levels continued to increase, peaking at 107,895 U/L and 2,453 U/L around 43 and 102 hours, respectively, after overdose. The patient was extubated 7 days later.

One week after extubation, purposeful involuntary movement and akathisia were noted after discontinuing lorazepam. Suspecting benzodiazepine withdrawal, lorazepam was resumed with pramipexole, 0.75mg/day, until the akathisia subsided 2 weeks later. The choreoathetosis remained, with frontal releasing signs (i.e., Luria test, glabellar reflex) and impaired recent memory, language, and executive function. An MRI scan revealed bilateral pallidal necrosis 7 weeks after admission (Figure 1 and Figure 2).

Discussion

A limited number of reports of antidepressant overdose-related bilateral pallidal necrosis have been published. Szólics et al. (1) reported similar pallidal necrosis with multiple functional changes and extrapyramidal symptoms after fluoxetine overdose, implying a complex relationship between serotonin and the nigrastriatal dopaminergic system. The bilateral pallidal necrosis in our patient could have been caused by transient hypoxia, but the toxicity of venlafaxine and/or bupropion could not be excluded. It is therefore worth being cautious when prescribing venlafaxine concomitantly with bupropion for patients at high risk of deliberate