Long-term Outcome, Suicidal behaviour, Quality of Life and Expressed Emotion in Adolescent Onset Psychotic Disorders

BY
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Abstract


This study investigated a consecutive cohort of 88 youngsters with onset of a psychotic disorder at age 15.7 (sd 1.5) years and followed-up 10.6 (sd 3.6) years after first admission at the age of 26.5 (sd 3.7) years. A subsample of 15 subjects were assessed with the Five Minute Speech Sample for measuring Expressed Emotion and subsequent recording of relapses during a two year period.

A diagnostic split between schizophrenia spectrum psychosis and affective psychotic disorder was usually stable over time. The main diagnostic shift was an influx to schizophrenia spectrum disorder of subjects with a better premorbid function and less insidious onset as compared to those with a stable schizophrenia diagnosis.

Early onset schizophrenia spectrum disorder usually had a poor functional outcome. Most subjects needed support in the form of a disability pension. Early onset affective psychotic disorder usually had a good functional outcome. Most subjects worked and enjoyed regular friendships. The functional level before onset of illness was the best predictor of future functional level in psychotic disorders. A family history of non-affective psychosis predicted a worse function in schizophrenia. Frequent episodes and low intelligence predicted a worse function in affective disorders.

Four men (4.5% of the sample) committed suicide. The risk of suicide was increased about 30 times. Almost a third of subjects attempted suicide. Females made more attempts. Suicide attempts were related to more depressive symptoms but less negative symptoms at first episode, to readmissions and to dependence on nicotine.

Subjects with schizophrenia spectrum psychoses were less satisfied with life than those with affective psychotic disorder. Subjective satisfaction in schizophrenia was strongly associated to depressive mood while in affective disorders it was associated to degree of employment. Adolescents with psychosis in families rated high or borderline high in Expressed Emotion either during first episode or after discharge had an increased risk of relapse.

Keywords: schizophrenia, affective disorder, bipolar disorder, outcome, suicide, quality of life, expressed emotion

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Do you like me?

Do you like me?
Although I’m like this
Do you care about me?
Although I show that I don’t want you to
Can you help me?
Although I might show that I don’t need it
Do you help me when I’m drowning?
Although I don’t show my need
Do you help me in my anxiety
because I need it
Do you like me?
Although I’m like this
Do you really want to get to know me well?
Although I don’t know who I am
Do you want to help me when I’m scared
Although I’m always scared
Do you care about me?
Although I show that I don’t want
Do you want to clutch my hand?
When it is cold from fear
Can you prove that you are not dangerous?
Although I might not believe you
Do you like me?
Although I’m like this

Poem written by a subject in the study
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>A-LvK</td>
<td>Anne-Liis von Knorring</td>
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<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
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<td>CFI</td>
<td>Camberwell Family Interview</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>DSM-III-R</td>
<td>Diagnostic and Statistic Manual of American Psychiatric Association, third edition revised</td>
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<td>EDA</td>
<td>Electrodermal activity</td>
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<td>EE</td>
<td>Expressed Emotion</td>
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<td>EOBBD</td>
<td>Early Onset Bipolar Disorder (onset before age 18 years)</td>
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<td>EOI</td>
<td>Emotional Overinvolvement</td>
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<td>EOMDD</td>
<td>Early Onset Major Depressive Disorder with psychotic features</td>
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<td>EOS</td>
<td>Early Onset Schizophrenia (onset before age 18 years)</td>
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<td>FMSS</td>
<td>Five Minutes Speech Sample</td>
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<td>GAF</td>
<td>Global Assessment of Functioning</td>
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<td>HJ</td>
<td>Håkan Jarbin</td>
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<tr>
<td>ICD-9</td>
<td>International Classification of Disorders, ninth edition</td>
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<td>ICD-10</td>
<td>International Classification of Disorders, tenth edition</td>
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<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
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<tr>
<td>LQOLP</td>
<td>Lancashire Quality of Life Profile</td>
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<td>PANSS</td>
<td>Positive and Negative Symptom Scale</td>
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<td>QOL</td>
<td>Quality of Life</td>
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<td>PPV</td>
<td>Positive Predictive Value</td>
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<td>S-C</td>
<td>Strauss-Carpenter scale</td>
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<tr>
<td>SCID</td>
<td>Structured Clinical Interview of DSM diagnoses</td>
</tr>
<tr>
<td>VEOS</td>
<td>Very Early Onset Schizophrenia (onset before age 13 years)</td>
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<tr>
<td>YO</td>
<td>Yngve Ott</td>
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INTRODUCTION

Diagnosis

History
There were descriptions already in the early 1800’s of severe mental disorder, psychotic disorders as well as mania, with onset in childhood or in adolescence [161]. Emminghaus published the earliest textbook on psychiatric disorders in childhood from the university of Tartu, Estonia in 1887 [55]. He not only distinguished cerebral neurasthenia as a possible precursor to psychotic states but also melancholia, mania, acute dementia and paranoid-hallucinating states. The major diagnostic distinction of psychoses has been attributed to Kraepelin [114]. More than a century ago, he distinguished the major dichotomy of endogenous psychoses as manic depressive psychoses with an episodic course and dementia praecox with a deteriorating course. Kraepelin also described the onset of the major types of psychoses both in childhood and in adolescence. The term “group of schizophrenias” implying different forms of schizophrenia was introduced by Bleuler in the early 1900’s [166].

As opposed to the early concept of continuity between childhood and adult manifestations of psychoses, the concept of “childhood psychoses” came from the 1940’s to the 1970’s to include all severe disturbances in the young including present-day psychoses, autistic disorders and severe personality disorders [91]. The epoch-making studies of Kolvin and Rutter from the early 1970’s established that autism and schizophrenia in children have different symptomatology, age of onset and family history [112, 182]. From the 1980’s there was a return to diagnosing the psychoses in children and adults with the same criteria starting with the DSM-III [5] and the ICD-9 [222]. The continuity between childhood, adolescent and adult onset of schizophrenia has subsequently been validated [22, 212].

Early-onset cases of mania fell into oblivion after Kraepelin. It was not until the 1960’s that manic-depressive illness in children was discussed by
Anthony and Scott [73]. They used very strict criteria thereby excluding
case but describing continuity from early adolescence to
childhood onsets but describing continuity from early adolescence to
adulthood in a few cases. In Europe, Annell successfully treated children
with presumed manic-depressive disorder with lithium. She noted that the
symptoms rarely resembled typical adult mania but were periodical and
included periods of stupor or mild hypomania [9].

Diagnosing psychotic disorders in childhood and adolescence

Children, adolescents and adults are categorised with the same criteria for
psychotic disorders in both DSM-IV [7] and ICD-10 [223]. However,
making a diagnosis in children and adolescents is often more difficult than in
adults as the various stages in the developmental process have to be taken in
account [45]. Furthermore, in psychotic disorders with early onset, the
clinical picture often diverges from the standard adult presentation.

Schizophrenia

Early onset cases (before age 18 years) and more so very early onset cases
(before 13 age years), as compared to adult onset forms, are characterised by
increased male preponderance [131, 180, 215], more premorbid
abnormalities in speech, motor development and social development
sometimes approaching autistic disorders [54, 74, 89, 147, 206, 215], a more
insidious onset [11, 134, 215], less frequent systematic delusions and
catatonic symptoms [180, 215] and increased family history of schizophrenia
spectrum disorders [52, 134, 145, 147, 214, 215]. Their thought disorder is
often influenced by developmental and language problems [180]. Early onset
schizophrenia, as compared to other early onset psychotic disorders, presents
with more impaired premorbid development, more enuresis and more
incontinence during psychosis [92].

Bipolar disorder

Manic-depressive disorder is, in modern classification, called bipolar
disorder. Bipolar disorder in older adolescents is well established and
resembles the adult onset form [61] but may have high rates of psychotic
symptoms [17, 136, 170]. It is possible to diagnose bipolar disorder in early
adolescence and also before puberty with the DSM-IV criteria [148] but
many prepubertal cases fall short of full criteria (labelled bipolar disorder not
otherwise specified). Early onset cases, compared to adult onset bipolarity,
more often present with mixed episodes (i.e. symptoms of depression and
mania simultaneously) or with prominent depression, a much more
protracted or even continuous course and a high degree of comorbidity with
attention deficit hyperactivity disorder, conduct disorder and anxiety disorders [61, 62, 120, 225].

Issues in classification

Despite advances in neuroscience and genetics, there are still no external objective criteria to validate the diagnostic distinctions of psychotic disorders. Our present classifications in psychiatry are based on presenting symptoms and signs. The reliability of the diagnoses was much improved with structured interviews, explicit criteria and decision rules in the DSM-III [5] and ICD-10 [223]. This has shifted the focus from the reliability to the validity of psychiatric diagnoses, i.e. to establish whether they are well-founded, applicable and able to predict outcome and response to treatment. Robins and Guze [169], suggested in 1970, five criteria to establish the validity of a psychiatric diagnosis: 1) clinical description, 2) laboratory studies, 3) delimitation from other disorders, 4) follow-up study, and 5) family study. By applying these criteria they distinguished schizophrenia with good prognosis from schizophrenia with poor prognosis. Their “good prognosis schizophrenia” was later distinguished as schizophreniform disorder in DSM-III [107]. Kendell and Jablensky question the validity of most diagnostic boundaries in psychiatry [107]. They argue that most mental disorders have no clear natural boundaries, as complex interactions between genes and environment and absence of clear “zones of rarity” between psychiatric disorders, rather support a continuous as opposed to a categorical classification. Few diagnoses in psychiatry are well demarcated and valid entities such as Huntington's chorea, fragile-X and Down's syndrome. Instead, Kendell and Jablensky propose the term utility in evaluating our present psychiatric diagnoses. They state

“...that a diagnostic rubric may be said to possess utility if it provides nontrivial information about prognosis and likely treatment outcomes, and/or testable propositions about biological and social correlates.”

Our categorical definitions of the major mental disorders are somewhat arbitrary. There will appear changes in our diagnostic tools with increased knowledge in the years to come. However, despite present shortcomings, studies of categorically defined psychiatric disorders can provide important information to improve treatment and ultimately the quality of life of the afflicted individuals.

The term “psychotic” has received different definitions ranging from a restrictive one with prominent hallucinations and delusions occurring in the absence of insight to more inclusive definitions. These have included hallucinatory experiences which the individual experience as hallucinations,
any grossly impaired functional impairment, loss of ego boundaries or any gross impairment in reality testing [7]. Thus, psychotic symptoms may not be part of a psychotic disorder and different psychotic disorders emphasise different aspects of psychotic symptomatology.

Diagnostic stability

Adult onset psychotic disorders
In adults, the long-term stability of the major psychotic disorders is generally high. Schizophrenia is the most stable (about 90%) but affective disorders also show high stability (about 80%) in most reports of first episode studies validating the original dichotomy by Kraepelin [57, 119, 128, 129, 196, 202]. The diagnostic drift has, in most cases, meant a shift over time to schizophrenia spectrum diagnoses [8, 41, 103, 128, 185].

Early onset psychotic disorders

Affective disorders misdiagnosed as schizophrenia
The lack of longitudinal stability has been a pervasive problem in early onset psychotic disorders. In the 1980s, studies from Anglo-Saxon countries noted that one half of patients with a bipolar diagnosis in adult age were diagnosed with schizophrenia at their first episode in adolescence [102, 215]. Eggers followed-up a German sample of schizophrenia with onset before age 13 years where 28% were reassessed with schizoaffective disorder 15 years later [52, 54]. Their characteristics with female preponderance, a family history of affective psychoses, acute onset after a normal premorbid development and a more benign prognosis raise doubts whether the diagnosis might satisfy DSM-IV criteria for bipolar disorder. McGlashan [136] noted that the symptom picture of bipolar adults with onset in adolescence usually satisfied criteria for DSM-III-R schizoaffective disorder during the first episode. As clinicians were alerted to this problem, early onset manic episodes were not diagnosed as schizophrenia but still in only one third of cases labelled as bipolar disorder at first episode [38]. Goodwin and Jamison [73] provide on page 107 an exhaustive list of pitfalls leading to a misdiagnosis of affective disorder as schizophrenia. Many of them are more prevalent in the young i.e. mixed states, irritability [61], paranoid ideation, incomplete interepisodic recovery, substance use comorbidity [36], flight of ideas and prominent delusions and hallucinations [17, 136, 170].
Personality and other non-psychotic disorders misdiagnosed as schizophrenia

On the other hand, a Swedish register based follow-up at age 30 years [64] of inpatients diagnosed with adolescent onset schizophrenia, found less than 60% still diagnosed with schizophrenia spectrum disorder while 40% were assigned chronic alcoholism or paranoid reaction with Asperger syndrome, personality disorder, atypical psychosis or a disability pension without a specific diagnosis. None was reassessed with affective disorder. A Danish register-based study noted that one third of inpatients originally diagnosed with schizophrenia before 18 years received other diagnoses at subsequent hospitalisations in adulthood. However, only 5% received an affective diagnosis later on whilst one fifth were hospitalised with a diagnosis of personality disorder [195]. This finding is in line with the high prevalence of hallucinations and delusions in non-psychotic conduct and emotional disorders [48, 60, 132] including posttraumatic stress disorder [56] in children and adolescents. Their psychotic symptoms including hallucinations can be regarded as dissociative and anxiety related symptoms [4, 94, 132] while formal thought disorder or negative symptoms are rarely present. However, child maltreatment does not exclude a diagnosis of psychotic disorder [132]. Caution in disregarding hallucinations or delusions in the young as part of a non-psychotic disorder are called for by a prospective population based study assessing delusions and hallucinations at age 11 years and observing a highly significant increased risk of being diagnosed with schizophreniform disorder at age 26 years [162]. It is worth noting that the risk of developing an anxiety disorder was also significantly increased and a more likely outcome and particularly if the psychotic symptoms at age 11 years were judged as mild.

Diagnostic problems in childhood

McKenna et al [137] reassessed children with clinically judged onset of schizophrenia before the age of 12 years (VEOS) applying the DSM-III-R criteria. They found that 3/4 had a non-schizophrenia DSM-III-R diagnosis including both affective disorders and developmental disorders with psychotic features. The largest group of about 30% did not fit into any specific DSM-III-R category and was labelled “Multidimensionally Impaired”. Their psychotic symptoms were brief and not clearly delusional and they were eager to relate but lacked social skills. Other symptoms were affective instability, impulsivity, neuropsychological deficits and an onset before age 7 years. A 2- to 8-year follow-up of this group of early onset unspecified psychotic disorder found half with an affective psychotic disorder and the other half non-psychotic but often with disoruptive
behaviour disorders [146]. A similar symptom presentation has also been
categorised as “Multiple complex developmental disorder” [199]. Almost a
tenth of the assessed sample was rediagnosed with pervasive developmental
disorders illustrating difficulties in separating premorbid personality
abnormalities from autism. Thus, a diagnosis of VEOS in a clinical setting
should be considered preliminary and re-evaluated by a specialist center.

There are follow-up studies of clinically diagnosed early onset psychotic
disorders reporting a substantial degree of diagnostic drift to both
schizophrenia and affective psychosis [134], and also reports of a moderate
[131] to high degree of stability of early onset schizophrenia [40, 184].
These findings were reported after variable observational periods, e.g. four
years [134], seven years [184], twelve years [40] or fifteen years [131].
However, studies employing a standardised diagnostic assessment at first
episode have found a high degree of stability of original diagnosis. Recently,
McClellan et al [132] prospectively, but not blinded, found the two year
stability to be 90% or more in schizophrenia and bipolar disorder. Hollis [90]
retrospectively reassessed diagnosis of first episode and blindly assessed
DSM-III-R diagnosis ten years later. The stability in both schizophrenia and
affective disorders was 80%.

Outcome

Psychosocial function
Studies assessing outcome in psychotic disorders are fraught with several
methodological problems making comparisons and conclusions difficult.
Westermeyer and Harrow [216] review the outcome literature on
schizophrenia and point to four major areas of potential inadequacies. These
areas are: a) outcome characteristics, b) course of illness, c) definitions of
schizophrenia, and d) comparison group.

They state that much of the confusion centers on the definition of
outcome and the cut-off points used. Vague terms such as “improved” or
“recovered” without adequate specification are difficult to compare. The
changing demands on function over the life cycle is further complicating the
matter. It could be less demanding to continue studies in late adolescence as
compared to wage earning employment in early adulthood.

The impact of different definitions of schizophrenia on outcome is clearly
illustrated in a review of one hundred years of outcome studies by Hegarty et
al. [83]. They found that after an average of five years, almost ½ were
improved with broad criteria, while just over ¼ were improved with narrow (i.e. Kraepelinian) criteria. The return to Kraepelinian criteria had lowered the rate of improvement to 36% in the latter part of the 1900’s but neuroleptic treatment was shown to contribute to a more positive outcome as compared to the early 1900’s.

Westermeyer and Harrow [216] argue that comparison groups are necessary to interpret the findings. They state that:

“A comparison of different diagnostic groups is of value to disentangle the relative predictive merits of various diagnostic and prognostic criteria, and to justify schizophrenia as a disease-specific concept.”

**Adult onset psychotic disorders**

A century after Kraepelin, Hegarty et al. [83], still conclude that adult onset schizophrenia has a variable course but leaves almost 2/3rd of the cases in a residual state. The area of greatest incapacity is work adjustment, where 20% of narrowly defined schizophrenia patients are employed full time at follow-up [216]. A recent European multisite 15 year follow-up of social disability in adult onset schizophrenia [218] found ¼ to be severely disabled with a trend to deterioration over time while 40% showed some disability and only 1/7 were without any disability. The study excluded subjects reclassified with other diagnoses and did not acknowledge household performance as sufficient for a good outcome. This contributed to a more negative picture. A Swedish 5 year follow-up of early adult onset schizophrenia found 30% with a good outcome [219]. However, some impairment was allowed in the criteria for “good outcome”.

In contrast to schizophrenia, affective psychoses in adults have a more favourable long-term outcome in about ¾ of cases without difference between bipolar or unipolar affective psychoses [201]. More recent 5 year follow-ups of subjects with bipolar disorder found some occupational impairment in half of the subjects [66, 67]. Recurrent episodes predicted poor functioning [66], while unipolar depressed patients had a better functional outcome [67].

**Early onset psychotic disorders**

_Schizophrenia_

Most long-term follow-up studies have found that 75-90% of altogether 177 subjects with early onset schizophrenia (EOS) are moderately to severely impaired at follow-up four to fifteen years after onset [40, 65, 90, 131, 134, 167, 215]. Median values on global assessment of functioning (GAF), when reported, are around 40, indicating a major impairment in at least one area of functioning [90, 131, 134, 215]. In contrast, Asarnow et al. [10] found good
outcome in 5 (¼) and moderate improvement in another 5 (¼) of 18 cases of very early onset schizophrenia (VEOS) at a 2-7 year follow-up. GAF values exceeded 50 in more than ½ of the cases. Extensive treatment in these children might have influenced the findings. In a very long follow-up study of schizophrenia with onset before age 14 years, Eggers [52] and Eggers and Bunk [54] found ¼ of subjects in complete remission and ¼ in partial remission. Salient features were a female preponderance and an acute onset of less than 4 weeks in ¼ of cases including all with a good outcome. Those with onset before age 12 had in 2/3 of cases an insidious onset and a worse outcome. Furthermore, Remschmidt et al. found that schizophrenia with onset before age 14 years had a more continuous and chronic course than adolescent onset cases [167]. Krausz and Muller-Thomsen [115] found, after eleven years, 30% of patients with EOS not handicapped and an additional 19% handicapped but employed. They also noted improvement between five and eleven years of observation and most so for women. After a seven year follow-up of a hundred patients with EOS, Schmidt et al. [184] found more than ½ with no or mild occupational impairment and almost ½ with no or mild social disability.

Studies comparing outcome in EOS to other psychoses report discordant results. Those reporting a more severe impairment in schizophrenia subjects are limited by follow-up in the teens [133, 134, 215], by very small numbers and many dropouts [40] and by comparisons based on adult follow-up diagnosis [134, 215]. This leaves one methodologically robust study [90] reporting a more severe impairment in adulthood of EOS compared to a group of affective, schizoaffective and unspecified psychosis. On the contrary, early-onset bipolar disorder (EOBD) cases were just as severely impaired as EOS in a Swedish register based study on outcome at age thirty years, albeit with few and possibly selected bipolar patients [65].

Two studies comparing functional outcome in adult-onset schizophrenia and early-onset schizophrenia (EOS) find a worse outcome in the EOS in Germany regarding social function [184] and in Japan regarding negative symptoms and performance-IQ [226] while no difference between adolescent or adult onset was found in a 15 year follow-up of ICD-9 schizophrenia from Singapore [200]. Instead, outcome in work function was better for early onset cases during the first ten years of observation. High rates of about ½ were able to work after 5-15 years of follow-up but quality and quantity of work performance were not specified.

**Affective disorders**

Studies comparing long-term functional outcome in adult-onset bipolar disorder and early onset bipolar disorder find a similar long-term outcome [37, 136] while a recent two year follow-up found lower rates of recovery.
and more comorbid substance abuse in adolescent onset cases [36]. Both a recent Indian 4-5 year follow-up [189] and a 20 year follow-up from the 1970’s of EOBD [37] found 3/5 of subjects functioning well. The few additional long-term follow-up studies of EOBD, all with small samples, have yielded contradictory results with poor outcome in 40-80% of cases [40, 65] while a Danish study from the pre-lithium era found 2/3 of EOBD functioning well at age 25 years but less than a third remained well at age 50 years [155]. In contrast, early onset depressive psychoses showed a poor outcome in only 1 of 8 subjects [65].

Thus, there are few studies examining the adult outcome of early onset psychotic disorders. This research is often hampered by frequent misdiagnosis [134, 215], use of end-point diagnosis rather than initial presentation [53, 54, 131, 134, 215], small sample size [40, 65, 134], selection biases or a low follow-up rate [40, 90, 134, 189], and absence of comparison group [10, 54, 131, 155, 189].

Predictors of outcome
A thorough list of predictive factors of adult onset schizophrenia is presented by Kaplan and Sadock [104]. Negative factors were, amongst others, young onset, insidious onset, poor premorbid functioning, withdrawn, family history of schizophrenia, negative symptoms, no remission and frequent relapses. Studies of EOS using multivariate methods have found negative predictors of overall function to be primarily low premorbid function [130, 213], severity of positive and negative symptoms at acute episodes [130] or state after first admission [213] while older age at onset predicted a worse occupational function [213]. One study with few EOBD subjects found premorbid function or IQ<80 to predict function at follow-up [213].

Suicide

Adult onset schizophrenia and affective disorders
Suicide is the most common cause of early death in schizophrenia [3, 35, 81] and in affective disorder [81, 87, 229]. The lifetime risk of suicide has been estimated to 10 % in schizophrenia [35] and to 15% in affective disorders [99]. However, a meta-analysis applying more sophisticated calculations of the data questioned the high figures and estimated the risk to 4% in schizophrenia and to 6% in affective disorder [99].

The risk of suicide in schizophrenia was shown to be highest in young patients and in the early phase of disorder [35, 81]. In a Swedish register study of psychiatric admissions for affective disorders, the highest risk of
suicide was in young persons below age 30 years and in the first years of disorder [229].

**Early onset psychotic disorders**

*Schizophrenia*

Reports of suicide in early onset psychotic disorders are scarce. There are studies reporting the rate of suicide to 13% in a 13 year follow-up of adolescent onset schizophrenia [116] and to 16% in a 22 year follow-up of adolescent onset schizophrenia [1] while other studies (all extending beyond age 25 years) have reported lower suicide rates i.e. 5% [52], 2% [131] or 0 [65]. Several studies do not report the cause of death [40, 90, 184, 215] or specific diagnosis of the deceased [40, 90, 184]. When reported separately, suicide is the definitive cause of death in 18 of 22 cases whilst only two deaths were definitely non-suicidal [1, 13, 40, 52, 116, 131]. Adding up all deaths in studies of EOS or psychotic groups with predominantly schizophrenia and a follow-up of minimum 4 and up to 22 years, yielded 38 casualties over 6068 observed years, i.e. a death rate of 0.6% /year [1, 13, 40, 52, 65, 90, 116, 131, 184, 215]. Forty (7.1%) of 564 subjects were deceased. This figure can expect to rise as almost ½ of the subjects had not yet reached age 25 years. A thirteen year follow-up of young adult onset schizophrenia with a mean age at onset of 21 years reported a suicide rate of 9% [217].

*Affective disorders*

A few, small and heterogeneous studies report suicide rates in early onset affective psychotic disorder [1, 65, 155, 189, 215]. A 25 year follow-up of an early onset bipolar sample selected with recurrent episodes from the pre-lithium era reported two (7%) cases dead from suicide [155]. Another Danish sample of nine early onset affective psychotic disorders reported 2 (22%) suicides over a 22 year follow-up [1] while one (3%) adolescent died from suicide in a five year follow-up from India [189] and none from the other studies [65, 215].

**Predictors of suicide**

A thorough list of risk factors for suicide in adult onset schizophrenia included male gender, white, socially isolated, depression, suicide attempts, family history of suicide, deteriorating health with high level of premorbid functioning, chronicity of illness with high symptom levels and a realistic awareness of future illness [35]. Risk factors for suicide in affective disorders were male gender, family history of bipolar disorder, suicide attempts, suicidal ideation and poor outcome. Mania was instead inversely
related to suicide [72]. Others noted family history of suicide, violent attempts [122] or complicated and comorbid clinical conditions [100] among suicide victims.

Suicide attempts

**Adult onset schizophrenia and affective disorders**
Many individuals with schizophrenia or affective disorders commit suicide attempts. Figures in schizophrenia range from 23%-55% [43, 58, 80, 139, 149, 152, 165, 174, 209] with a weighted mean of 30% and in affective disorders from 27%-60% [33, 51, 126, 156, 173, 175] with a weighted mean of 43%.

A previous suicide attempt was the strongest risk factor of suicide increasing the risk about 40 times in a large meta-analysis [81]. A history of parasuicide is even more frequent among young adults committing suicide [179]. A suicide attempt is also more often preceding suicide in subjects with schizophrenia than in non-schizophrenia suicides [85]. Suicides and suicide attempts can in most aspects be regarded as two overlapping populations with common background factors [19]. Factors distinguishing suicide victims from attempters were diagnosis of non-affective psychosis, male sex and being older.

**Early onset psychotic disorders**
Reports of attempted suicide in early onset psychotic disorders are rare. German samples reported 36% of EOS [116] and 20% of VEOS [52] to have attempted suicide after about fifteen years of observation while a small U.S. sample of VEOS reported 38% attempting suicide after about five years follow-up. A Finnish follow-up of adolescent suicide attempters found that an attempt in a youngster with symptoms of psychosis is more often followed by a suicide in the next five years than an attempt by a non-psychotic adolescent [113]. Krausz reported that 7 of 8 suicides in EOS were preceded by attempts [116].

**Predictors of suicide attempts**
Risk factors of suicide attempts in schizophrenia have been in some studies younger age [152, 165, 204] but not in all [43], female sex [2, 149, 152] but not in other [80, 204, 209]. An association to suicide attempts have consistently been symptoms of depression and anxiety [2, 43, 46, 58, 139, 149, 152, 174, 209, 227], auditory hallucinations [43, 149, 204] lower scores on thought disorder [43, 149], more negative symptoms [43] or a trend to
less negative symptoms [58] and more intimate relations [149]. Suicide attempters with schizophrenia have experienced more psychiatric admissions [2, 174] [80, 204] [210] while some report increased abuse of illegal drugs [46, 204, 209, 210] or alcohol [209]. Risk factors to suicide attempts in affective disorders have been a diagnosis of bipolar disorder [173], bipolar II disorder [33, 198], cluster B personality disorder [126], number of episodes [126, 156, 173, 175], abuse of illegal drugs [42, 126, 198], abuse of alcohol [33, 51, 126], young age [33, 173, 198], parental death [126], parental divorce [51], family history of suicidal behaviour [126], being single [33, 173], aggressive traits [126, 156] and fewer reasons for living [156] while the sex distribution is less clear [156, 175].

Quality of life measures have gained increased use for assessing outcome [142, 157], see below, but this aspect has rarely been linked to suicide and not to suicide attempts. A poor life satisfaction has been shown to predict future suicide in a large twin cohort [109] and suicidal ideation was associated to lower scores on subjective quality of life measures in an adult community survey [68].

Quality of life

Quality of life (QOL) assessments and other subjective appraisals of wellbeing are increasingly being recognised as important outcome dimensions in chronic disorders [142, 157]. The QOL concept encompasses two objective dimensions: functional status and access to resources, and the subjective dimension sense of well-being [117]. Within these dimensions, certain life domains have been identified such as social relations, family relations, finances, living situation etc. Measurement of the complex QOL concept is not a straightforward task. The tools used need to be adapted to the group of individuals or specific problem under study, such as the general population, patients or individuals with certain diseases such as severe mental disorders. Further, they should address both objective and subjective aspects in different domains of life [117].

QOL in schizophrenia and in affective disorders

Individuals with schizophrenia usually assess their QOL to be lower than healthy controls [25, 111, 118, 153, 168, 186]. The specific areas of subjective dissatisfaction in schizophrenia have mostly concerned finances, work, social relationships and health [59, 78, 118, 186]. Studies comparing QOL in depression and in schizophrenia have found a lower subjective QOL in depression [14, 75, 110], or no difference between the diagnostic groups [39] as opposed to objective QOL measures where individuals with schizophrenia were in a more impaired situation [14, 110]. Comparative
reports on QOL in bipolar disorder are scarce and divergent. Patients diagnosed with bipolar disorder reported lower QOL than patients with schizophrenia in one study [14], while in another report, only individuals with bipolar depression and not those in a manic phase rated themselves lower than individuals with schizophrenia [181]. In contrast, a mood disordered sample where 50% had experienced manic episodes was more satisfied with social relations than a schizophrenia group but consistently less satisfied than a healthy control group [168].

To my knowledge, there are no studies reporting subjective aspects of QOL in early onset psychotic disorders while reports of objective functioning are summarised on pages 7-9 above.

Predictors of quality of life

Depression is often inversely associated with subjective QOL in schizophrenia [44, 49, 59, 78, 96, 110, 138, 168] but not in all studies [18]. Other clinical variables also associated to subjective QOL are anxiety [59, 96], positive symptoms [59, 150], negative symptoms [158], tardive dyskinesia and other medication side effects [16, 168]. Clinical variables determine up to 50% of variation in subjective QOL in schizophrenia [15, 16, 59, 77, 110]. Observer rated QOL are associated with different factors, i.e. negative symptoms, duration of illness, hospitalisations and age but rarely with general or positive symptoms [31, 32, 150, 197]. Psychosocial variables associated with subjective QOL include having a friend [59, 78], frequency of contact with family [59] and social support [44, 78, 110, 168]. Self-esteem [78], self-directedness [77], coping style [168], life skills [150] and other measures of personality style have also shown association with subjective QOL. Non-clinical variables determine up to 50% of variation in subjective QOL in schizophrenia when studies reporting domain satisfaction as associated with global satisfaction are excluded [78, 110, 168]. Some reports emphasise the importance of psychosocial factors [78, 168] while others find clinical factors to be more prominent [16, 59, 77]. Sociodemographic characteristics and objective indicators of quality of life have shown inconsistent and weak associations with subjective QOL. Reports on associated factors to subjective QOL in mood disorders are few. Non-clinical variables e.g. self efficacy, obsessiveness [168], social support and problem-solving ability [110] are most prominent. Self-rated depression [110] and severity of disorder [168] also contribute to subjective QOL in mood disorders.

The studies above are describing QOL in patients presently suffering from a psychiatric disorder and receiving treatment at various centers as inpatients or outpatients. Several studies are recruiting patients during an inpatient stay [168, 181] or include only patients with a certain frequency of
visits [110]. That raises the question of representativity and more so for mood disordered patients with great variation both in clinical status and in the need for treatment over time.

Expressed Emotion
In the late 1950’s, Brown and colleagues first reported a link between relapse in schizophrenia and the psychosocial environment. They observed that patients with a diagnosis of schizophrenia who returned to live with their parents were more prone to relapse than if they lived in lodgings or with siblings. Brown and colleagues hypothesised that it had to do with aspects of family atmosphere and named the characteristics Expressed Emotion (EE) [29, 30]. Interviews with parents to elicit information were modified and shortened to the 1.5 hour Camberwell Family Interview (CFI) [207]. The CFI rates three aspects: critical comments, hostility and emotional overinvolvement (excessive anxiety, overconcern or overprotectiveness). If the rating of any of the variables exceeds the cut-off, the relative is classified as high-EE. The CFI has been utilised in the large majority of EE-studies but less time consuming methods have been introduced, i.e. Five Minutes Speech Sample [125] and self report questionnaires [76, 106].

Family interaction and stress
EE is best conceptualised within the stress-vulnerability model of schizophrenia proposed by Zubin and Spring [228]. The stressor EE brings about an increase in positive psychotic symptoms and subsequently a relapse in a vulnerable patient [93, 105]. Rather than being a parental trait, the EE measure is viewed as tapping an ongoing chain of interactions in the family. EE is shown to correlate well with concurrent measures of conjoint family functioning i.e. the affective style coding system [140, 190]. Parents judged as critical in the EE coding expressed more critical comments in the family setting while emotionally overinvolved parents more often made intrusive or invasive (mind-reading) statements [140]. On the other hand, patients have also been shown to contribute to the high EE situation by expressing more criticism [70], hostility or unusual or odd behaviours [71, 221] in the family setting. Burden of care has been shown to play a role. It was the best predictor of change from a high to a low EE along with a reduced number of hours of contact with the patient [183]. The increased rate of high EE in one parent families is also suggestive of the impact of an increased burden of care [105]. Relatives reporting long-term distress and depression were assessed as a high in the emotional overinvolvement aspect [27]. Other
contributors to a high EE were patients not working or studying, more face-
to-face contact and higher perceived family burden [26]. A bi-directional
transactional pattern contributing to relapse has also been noted in bipolar
disorder [171]. The link from high EE interaction to a measurable stress
reaction has been the findings in electrodermal activity (EDA). EDA can be
viewed as a measure of autonomic hyperarousal [194] and act as a link
between stress and response in the stress-vulnerability model. High EE
relatives increased EDA in patients both if the parent was assessed as
critical, hostile or overinvolved [193]. It was only in the group of patients
with high daily contact with a high EE relative that the effect persisted over
nine months [194]. Autonomic hyperarousal and increased EDA as a
mediator of relapse is further validated by the finding of increased EDA after
life events in patients with schizophrenia [151]. Life events have been shown
to precipitate relapse [151, 228].

**Adult onset psychotic disorders**

EE-CFI has not only been consistently linked to an increased risk for relapse
in schizophrenia [21, 30, 34, 105, 160, 207] but also in bipolar disorder [34,
141] and non-psychotic psychiatric disorders [105]. The risk of relapse
within a year in schizophrenia is about 50-65% for patients living in high EE
families and 23-35% for patients from low EE families [34, 105]. The effect
was stronger for more chronic cases of schizophrenia. EE was shown to
explain one third of relapses that had occurred and two thirds of non relapses
within the first year after discharge [34]. The risk of relapse was particularly
high when high-EE parents were in longer daily contact with the patient [20,
207]. EE has been linked to relapse independently of medication [21, 105].
Most studies report that about 50-60% of households are high EE as assessed
after an acute admission [105]. This applies to most studies from western
countries while households in developing countries like India have lower
rates [101].

**Early onset psychotic disorders**

Although there is a large body of research on EE in adult samples, there is
very little research on EE in adolescents. Expressed emotion was the major
predictor of relapse in a Dutch study of young adults with schizophrenia and
a mean age of 20.5 years [123]. High-EE correlated with better premorbid
functioning. A high EE increased the risk of one year relapse (hazard ratio)
by 4.9. Goldstein followed adolescents with a family history of
schizophrenia in the UCLA High Risk Project. They found an increased risk
of psychosis at age 30 when the family atmosphere was characterised by
both a high EE and a negative affective style and the parents were judged as
having problems with maintaining a focus of attention (communication
deviance) [69]. All families in a Norwegian two year follow-up of early onset schizophrenia (mean age 16 years) were assessed as high EE at admission. Improvement in functional level was seen in families who changed from high to low EE [176]. The relationship between family EE and relapse in adolescent onset psychosis has not been demonstrated.
AIMS OF THE STUDY

Our current knowledge indicates that an episode of psychotic disorder in adolescence might have serious consequences for the afflicted. Some knowledge is at hand regarding functional outcome in schizophrenia but little is known about affective psychotic disorder. The same applies to the risk of suicide and suicide attempts while we know even less about subjective aspects of life further on. We also know very little about the impact of family atmosphere on the risk of relapse.

The principal aims of this thesis were
• to gain better knowledge on outcome in adult life in patients from a representative sample of hospitalised first onset psychotic disorders in childhood or adolescence.
• to compare outcome in schizophrenia spectrum and affective psychotic disorders.

The specific aims were
1. to examine the long-term stability of a retrospectively assessed DSM-IV diagnosis of a psychotic disorder.
2. to describe and analyse a possible drift in diagnosis.
3. to examine and compare the adult global outcome including occupational and social aspects.
4. to determine factors which could predict functional outcome
5. to assess the risk of suicide and suicide attempts.
6. to describe the characteristics of suicide attempters in general and with special regard to quality of life assessment and to determine factors which could predict suicidal behaviour.
7. to examine and compare the subjectively assessed quality of life at adult age and to cross-sectionally analyse which clinical and psychosocial factors were most closely related to quality of life.
8. to explore the predictive value of Expressed Emotion measured both during initial admission and after discharge on relapse rates at one and two years after discharge from a first episode of psychosis.
MATERIAL AND METHODS

Subjects

Selection of the subjects
The subjects in papers I-V are all from the main study sample (n=88) followed up at an early adult age. All patients admitted to the in-patient unit at the department of Child and Adolescent Psychiatry, University Hospital of Lund, Sweden between 1982 and 1993 with a retrospectively assessed first episode of a psychotic disorder were included in the study. The unit had a primary responsibility for a population of 550,000 and served as a secondary level to another 900,000 inhabitants. Patients (n=88) with a DSM-IV diagnosis [7] of toxic psychosis (code 292, n=3), schizophrenic psychoses (code 295.1-4 and 295.9, n=32), schizoaffective disorder (code 295.7, n=7), bipolar disorders (code 296.0 and 296.4-9, n=25), major depressive disorder with psychotic features (code 296.2+3, n=17) or atypical psychoses (code 298, n=4) were selected for follow-up. The participation of subjects and recruitment area in the different papers are presented in table 1. The inclusion criteria in paper V was a DSM-III-R [6] diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or affective psychoses, subjects living with parent(s) and parents fluent in Swedish. Patients with mental retardation, organic psychosis or toxic psychosis were excluded.
Table 1. Number of subjects included and area of recruitment in the different papers

<table>
<thead>
<tr>
<th>Paper</th>
<th>Eligible for study N</th>
<th>Participating in study N (%)</th>
<th>Local area N (%)</th>
<th>Drop-out analysis Yes/no</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>88</td>
<td>68 (77%)</td>
<td>57 (84%)</td>
<td>Yes</td>
</tr>
<tr>
<td>II</td>
<td>81</td>
<td>81 (100%)</td>
<td>67 (83%)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>III</td>
<td>88</td>
<td>88 (100%)</td>
<td>74 (84%)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>IV</td>
<td>76</td>
<td>53 (70%)</td>
<td>46 (87%)</td>
<td>Yes</td>
</tr>
<tr>
<td>V</td>
<td>24</td>
<td>15 (62.5%)</td>
<td>13 (87%)</td>
<td>No</td>
</tr>
</tbody>
</table>

Drop-out analyses

**Paper I**
Twenty subjects were excluded from analysis of diagnostic stability because there was no PANSS or SCID from a personal follow-up interview available. These 20 cases had a longer duration of time between first admission and follow-up (p<0.05) and a lower GAF level the year before onset of psychosis (p<0.05). There were no differences in sex, ethnicity, social class of parents, duration of prodromal phase, diagnostic groups or any other first episode measure between the included and excluded samples. At follow-up, there was a trend towards more individuals with a poor outcome in the excluded group (p=0.055).

**Paper IV**
There were 24 subjects not included in the quality of life analyses. These cases either lacked a LQOLP and PANSS interview (n=21) or the LQOLP interview was deemed highly unreliable (n=3). The excluded subjects with a lifetime schizophrenia or schizoaffective diagnosis (n=15) had a longer duration of time between first admission and follow-up (p=0.01) compared to the included subjects with the same lifetime diagnosis. They also had a lower GAF at follow-up (p<0.01), a lower score on S-C employment (p<0.05) and a higher load on PANSS positive subscale (p<0.05) and PANSS negative subscale (p<0.05). The excluded subjects with a lifetime diagnosis of bipolar disorder or major depressive disorder with psychotic features (n=8) were in most cases lacking outcome data precluding a drop-out analysis.
Procedures

Paper I-IV
All hospitalisations during the years 1982-1993 were checked in the registers. Cases with a facility diagnosis of a psychotic disorder, depression, personality disorder or any inpatient stay of more than two months were reviewed according to DSM-IV criteria [7] and those with a reassessed diagnosis of psychotic disorder were selected for the study. First episode measures were extracted from the selected records by the author. These individuals were then located by the national population register. A follow-up interview was conducted by the author with full knowledge of previous records and often a personal knowledge of the subjects as well. Finally, further information from hospital and other registers was collected. Primary source of follow-up data for every case is outlined in table 2.

Table 2. Primary source of follow-up data in papers I-IV

<table>
<thead>
<tr>
<th>Source of follow-up data</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal interview</td>
<td>65 (77%)</td>
</tr>
<tr>
<td>Interview with parents/case managers</td>
<td>14 (17%)</td>
</tr>
<tr>
<td>Registers from adult psychiatry</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Registers from child psychiatry and official registers</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

Paper V
Parents of patients hospitalised and diagnosed with a psychotic disorder during the years 1990-1993 were asked to be interviewed with the FMSS. The FMSS was audiorecorded and assessed twice with each parent, first during the initial phase of the hospitalisation (admission EE) and thereafter during the first 7 months after discharge (discharge EE). The admission FMSS was obtained during the first month after hospital admission in 7 cases, during the second month in three cases, and in the third month in the remaining five cases. The discharge FMSS was missing in two cases because of lack of consent. All mothers were interviewed but the fathers were unavailable in two cases. Only parents in weekly contact with the patients were selected for FMSS interviewing. All speech samples were audiorecorded and transcribed for EE ratings by a trained and certified rater (Rolf W Gråwe, trained to a Kappa level of > 0.80 with another sample of patients at the UCLA Family Project) and blind to all other information about the patients. The principal investigator (HJ) established the diagnoses based upon patient and family interviews but unaware of the EE-status.
Assessments

Background and first episode measures
The following fourteen variables were extracted from clinical records (partial list in table 3); sex, family history in 1st or 2nd degree relatives of psychotic or affective illness, IQ (≥80 versus <80 from psychological testing before onset), GAF level of functioning [7] during the best three month period the year before first psychotic symptom, duration of prodromal phase (≥12 weeks versus <12 weeks), age at first psychotic symptom, auditory hallucinations (any versus none), delusions (any versus none), mood-incongruent delusions (any versus none), negative symptoms (marked versus none), depression (marked versus none) and if suicide was ever attempted or illegal drugs tried. Further data on family history from systematic inquires at follow-up and from additional psychiatric records was included.

Expressed Emotion
The Five Minute Speech Sample (FMSS) [125] is a brief procedure for assessing family EE based upon how the relative of a psychiatric patient spontaneously talks about the patient during five minutes while audiorecorded. The parent is asked to talk for five minutes, without interruptions, about their adolescent son or daughter and how they get along together. The high-EE categorisation is based upon the presence of criticism (i.e., the presence of a negative initial statement, a negative relationship, or one or more critical remarks) or the presence of emotional overinvolvement (EOI, i.e., the presence of extreme self-sacrifices, excessive praise or details about past, or signs of emotional display) during the five minute interview. A category of borderline high-EE was assigned if the parent indicated some definite features of high-EE, but not enough to meet the criteria for a high-EE rating, e.g., dissatisfaction but not criticism, praise or details that fell just short of criteria. A family was categorised as high-EE if either of the parents were rated high. Borderline high-EE ratings were categorised as a low-EE group.
Table 3. Partial list of characteristics of the subjects diagnosed with schizophrenia spectrum or affective psychotic disorder at first episode (n=81)

<table>
<thead>
<tr>
<th></th>
<th>SCZ n=32</th>
<th>SA n=7</th>
<th>BPD n=25</th>
<th>MDD n=17</th>
<th>comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history, n(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bipolar</td>
<td>3 (9)</td>
<td>5 (71)</td>
<td>7/23 (30)</td>
<td>1/16 (6)</td>
<td>sa&gt;scz**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>sa&gt;mdd**</td>
</tr>
<tr>
<td>non-aff psychosis</td>
<td>11 (34)</td>
<td>2 (29)</td>
<td>4/23 (17)</td>
<td>2/16 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>21 (66)</td>
<td>3 (43)</td>
<td>6 (24)</td>
<td>0</td>
<td>scz&gt;bpd*</td>
</tr>
<tr>
<td>IQ&lt;80, n(%)</td>
<td>5 (16)</td>
<td>1 (14)</td>
<td>2 (8)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Prepsychotic GAF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>60</td>
<td>65</td>
<td>80</td>
<td>70</td>
<td>bpd&gt;scz**</td>
</tr>
<tr>
<td>range</td>
<td>30-85</td>
<td>40-80</td>
<td>50-90</td>
<td>65-90</td>
<td>bpd&gt;sa*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mdd&gt;scz**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mdd&gt;sa*</td>
</tr>
<tr>
<td><strong>Age at onset, (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>15.6</td>
<td>16.8</td>
<td>15.2</td>
<td>16.2</td>
<td>NS</td>
</tr>
<tr>
<td>range</td>
<td>11.8-18.7</td>
<td>12.3-17.5</td>
<td>13.1-17.7</td>
<td>13.4-17.7</td>
<td></td>
</tr>
<tr>
<td><strong>Duration since index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(years)</td>
<td>median</td>
<td>10.5</td>
<td>7.25</td>
<td>10.75</td>
<td>10.8</td>
</tr>
<tr>
<td>range</td>
<td>5.1-18.2</td>
<td>6.3-9.0</td>
<td>5.5-17.6</td>
<td>5.1-16.7</td>
<td></td>
</tr>
<tr>
<td><strong>Age at follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(years)</td>
<td>median</td>
<td>26.7</td>
<td>23.8</td>
<td>26.6</td>
<td>27.7</td>
</tr>
<tr>
<td>range</td>
<td>21.6-32.6</td>
<td>21.6-26.1</td>
<td>20.5-35.2</td>
<td>21.2-31.7</td>
<td></td>
</tr>
</tbody>
</table>

Note: Scz = Schizophrenia or Schizotypal Disorder; SA = Schizoaffective Disorder; BPD = Bipolar Disorder; MDD = Major Depressive Disorder with Psychotic Features; NS = not significant.

* p<0.05, ** p<0.01.

Reliability of first episode data

Paper I-IV

Thirty-four records (39%) were chosen by a random method for blind review on diagnosis and type of onset by adult psychiatrists. In 25 of 34 cases there was an agreement on the 6 major diagnostic groups with a kappa = 0.66. A third and senior researcher (A-LvK) was consulted if consensus was not achieved and in other diagnostic difficulties, and a final best estimate was
arrived at. There was agreement in 29 of 32 cases on duration of prodromal phase with a kappa = 0.81.

Paper V
The diagnosis were blindly reassessed from hospital records by a resident in adult psychiatry. The same diagnosis was given 14/15 patients regarding schizophrenia versus affective dichotomy and in 13/15 patients regarding diagnostic subgroups yielding Cohen kappa values of 0.83 and 0.79.

Follow-up measures
The follow-up measures are summarised in table 4 and described below.

Lifetime diagnosis
In order to arrive at a best estimate DSM-IV diagnosis, all available information was used and adapted to the Structured Clinical Interview for DSM-III-R diagnosis (SCID) interview for psychotic or affective syndromes [188] after minor changes for meeting the DSM-IV criteria. This included a semi-structured personal interview, interviews with parents, case managers or psychiatrists and medical records. When there had not been any subsequent episode, the initial diagnosis was used as the lifetime diagnosis.

Symptoms
Psychopathology at follow-up was assessed with the 30 item Positive and Negative Symptom Scale (PANSS; 1, no symptom, to 7, severe symptoms) [220] and with the item suicidality from the Brief Psychiatric Rating Scale (1, no thoughts of suicide or weariness of life, to 7, planning suicide) [208]. The PANSS ratings were also subdivided into five dimensions of anxiety-depressive, negative, positive, cognitive and agitated symptoms (paper III) [121].
Table 4. Assessment methods, and time frame of diagnosis in the different papers

<table>
<thead>
<tr>
<th>Paper</th>
<th>Assessments</th>
<th>Diagnosis used</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>SCID</td>
<td>first episode</td>
</tr>
<tr>
<td></td>
<td>PANSS</td>
<td>(lifetime)</td>
</tr>
<tr>
<td>II</td>
<td>Strauss-Carpenter</td>
<td>first episode</td>
</tr>
<tr>
<td></td>
<td>GAF</td>
<td>(lifetime)</td>
</tr>
<tr>
<td></td>
<td>Official registers</td>
<td></td>
</tr>
<tr>
<td>II addendum</td>
<td>GAF</td>
<td>lifetime</td>
</tr>
<tr>
<td>III</td>
<td>Suicide attempt form</td>
<td>lifetime</td>
</tr>
<tr>
<td></td>
<td>Abuse form</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LQOLP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PANSS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All paper II assessments</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>LQOLP</td>
<td>lifetime</td>
</tr>
<tr>
<td></td>
<td>PANSS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All paper II assessments</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>FMSS</td>
<td>first episode</td>
</tr>
<tr>
<td></td>
<td>Relapse form</td>
<td></td>
</tr>
</tbody>
</table>

24
Functional level

1. the Global Assessment of Functioning Scale (GAF) scale from the DSM-IV manual [7] for the best three month period the year before follow-up.

2. the Strauss-Carpenter scale [191] divided in the variables employment, social contacts, hospitalisation and symptoms and rated on a five point scale (0-4). Symptoms (0, continuous and severe symptoms, to 4, no symptoms of psychosis) were rated for the previous month while ratings for employment (0, no activities to 4, fully employed or studying), social contacts (0, no contacts, to 4, seeing friends every week) and hospitalisations (0, admitted more than 10.5 months, to 4, not admitted) covered the preceding year. Number of re-admissions and time spent in psychiatric wards were also extracted from clinical records for the first five years after being admitted for a first episode and for the entire span of follow-up. Employment in the S-C included studies, housework, sheltered employment and day center activities. If specific information was lacking, cases were believed to be holding a full time job if their income from employment amounted to twice or more of a disability pension. Social contacts did not include parents/family of origin and treatment staff.

3. data on living independently versus with parents, in sheltered apartments or in other treatment facilities, on having been married or living together, on parenthood and on disability pension. Disability pension was assumed when information from tax authorities on income was precisely the amount of a disability pension from the Swedish health insurance.

Functional outcome was operationalised into major outcome criteria (table 5) according to Maziade et al. [131], which are modified from the major categories as proposed by Westermeyer and Harrow [216].

**Table 5. Major outcome criteria**

<table>
<thead>
<tr>
<th></th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>GAF&gt;70 or full employment (if GAF not available)</td>
</tr>
<tr>
<td>Intermedi</td>
<td>GAF 70-51 or par-time employment (if GAF not available)</td>
</tr>
<tr>
<td>Poor</td>
<td>GAF 50-41 or early pension (if GAF not available)</td>
</tr>
<tr>
<td>Very poor</td>
<td>GAF&lt;41</td>
</tr>
</tbody>
</table>
Suicide and suicide attempts

The Swedish Register of Deaths was contacted in all cases of death at follow-up. Specific questions regarding suicide attempts were asked at every follow-up interview with patients, parents or caregivers and information on suicide attempts was searched for in psychiatric registers and case records. A suicide attempt was defined as an act of deliberate self harm with an intent to die. This excludes serious thoughts only (e.g. seriously considering jumping but not doing so) and also manipulative gestures in anger or in the presence of others.

Abuse

At follow-up, a detailed drug history included ever having used illegal drugs, present consumption of alcohol (no more than 1 bottle of wine or equivalents per week versus more than bottle of wine per week the month before follow-up) and dependence on nicotine at follow-up (daily smoker of at least 5 cigarettes and/or used moist snuff [containing nicotine] daily versus not). Information on illegal drug use from hospital records was included if applicable.

Quality of Life

Quality of life was assessed with the Lancashire Quality of Life Profile (LQOLP) [154]. The LQOLP is a structured self-report interview to be administered by trained interviewers. It assesses objective quality of life and subjective life satisfaction in nine life domains: work (including rehabilitation or being on disability pension if applicable), leisure, religion, finances, living situation, safety, family relations, social relations and health. It also includes a global well-being scale, a patient global assessment of quality of life (Cantril’s ladder), and an interviewer assessment of the individual’s global quality of life, an affect balance scale, a self-esteem scale and a happiness scale. Objective quality of life and personal characteristics are assessed by categorical or continuous measures depending on the content of the item. They include having a close friend; having a reliable friend; having seen a friend last week; living independently versus with parents, in sheltered apartments or in other treatment facilities; being married or in a steady relationship and frequency of contact with family of origin (1, daily, to 5, less than once a year). Subjective quality of life ratings are made on a seven-point Likert-type scale (1, couldn’t be worse, to 7, couldn’t be better). The LQOLP has been used in a number of international studies. It has been
translated into several languages including Swedish. The LQOLP has in reliability and validity tests shown satisfactory results [79, 154, 205].

Early relapses
A relapse was defined as a major exacerbation of psychotic symptoms accompanied by increased functional impairment and with a duration of at least two weeks. Relapse was assessed from hospital records by two independent raters without knowledge of EE status.

Reliability of follow-up data

Paper I-IV
In 19 of the interviews (n=68) and in an additional 4 of the outcome measures from records in the excluded group (n=20) there was a second rater (YO). The same interviewer (HJ) conducted all the interviews. The second interviewer (YO) asked clarifying questions when necessary and performed independently all ratings and a final lifetime diagnosis, which included the information from available medical records. There was inter-rater agreement on diagnosis in 19 of 21 cases, kappa = 0.88. The two cases with disagreements and an additional eight cases were discussed with the senior researcher (A-LvK) to reach a final best estimate diagnosis. The agreement in GAF score was 0.97 (Pearson’s correlation, p<0.01), in the Strauss-Carpenter scale 0.94 (Spearman’s correlation, p<0.01) and in the PANSS scale 0.95 (Spearman’s correlation, p<0.01).

Paper V
Relapse was assessed from records by two independent raters. The inter-rater reliability of the relapsed/non-relapsed dichotomy revealed a Cohen’s kappa of 0.65. The disagreements concerned four patients with a major exacerbation of psychotic symptoms who had received an increased dose of antipsychotic medication resulting in attenuating symptoms within the two week period. Adding the additional criteria “unless successfully treated” to the two week duration made the raters agree in all cases.
Statistical methods

Comparisons between groups were non-parametric as the numbers usually were rather low and the variables not normally distributed. Thus, differences between groups were assessed with the Mann-Whitney rank test (paper I-IV) and correlation between groups with Spearman’s rank correlation test (paper II addendum+III+IV). Categorical data was analysed with the chi-square test or Fischer’s exact probability test when indicated due to less than five expected numbers in a cell (paper I-V). Inter-rater tests were performed with Cohen’s kappa for diagnoses and with Spearman’s rank correlation for scales. However, differences in GAF and QOL were evaluated with t-test as these variables could be regarded as normally distributed.

Multivariate regression analyses were applied to predict outcome in terms of quality of life (paper IV), to assess possible confounding variables (paper II) and in the additional analysis of predictors of functional outcome (addendum paper II). A logistic regression analysis was used to assess factors associated to a lifetime risk of a suicide attempt (paper III) and confounding variables to the dichotomised outcome (paper II). To reduce the number of covariates in the models only variables with a significant correlation to the dependent factor were tested in the regressions (paper II+IV).

Positive Predictive Validity (PPV) expressed the proportion of individuals, in a diagnostic category at first admission, that retained the same diagnosis at follow-up (paper I) or experienced a relapse after initial assessment as high-EE (paper V). Sensitivity expressed the proportion of individuals in a diagnostic outcome category at follow-up that a previous test (e.g. diagnostic procedure) could identify (paper I+V).

The analysis of diagnostic change (paper I) classified subjects into three groups; those with a schizophrenia spectrum diagnosis or affective psychotic diagnosis both at first episode and at follow-up, and those subjects whose diagnosis shifted into a schizophrenia spectrum disorder.

Odds ratio expressed the relation between observed and expected suicides (paper III). The expected number of suicides was calculated for the patients with the assumption that their risk of suicide coincided with the average risk of the Swedish population between 15-24 years through the years 1985-1999 for observed years up to age 25 and with the average risk of the Swedish population between 25-44 years through the years 1995-1999 for observed years age 25 and above from the Swedish Agency of Statistics (SCB). A significance level of 5% and two-sided tests were used. However, other degrees of significance are also indicated (paper I-V).
RESULTS

Stability of diagnosis (paper I)

The Positive Predictive Validity from the first episode of the three most prevalent initial diagnoses was 100% for schizophrenia, 79% for bipolar disorder and 64% for major depressive disorder (Table 6). The sensitivity of identifying the same diagnosis at first episode was 72% for schizophrenia, 79% for bipolar disorder and 100% for major depressive disorder. The overall rate of consistency was 72%, 49 of 68 subjects received the same 8-category diagnosis at both points in time. Restricting the analysis to the major dichotomy of schizophrenia spectrum or affective disorders increased both PPV and sensitivity to 82% or more. Schizoaffective disorder had a low PPV of 60% and an even lower sensitivity of 37.5%. Schizophreniform disorder had the lowest PPV of only 17% while the only case with a follow-up schizophreniform diagnosis was detected at first admission.

Characteristics of patients with a diagnostic shift to schizophrenia

The shift to schizophrenia spectrum disorder was the most frequent diagnostic change (n=6). The initial diagnosis was bipolar disorder (n=3), psychosis NOS (n=2) and major depressive disorder (n=1). This group was singled out and compared with the patients that either were stable in the schizophrenia spectrum or the affective diagnosis from first admission to follow-up. In the background and first episode characteristics, the change to schizophrenia spectrum group presented a better prepsychotic functioning (p<0.05), a shorter duration of the premorbid phase (p<0.05) and fewer mood-incongruent delusions (p<0.05) than the stable schizophrenia group. On the other hand, the change to schizophrenia spectrum group had more non-affective psychosis in 1st or 2nd degree relatives than the stable affective group (p<0.05). In the follow-up characteristics, the change to schizophrenia spectrum group were, with few exceptions, indistinguishable from the stable
schizophrenia spectrum group. However, the changed group had a better score on social relations (p<0.05) and fewer negative symptoms (p<0.05). They also had a longer time between first admission and follow-up (p<0.05). Compared to the stable affective group, the changed group did worse on global outcome (p<0.05), GAF (p<0.01), employment (p<0.01) and PANSS positive (p<0.01), negative (p<0.01) and general symptoms (p<0.01).

**Table 6. Cross-Tabulation of initial and lifetime DSM-IV diagnoses in adolescent onset psychotic disorders**

<table>
<thead>
<tr>
<th>Initial diagnosis</th>
<th>Lifetime diagnosis</th>
<th>Sz spectrum disorders</th>
<th>Affective disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
<td>SZ</td>
<td>SA</td>
</tr>
<tr>
<td>Sz spectr.</td>
<td></td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>SZ</td>
<td>18</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>SA</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>SF</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Affective</td>
<td></td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>BPD</td>
<td>19</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>MDD</td>
<td>14</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other psy.</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>TOTALS</td>
<td>68</td>
<td>34</td>
<td>25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PPV (%)</th>
<th>Sens (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>97</td>
<td>82</td>
</tr>
<tr>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>60</td>
<td>37</td>
</tr>
<tr>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>82</td>
<td>96</td>
</tr>
<tr>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>64</td>
<td>100</td>
</tr>
</tbody>
</table>

aSZ indicates schizophrenia; SA, schizoaffective disorder; SF, schizophreniform disorder; BPD, bipolar disorder; MDD, major depressive disorder with psychotic features; Positive predictive value = percentage of initial cases with the same diagnosis at follow-up; Sensitivity = percentage of follow-up cases with the same diagnosis at initial evaluation.
Global measures

There were significant differences between patients with EOS and affective psychotic disorders in major outcome categories (see Figure 1). The results were dichotomised to good (good or intermediate) or poor (poor, very poor or suicide). Patients with EOBD had a better outcome than both patients with EOS (p<0.01) and schizoaffective disorder (p<0.05). The depressive group also had a better outcome than the schizophrenic group (p<0.01) and the schizoaffective group (p<0.01). There were no differences in major outcome categories between schizophrenia and schizoaffective disorder or between bipolar and depressive psychotic disorder. The outcome was gloomy in schizophrenia spectrum disorder (DSM-IV code 295), where
patients (5%) had committed suicide, another 22 (56%) had a very poor outcome and a further 7 (18%) had a poor outcome. The two patients with a good outcome in the schizophrenia group consisted of one patient re-evaluated with bipolar disorder and one true schizophreniform case. On the other hand, the outcome was more favourable in the affective groups, where 31 patients (71%) had a good or intermediate outcome. Those with affective disorders and an unfavourable outcome consisted of 5 patients (12%) with a progression to a schizoaffective disorder, 3 (7%) with mild mental retardation, one woman (2%) with severe and persistent anorexia nervosa and finally 2 patients (5%) with a “pure” bipolar disorder at follow-up. Excluding patients with mental retardation, 6/22 (27%) persons with EOBD were left with an unfavourable outcome.

![Figure 2. GAF at follow-up from first episode diagnosis](image)

The GAF value in the schizophrenia group (see Figure 2) was very low and significantly lower than in the depressive group (p<0.01) and in the bipolar group (p<0.01). The small schizoaffective group had a median of 45 and was
significantly lower than the depressive group (p<0.01) but not lower than the bipolar group (p=0.13). A normal functional level expressed as a GAF above 70 was reached by 10/15 of the EOMDD and by 8/21 of the EOBD, which did not reach statistical significance (p=0.38).

Occupational function

Employment according to the Strauss-Carpenter scale (Figure 3), was particularly low in patients with schizophrenia (p<0.01 versus both the affective groups). Half of the patients with EOS were not employed in any activity and not active in a day care center while 67% of the EOMDD and 43% of the EOBD patients were fully employed at follow-up.

There were striking differences in disability pension between patients initially diagnosed with schizophrenia or with affective psychosis (p<0.01). The vast majority (87.5%) of patients initially diagnosed with schizophrenia received a disability pension at follow-up while 67% of EOBD and 71% of EOMDD could support themselves at follow-up.

Figure 3. Degree of employment at follow-up from diagnosis at first episode (abbreviations explained in legend to Figure 1)
Social function

Patients with schizophrenia also had significantly less social contacts compared with patients with EOMDD (p<0.01) and with EOBD (p<0.05) at follow-up. Almost half of patients with an initial diagnosis of schizophrenia did not meet with friends beyond organised activities. There was a trend towards a better outcome in the depressive group versus the bipolar group on social contacts (p=0.07). All patients with EOMDD met with friends regularly while a third of the patients with EOBD met with friends monthly or less. There were no differences in parenthood or marriage in this cohort with a mean age of 26.3 years. Persons with an initial diagnosis of schizophrenia were less often living independently compared to both the bipolar group (p<0.01) and to the depressive group (p<0.01). Women with an initial diagnosis of schizophrenia had significantly more often been living in a heterosexual relationship than men with schizophrenia (4/10 versus 1/21, p<0.05).

Figure 4. Social relations at follow-up from diagnosis at first episode (abbreviations explained in legend to Figure. 1)
Family history and outcome

Patients with schizophrenia or schizoaffective disorder and a family history of non-affective psychosis (n=13) as opposed to those without (n=26) had a significantly higher risk of a poor outcome (13/13 versus 18/26; p<0.05), lower GAF (median 26 versus 43; p<0.05), and lower score on the S-C scale (median 5 versus 10; p<0.01). A family history of bipolar or affective disorder did not increase the risk of poor outcome in the patients with affective psychosis.

Lifetime diagnosis and outcome

From the original sample (n=88) 2/39 patients (5%) shifted from schizophrenia spectrum disorder to affective disorder and 8/49 (16%) shifted from nonschizophrenia to schizophrenia spectrum disorder. If the lifetime diagnosis was used as the independent variable, a good outcome was seen in 83% of EOMDD (n=12), in 52% of EOBD (n=25) but in only 10% of the early onset schizoaffective disorder (n=10) and in no case of EOS (n=34). An intermediate outcome was seen in 8% of EOMDD, in 28% of EOBD, in 10% of early onset schizoaffective disorder and in 18% of EOS. An unfavourable outcome (poor, very poor or suicide) was seen in 82% of 44 cases in the lifetime schizophrenia spectrum disorder but in only 16% of 37 cases of lifetime affective disorder.

Table 7. Predictors of GAF at follow-up (percent variance predicted) for different lifetime diagnosesa

<table>
<thead>
<tr>
<th>Predictors</th>
<th>All psychoses (n=67)</th>
<th>SZ+SA (n=41)</th>
<th>BPD (n=18)</th>
<th>All affective (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heredity non-aff psychosis</td>
<td>-</td>
<td>14%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Premorbid IQ&lt;80</td>
<td>5%</td>
<td>-</td>
<td>-</td>
<td>40%</td>
</tr>
<tr>
<td>Prepsychotic GAF</td>
<td>38%</td>
<td>13%</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>Diagnosis first episode</td>
<td>3%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Inpatient stay 0-5 years</td>
<td>13%</td>
<td>-</td>
<td>-</td>
<td>19%</td>
</tr>
<tr>
<td>Readmissions</td>
<td>-</td>
<td>-</td>
<td>56%</td>
<td>-</td>
</tr>
<tr>
<td>Total predicted</td>
<td>59%</td>
<td>27%</td>
<td>71%</td>
<td>60%</td>
</tr>
</tbody>
</table>

aSZ indicates schizophrenia; SA, schizoaffective disorder; BPD, bipolar disorder.

Predictors of outcome (paper II addendum)

It was possible to predict 59% of the variance in GAF at follow-up in psychotic disorders (n=67) mainly with prepsychotic GAF and length of inpatient stay year 0-5 but also to a small extent with premorbid IQ<80 and
diagnosis at first episode (table 7). In subjects with a lifetime schizophrenia spectrum psychosis GAF was predicted to 27% by family history of non-affective psychosis in 1st or 2nd degree relatives and prepsychotic GAF. In lifetime bipolar disorder, readmissions was the main predictor of outcome but prepsychotic GAF also contributed, while IQ<80 and length of inpatient stay predicted GAF at follow-up in the combined affective group.

Suicide and Suicide Attempts (Paper III)

Table 8. Estimated risk ratios for completed suicide in different diagnostic groups of adolescent onset psychoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Estimated risk ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All psychotic disorder (n=88)</td>
<td>28.3****</td>
<td>9.3-85.4</td>
</tr>
<tr>
<td>Schizophrenia spectrum (n=45)</td>
<td>28.8****</td>
<td>7.2-116</td>
</tr>
<tr>
<td>Affective psychotic disorder (n=37)</td>
<td>34.4****</td>
<td>7.8-151</td>
</tr>
<tr>
<td>Bipolar disorder (n=25)</td>
<td>48.1****</td>
<td>10.9-212</td>
</tr>
</tbody>
</table>

Completed suicides

Table 8 shows the estimated risk ratios in the entire study and in different diagnostic groups. All deaths were assigned suicide in the Swedish Register of Deaths. Four (4.5%) of 88 subjects committed suicide during the observation period, which was 28 times more (p<0.001) than the expected number 0.15. The risk was increased 29 times in schizophrenia and 48 times in bipolar disorder. There was not any suicide in the small group of major depression with psychotic features.

Suicide attempts

There was a total of 95 suicide attempts. Eight subjects (10%) had made a suicide attempt before or during their first episode. An early attempt was more often seen in patients with a lifetime DSM-IV diagnosis of major depressive disorder. Twenty-three subjects (26%) had made 87 suicide attempts or 9.3 attempts/100 observed years. At follow-up, 62 (70%) of the subjects had never made a suicide attempt while 12 (14%) had made one attempt and 14 (16%) two or more attempts. Ever having attempted suicide was just as common among the sexes and among the major diagnostic groups. The methods used were: intoxication (66%), cutting (22%), hanging (10%), drowning (3%) and other (2%). Fifty-one (54%) of the attempts were
committed by four females and one male. Females attempted suicide more often than males (59/95 versus 36/95, p<0.05). Males made just one attempt in 9 of 14 cases (64%) while females made in 9 of 12 cases (75%) two or more attempts (p=0.045). Males died more often from a suicide attempt than females (4/36 versus 0/59, p<0.05).

Characteristics of suicide attempters

**Age of onset and symptoms at first episode**
Patients with schizophrenia spectrum disorder and a history of suicide attempt experienced their first psychotic symptom at a higher age (p=0.027) than those who had not committed a suicide attempt. In this respect there was not any difference among persons with affective psychotic disorder. A trend to a higher age of onset among those who have attempted suicide was observed in the full sample (p=0.053). At first episode, symptoms of depression were observed more often among suicide attempters with schizophrenia spectrum disorder (p<0.001) and with psychotic disorders (p<0.001) but not in those with affective psychotic disorder. On the other hand, there was less often documented negative symptoms at first episode among suicide attempters with schizophrenia spectrum disorder (p=0.009) and with any psychotic disorder (p=0.007). There was not any difference in the rate of auditory hallucinations between attempters and non-attempters reported in the hospital records.

**Substance abuse**
Eighteen of 84 (21%) had tried an illegal drug. Subjects with schizophrenia who had attempted suicide had more often (p=0.036) tried an illegal drug. A similar trend (p=0.071) was seen in the full sample. However, subjects with an affective psychotic disorder and a history of suicide attempts were just as unlikely (12%) to have tried an illegal drug as those without a suicide attempt (11%). No more than four patients (6%) declared a weekly consumption of alcohol exceeding one bottle of wine at follow-up. There were not any differences in alcohol consumption among attempters or non-attempters. At follow-up, 25 of 80 (29.8%) smoked cigarettes regularly while 5 of 80 (5.9%) used nicotine by moist snuff only. In total 35.7% of patients were dependent on nicotine at follow-up. Patients with psychosis and dependence on nicotine had more often attempted suicide (p=0.001) as well as patients with schizophrenia and nicotine dependence (p=0.012). A trend (p=0.074) towards more subjects dependent on nicotine among suicide attempters with affective psychotic disorders was also observed.
Admissions
There were more psychiatric admissions among suicide attempters with any psychiatric disorder (p=0.006) and a trend towards more admissions in persons with affective psychotic disorder (p=0.073) but not among persons with schizophrenia spectrum disorder.

Psychosocial function at follow-up
There were not any significant differences in GAF levels between attempters and non-attempters of suicide at follow-up. Subjects with schizophrenia who had committed a suicide attempt had a better score on social relations (p=0.019) at follow-up than those who had never committed an attempt. Subjects with affective psychotic disorders and suicide attempts had a lower degree of employment (p=0.050) at follow-up than those with no attempt. These differences did not emerge in the full sample.

Symptoms at follow-up
Subjects with a suicide attempt presented, at follow-up, more symptoms on the anxiety-depressive subscale of PANSS in psychotic disorders (p=0.001) and in schizophrenia spectrum disorders (p=0.005). Subjects with an episode of affective psychotic disorder had few symptoms on the anxiety-depressive subscale at follow-up without any difference relating to suicide attempts or not. Subjects in the full sample with a history of suicide attempt(s) expressed more thoughts of hopelessness and other symptoms of suicidality (p=0.033) but this difference was not found in the smaller subsamples.

Quality of life measures at follow-up
Patients with no suicide attempt and psychotic disorders reported a better subjective quality of life in the domains religious belief (p=0.005), health (p=0.008), family relations (p=0.01) and safety (p=0.031). In the schizophrenia spectrum subsample, subjects without a history of suicide attempt(s) reported more satisfaction with safety (p=0.012) and a trend to more satisfaction with health (p=0.052). Self-esteem was rated lower among suicide attempters (psychotic disorders, p=0.028; schizophrenia, p=0.024). There was not any difference in any domain of subjective quality of life or in self-esteem in subjects with affective psychotic disorders.

Predictors of suicide attempts
Logistic regressions were performed with never attempted suicide versus suicide attempt as a dependent variable and dichotomised covariates excluding symptoms and quality of life measures at follow-up (table 9). A significant prediction of suicide attempt in all psychotic disorders (n=80)
was ascribed depression at first episode, nicotine dependence at follow-up, number of admissions during follow-up and not showing prominent negative symptoms at first admission. This model explained 61% of the variance and correctly predicted 84% of the cases as suicide attempters or non-attempters. If symptom and quality of life assessments at follow-up were included, the anxiety-depressive subscale score at follow-up would be the only new item accepted in the model (n=68, p=0.002) but the statistical model would become unstable with very large confidence intervals.

Table 9. Logistic regressions of psychotic disorder (n=80) to predict suicide attempt(s)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms at first episode</td>
<td>29.5</td>
<td>3.2-271</td>
<td>0.003</td>
</tr>
<tr>
<td>Negative symptoms at first episode</td>
<td>0.055</td>
<td>0.003-1.0</td>
<td>0.053</td>
</tr>
<tr>
<td>Nicotine dependence at follow-up</td>
<td>17.4</td>
<td>2.8-108</td>
<td>0.002</td>
</tr>
<tr>
<td>Psychiatric admissions lifetime</td>
<td>11.9</td>
<td>2.2-64.8</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Quality of Life (Paper IV)

Subjects in the psychotic mood disorders group were more satisfied with perceived overall quality of life compared to people with schizophrenia. They were also more satisfied with the domains leisure, health, social relations, living and safety while there was not any significant difference concerning work, religion, finances or family relations. Individuals with psychotic mood disorders were most satisfied with the domains safety and health and least satisfied with finances and work. Individuals with schizophrenia were most satisfied with the domains safety and religion and least satisfied with social relations and living conditions.

Factors associated to QOL

For the schizophrenia group, we found depressive mood from PANSS overshadowing all other contributions and explaining 49% of the total variance in perceived QOL. For the mood disordered group, the predictive model included only the item employment from the Strauss-Carpenter scale explaining 39% of the total variance in perceived QOL.

Schizophrenia group

The domains where satisfaction could be explained to a large extent were for the schizophrenia group social relations (62% predicted), safety (46%
predicted) and work/activity (39% predicted). Satisfaction in these domains was mostly inversely related to symptom factors. The PANSS psychotic subscale factors of hostility and grandiosity were inversely related to satisfaction with work while the PANSS general subscale factors of somatic concern, depressive mood and uncooperativeness were inversely related to safety, health and social relations. However, satisfaction with social relations was strongly (predicted 50%) related to having a reliable friend and the subjective factor of self-esteem was also related to satisfaction with health.

**Mood disorder group**

The domains where satisfaction could be explained to a large extent were for individuals with mood disorders health (79% predicted), social relations (76% predicted) and living conditions (52% predicted). Satisfaction in these domains was mostly related to non-symptom factors. The psychosocial factor employment (S-C) explained most (66%) satisfaction with health. Subjectively appraised affective balance from LQOLP explained most (64%) satisfaction with social relations but having seen a friend last week also contributed. Among the PANSS symptom factors, poor impulse control and, to a lesser extent tension, inversely contributed to satisfaction with living conditions while guilt feelings to a small extent inversely contributed to satisfaction with health.

**Expressed Emotion (Paper V)**

Expressed emotion at hospital admission was categorised as high in five (33%), as borderline high-EE in two (13%), and as low-EE in 8 (53%) of the 15 families. After discharge 13 families (two withdrew consent) were evaluated and four (31%) were categorised as high-EE and one (8%) as borderline. All of the five admission high-EE families were rated as low-EE at post discharge. However, two of the families rated as high-EE at post discharge were rated as low-EE at admission. Both admission borderline high-EE families turned out to become high-EE after discharge. A high-EE was based upon criticism subscores in 55% and upon EOI subscores in 45% of the ratings. Eight patients (53%) had experienced a relapse the first year after discharge and 11 (73%) had experienced a relapse within two years from discharge.

There was not a significant relation between admission EE and one and two year relapse rates. If the borderline high-EE patients were classified among the high-EE group a trend between high-EE and two year relapse emerged (Fisher p=0.08). The post discharge EE data was not associated to relapse. The predictive value of the admission EE-FMSS with regard to one
and two year relapse was strong (0.8 and 1.0, respectively, i.e. a high-EE at admission implied a 80-100% probability of suffering a relapse). The sensitivity of admission high-EE after one and two years was moderate (0.5).

The relationship between admission EE and relapse became stronger when an aggregated measure of EE was used, i.e. assessing a high-EE if any of the two EE assessments were scored as high. The aggregated EE showed a tendency toward predicting relapse after two years (p=0.08). When borderline ratings were included in the high-EE group the aggregated measure significantly predicted relapse after one and two years (p=0.035). The aggregated EE measure showed a very good sensitivity and predictive power (0.8-1.0) with regard to one and two year relapse.

In a stepwise logistic regression analyses of possible confounding factors, diagnosis, premorbid functioning, age, sex or length of the initial hospital stay did not predict one or two year relapse rates. Prophylactic medication during follow-up versus no medication or non-compliance did not significantly (p=0.23) contribute to relapse but all of the four non-relapsed patients at two years were on medication. Among the relapsed patients, six were on and five were off medication (three from the latter group were non-compliant). The three patients having high-EE on admission and without adequate medication relapsed during the two years.
DISCUSSION

Methodological considerations

The sample
The main strength of this study was the composition of the cohort. This included a consecutive cohort from a defined catchment area of all psychotic disorders. Only about 15% of the sample (table 1 above) were recruited as patients for tertiary care. There was no other facility for in-patient treatment of psychotic disorders below age 18 years in the area and adult psychiatry units did not admit adolescents below age 18 years at the time. This has been validated in personal communication with several psychiatrists but not through a search of the registers.

Furthermore, the follow-up rate was very high concerning information on functional level and attempted suicide. It was complete regarding early death. In a couple of cases, the major outcome category had to be derived from circumstantial information such as tax authority files and other public registers. In other measures i.e. GAF and Strauss-Carpenter, the number is lower but the excluded cases were still few (6%) precluding a drop-out analysis.

The results on diagnostic stability were based on a subsample and a more disabled and older group were excluded as they did not consent to the necessary interviews. However, when all 88 patients from the cohort were included with available but less accurate information of diagnostic stability, the findings of stability would not be different from the results presented above.

Likewise, the QOL analysis excluded subjects with schizophrenia and a more severe course where QOL ratings possibly would be different and associated with different factors. Still the GAF rating in our schizophrenia cohort is lower than in any other QOL study [59, 77, 78, 110, 224].

The sample in the EE study mostly consisted of schizophrenia spectrum disorders. Two families did not consent to the second FMSS interview.
The instruments

Background factors and the initial diagnosis were assessed retrospectively from records from a number of different clinicians. The records from the earliest one third of the sample were sometimes scant in description of symptoms and premorbid function. Thus, there is probably some lack of information and an over-estimation of the premorbid GAF level. Information on family history was rather well covered in the records and again probed in a structured way at follow-up. The data was, in most cases, not supported with interviews of family members. Therefore, we limited data to obvious cases of psychosis or bipolar disorder. Still, the reported figures on family history are possibly underestimating the true prevalence.

There was some disagreement between raters when reassessing the initial diagnosis. It concerned whether the affective symptoms were to be judged as part of an affective disorder or of EOS. However, the frequency of diagnostic shift during the observation period was comparable to a recent study with an independent diagnostic reassessment at follow-up [90]. The diagnostic drift in our sample tended to underestimate the magnitude of difference between the initial diagnoses of schizophrenia or affective psychosis. The finding that patients in the “change to schizophrenia” subgroup were older at follow-up could partly be attributed to the less complete clinical descriptions and hence a lower accuracy of diagnosis from the earlier records. Therefore, diagnostic continuity could possibly be further increased if a more thorough evaluation according to modern criteria was to be carried out at first admission.

The GAF in DSM-IV is well known and widely used. A problem is the merging of symptoms, relational and occupational aspects into one variable. If these aspects were separated, the GAF correlated with “occupational GAF” (r=0.96, p<0.0001) and with “relational GAF” (r=0.89, p<0.0001) indicating that the GAF presented was very closely linked to functional status.

The strength of the Strauss-Carpenter (S-C) scale is the broad coverage of the major dimensions of outcome and a high inter-rater reliability. A weakness in the S-C symptom scale is the lack of differentiation between positive and negative symptoms. It is also not differentiating working capacity on the open market from participation in well supported day center activities. This aspect is better distinguished by the GAF.

The major outcome criteria chosen are conservative and sensitive to any kind of deteriorated function. Comparisons with other studies are not straightforward. When comparing with other studies that also utilised the Strauss-Carpenter measure, the classification of outcome groups differ. The Chestnut lodge study sample [135] with “good outcome” would be considered “intermediate” in our study, their “moderate outcome” would be
considered “poor” in our study etc. Subjects labelled “intermediate” in the Uppsala schizophrenia study [219] would in our study fall in category “very poor” (69%), “poor” (27%) and “intermediate” (3%) while the “good” outcome in Uppsala corresponds to “poor” (10%), intermediate (34%) and “good” (56%) in our study. Thus, intermediate outcome in the above studies would be considered “poor” outcome or worse with our criteria. This difference stems from using GAF ratings, which relate to age appropriate function, as anchoring points in our study.

The assessment of suicide attempts was not corroborated by medical records. However, the recording was conservative as self destructive gestures without intent to die were excluded. The prevalence of attempted suicide is possibly underestimated as information in 6% of cases relied on registers only while another 17% relied on registers and interviews with a relative or case manager, which might not have brought up information on attempts that did not receive clinical attention.

Our study did not include a measure of side-effects, which may have ignored the importance of this factor for the quality of life assessment.

The FMSS has shown a reasonable degree of correspondence with EE ratings from the CFI. It underestimates the levels of high EE compared to the CFI [106] which could be an argument for including the borderline ratings in the high EE group.

The measurement of relapse is perhaps overly sensitive. The usual measure of readmission to hospital was not applicable as most exacerbations were handled with increased support in the out-patient setting.

The procedures

The diagnostic reevaluation and other interviews at follow-up were not blind to initial research diagnosis. Rather, all clinical information was used as in everyday clinical practice and there was in two thirds of the cases a prior personal knowledge. However, standardised instruments were applied and inter-rater reliability was good. Still, it can be assumed that the unblinded procedure increased the stability of diagnosis. On the other hand, our level of stability was in line with a recent study [90], which blindly reassessed a similar sample of adolescents with psychotic disorders. Further, the inter-rater agreement on outcome measures was generally very good. Interviews carried out by a known person might yield a more complete rapport on sensitive matters such as substance abuse or suicide attempts.

The initial FMSS was not always performed as close to admission as in other studies. However, the number of high-EE relatives in this study was comparable with other studies using the FMSS [12, 203].
The statistics

The main weakness of this study is the sample size in relation to the number of variables and subgroups analysed. Data on subgroups are presented (eg. on depression, bipolar disorder and schizoaffective disorder) but the power to detect differences between subgroups is rather low while numbers are reasonably sufficient concerning the major dichotomy of schizophrenia spectrum versus affective psychotic disorder.

The number of variables are very large in the analysis of quality of life data and in the characteristics of suicide attempters. A Bonferoni correction due to the many covariates (29 in suicide prediction and 47 in prediction of quality of life) has not been included as this would raise the level of detection to a degree that almost every association would disappear. The statistical basis of the results are thus weakened by a risk of both not finding meaningful differences due to the low numbers and also to find random associations due to the many factors explored. On the other hand, it seemed pertinent to include known risk factors to suicide attempts to be contrasted to the explored quality of life data and to include the domains of quality of life instead of just an overall score to increase the likelihood of finding clinically relevant associations. In the quality of life analysis, covariates were reduced by only selecting covariates with a significant (p<0.05) relation to the dependent variable. However, the main association to overall QoL in both schizophrenia and mood disorders and factors explaining more than 30% of variance in the different domains would still be significant after a Bonferoni correction to p<0.0011 in the Spearman analysis. The multivariate analyses regarding predictors of outcome in subgroups (paper II addendum) and predictors of quality of life are performed with numbers just below 30 (QOL) and around 20 (outcome in affective and bipolar group) where the assumption of a parametric distribution is questionable. Thus, these findings must be considered exploratory.

The numbers, and hence the power in the analysis of prediction of relapse from EE assessments, is very low and not sufficient to detect the expected magnitude of difference in relapse rate from studies in adult onset disorders. Along with the lower sensitivity of the FMSS tool to detect high EE, it seemed reasonable to make further analysis both including borderline ratings in the high group and merging the ratings from two points in time to arrive at a high EE group with high or shifting high EE status (the aggregated group).
The results

Diagnostic stability (paper I)

The high degree of stability (positive predictive value) in the major dichotomy of schizophrenia spectrum and affective disorders is in line with the recent study by Hollis [90] and also with studies of stability of adult onset schizophrenia and affective psychotic disorders [57, 119, 128, 129, 196, 202]. The large diagnostic drift from early onset studies based on clinical diagnosis did not emerge. In contrast, the stability was, as expected, very low for schizophreniform disorder as this diagnosis is mostly of a provisional nature. The stability was also moderate for schizoaffective disorder albeit with very low numbers and for major depressive disorder with psychotic features. The expected shift from depression to a bipolar diagnosis emerged. Cycling into mania within the first two months after being discharged from a depressive episode was included in the initial diagnosis and therefore lowering the frequency of shift to one fifth. The stability of bipolar disorder was fairly high. One sixth of bipolar patients were re-evaluated as suffering from schizoaffective disorder. Similar results were found in the adult study of Marneros [128]. In our study the reassessments of initial diagnosis from records was possibly influenced by the striking findings of large proportions of patients with early onset bipolar disorder diagnosed with schizophrenia in adolescence [102, 215] and thus maybe being overly sensitive to signs of affective symptomatology. The more conservative European tradition in diagnosing schizophrenia can also have contributed. However, a diagnostic shift from affective disorder to schizophrenia spectrum disorder or vice versa concerned only 10% of cases.

Diagnostic change

In the analyses of diagnostic change, the schizophrenia spectrum diagnoses received the greatest influx of cases, which amounted to one fifth of schizophrenia spectrum cases. A surprising finding was the similarity of this group to the stable affective group in characteristics that otherwise sharply divided the stable schizophrenia spectrum and the stable affective groups, namely functional level before onset of psychosis and duration of prodromal phase. In the change to schizophrenia cases, the deteriorating process seemed to have started later in adolescence and caused a first hospitalisation at a stage when a schizophrenia spectrum diagnosis was not yet apparent. Another possible interpretation is a diagnostic error with an over-reliance on a neurodevelopmental picture when diagnosing schizophrenia spectrum disorder in adolescence along with vigilance on
affective symptomatology in the diagnostic process. Schwartz et al. blindly assessed DSM-IV diagnosis at six months and two years in subjects with a first episode of psychosis [185]. They found that the most frequent shift in diagnosis at two years was to schizophrenia. These subjects had an equally low adolescent social adjustment, a similar symptom load and functional level at two years as the stable schizophrenia cases. The authors emphasised that the diagnostic change was mostly attributable to the evolution of illness and that a rigid adherence to DSM-IV requirements might have led to an under-diagnosis of initial schizophrenia. Contrary to the Schwartz et al. [185] study in adults, our change to schizophrenia cases had deteriorated in terms of symptomatic and functional aspects to a similar level as our stable schizophrenia cases at follow-up but showed less negative symptoms and a better social function. A possible interpretation of this divergence is that our adolescent change to schizophrenia group represents a clinically distinct subgroup with less marked neurodevelopmental and social deficits compared to the stable early onset schizophrenia cases with marked deficits in adult age. The high degree of non-affective psychosis in first and second degree family members in our study of those cases who changed diagnosis to schizophrenia, underscores the importance of information on family history in arriving at a correct diagnosis in early onset cases. A recent report has also pointed out family history as more prominent in very early schizophrenia as opposed to adult onset cases [147].

Functional outcome (paper II)

Global measures

Our results are in line with earlier studies at a similar length of follow-up reporting a severe impairment in the long-term outcome of EOS [65, 90, 131]. These results also lend some support to the findings of increased severity of adolescent versus adult onset schizophrenia [184, 226] as none of the subjects with a lifetime schizophrenia diagnosis were considered recovered. The more positive outcomes [10, 54, 115, 184, 200] are not replicated. Possible explanations are less strict criteria for diagnosis [54, 200], for “good outcome” [54, 115, 184, 200] and that demands are higher when a follow-up is performed in adult age compared to when studying during adolescence [10]. Family history of schizophrenia as a negative predictor in adult onset schizophrenia has been questioned [108, 219] but more recent reports with strict design support the notion of increased severity in familial cases [143, 211]. Other recent studies have established family history of schizophrenia spectrum disorder as more prominent in VEOS than in adult onset schizophrenia [145, 147]. This parallels a high rate
of family history in our EOS group and also an exceptionally poor outcome in this subgroup. However, this finding should be interpreted with caution due to the post hoc nature of the family data.

In contrast to EOS, our results support the more benign course of early onset affective psychoses. This is well in line with the benign outcome of adult onset bipolar cases and the similarly sized studies by Carlson et al. [37] and Srinath et al. [189] but in sharp contrast to the gloomy outcome of six of seven individuals with EOBD at age 30 years in the Gillberg et al. study [65]. This difference might be explained by the fact that the adolescents in the Gillberg’s study were mostly treated in adult psychiatry which probably lead to a selection towards more severe cases than we had in our study. Also, the majority of the cohort in our study received out-patient treatment at a specialised unit and very few suffered from a substance abuse at follow-up. The benign outcome of depressive psychosis in adolescence in the Gillberg et al. [65] study is confirmed in this study. The overall picture of the long-term outcome of adolescent onset affective psychoses without mental retardation is quite optimistic with 79% of cases in the good or intermediate outcome group. This is well in line with, or better than, in adult onset affective psychotic disorder cases [201].

**Occupational function**

Work performance contributed strongly to the poor outcome in the schizophrenia group in this study. This finding is in line with work adjustment as the area of greatest incapacity in adults with schizophrenia [216]. Disability pension was granted to 65% of the schizophrenia cases in the Swedish study by Gillberg et al. [65] but to 87.5% in the present study. This significant increase might be attributed to higher demands on cognitive performance in the Swedish labor market in the late 1990’s. The Japanese study by Inoue et al. [98] also used the Strauss-Carpenter measure on work adaptation and reached similarly poor figures after 3 years of disorder. Half of EOS patients in this study did not participate in any organised daily activity at follow-up compared to one third of the patients in the Japanese study. Werry et al. [215] similarly reported half without any occupational activity 3 years after discharge. In contrast, the German follow-up studies in EOS have found half with none or mild impairment in employment and in social functioning [115, 184]. This divergence could be explained by different methodology and a softer judgement of impairment. Schmidt et al. [184] assessed present level of employment or education in relation to the premorbid level but not the degree of impairment. Krausz and Muller-Thomsen [115] judged those in training as not impaired. Furthermore, only 31% were receiving a disability pension while half were supported by
parents or a spouse possibly reflecting a different system of social support or a different attitude towards mental illness and help seeking [184].

The affectively ill did as well or better in work performance than in comparable studies. Excluding the four EOBD with mental retardation would leave half of the bipolar group in full occupation, which is in line with the study by Werry et al. [215]. Again, excluding the mentally retarded, 22% of the EOBD were left with a disability pension, which is significantly below the 86% in the Gillberg et al. [65] study. In sharp contrast to EOS, early onset affective disorder usually does not result in an inability to work or study.

Social function
There was a great disadvantage in the EOS group. More EOS patients did however see friends every week than managed to hold a full time job or study. In the recent study by Hollis [90] in the U.K., only 14% of EOS patients at age 27 years met with friends twice a month or more. In our study significantly more (45%) did. Notably, the U.K. study was conducted in the London metropolitan area and a majority of patients were selected to tertiary care. Our sample were not selected and lived in smaller cities or in the countryside, where social networks and maybe also professional services provide better possibilities for social relations for individuals with severe mental disorders. Likewise significantly more, but still only 16%, of EOS subjects in our study have had a partner. Notably, these were with one exception, females. The only man with an initial diagnosis of schizophrenia and living in a relationship was re-evaluated with bipolar disorder. This makes the sex difference in heterosexual relations in schizophrenia even more striking. There were no observable sex differences on other relational measures such as the GAF “relational” subscale or Strauss-Carpenter “social contacts” subscale. It appears that men with EOS have less success in establishing a heterosexual relationship in the Swedish society possibly due to cultural demands that men ought to be more active in establishing a partnership.

In contrast to schizophrenia patients, affectively ill patients enjoyed regular friendships and usually met with friends once a week. McGlashan [136] found lower scores on the Strauss-Carpenter scale for social contacts and employment in EOBD excluding mental retardation at age 45 years compared to the findings in this study. This difference might be due to the different age of follow-up between the two studies.

Predictors of functional outcome
The most consistent finding from the adult and early onset literature of premorbid function as the best predictor of later function was replicated. Our
study did not report the variable “discharged impaired” as in the study by Werry et al. [213] but the item “duration of inpatient stay” from our study might represent similar aspects.

The contribution of “schizophrenia diagnosis” was in both studies significant but small compared to premorbid function. Family history of non-affective psychosis was a negative predictor among schizophrenia spectrum disorders. The findings from the study of Maziade et al. [130] of negative symptoms at first episode predicting a worse outcome could not be directly tested in our retrospective methodology. However, in our schizophrenia spectrum group there was a correlation between family history of non-affective psychosis and negative symptoms at follow-up (p=0.04) indirectly supporting the findings of Maziade et al. Interestingly, there appeared a trend (p=0.09) in the schizophrenia spectrum sample linking earlier age of onset with lower GAF at follow-up. This is weak evidence contradicting the surprising finding in the study by Werry et al. where older age of onset contributed to a worse outcome among all psychotic disorders. Rather, it is more in line with increased severity of earlier age of onset in schizophrenia [104].

The results of regressions in the affective groups have to be interpreted with great caution as numbers are too low for the analysis. The findings were as expected. Low IQ contributing to a poor outcome is in line with Werry et al. [213] while frequent episodes in bipolar disorder have been shown to result in more functional impairment [66].

Suicide and suicide attempts (paper III)

The suicide rate of 4.5% over the first ten years of disorder is in line with other findings from the adult onset psychotic disorders [47, 58, 99] but less than (p<0.05) the 6.6% deceased in the pooled child and adolescent follow-up studies (see p. 10 above). Further, the high suicide rate from the adolescent onset schizophrenia study [116] was not observed in our sample but the low numbers in both studies precluded statistical significance of the difference. The rate of suicide attempts was also in line with the studies on EOS [116], VEOS [52] and the literature on adult onset disorders both concerning the proportion of attempters [33, 43, 51, 58, 80, 126, 139, 149, 152, 156, 165, 173-175, 209], the number of attempts in a defined period of time [198] and intoxication as the most frequent method [152]. We did not observe more suicide attempts among young adults with bipolar disorder versus major depression [42, 173]. However, our results were in line with another study on adults [165] in observing the tendency in absolute numbers of more subjects with depression and schizoaffective disorder attempting suicide.
compared to subjects with bipolar disorder or schizophrenia but without reaching a statistical trend due to low numbers in our subgroups.

**Sex differences**

All suicide victims were males. A male preponderance was expected from reports on early onset cases [3, 28, 35, 47, 72, 84, 116, 152, 172, 178]. Six of 8 victims with adolescent onset schizophrenia [116], 49 of 63 with schizophrenia with onset at age 19 [47], 9 of 10 with psychotic disorders and death from suicide in their third decade [177] and 20 of 26 victims with onset of psychotic disorders by age 21.5 [217] were male. Altogether 88 (79.3%) of 111 suicide victims with onset in their teens or around age 20 were male. However, an increased relative risk of suicide among female subjects with schizophrenia [3, 35, 58] and affective disorders [229] have been reported. Severe mental disorder appears to diminish the generally observed inhibition to suicide in women and, for example, in schizophrenia from 3:1 to 2:1 [35]. The observed greater increase in suicide risk among adult women with psychotic disorders does not seem to hold true for the early onset cases where the great majority of suicides are male.

In this study, males and females had just as often attempted suicide in line with some adult onset studies [80, 204, 209]. In several other adult studies females have more often made suicide attempts [2, 149, 152]. This underlines again the severity of early onset psychotic disorders in males. There was a higher proportion of females in the small group of attempters with affective disorders. This female preponderance vanished when the two fatal attempts by males were taken into account. There was a sex difference in number of attempts. Males made usually only one attempt while females usually made several attempts. This is in line with more attempts and a longer time span from first attempt to suicide in females versus males in an earlier study of young adult suicide [179].

**Associated factors**

**Schizophrenia**

Contradictory pattern between attempters with schizophrenia spectrum disorder and affective psychotic disorder was found. Subjects with a diagnosis of schizophrenia and a history of suicide attempts had many characteristics which are usually associated with a better prognosis. They were older at first symptom, had less often prominent negative symptoms at first presentation and appeared instead more often depressed. At follow-up, they had more social relations, had more often tried illegal drugs and had more symptoms of anxiety-depression. Furthermore, there was a non-significant tendency of higher GAF and less negative and less cognitive
symptoms. Due to low numbers and large standard deviations, these latter figures did not differ statistically. At follow-up, a high prevalence of symptoms of depression and a higher rate of substance abuse is expected but attempts are usually associated to younger age of onset [152, 165, 204] as opposed to our results. Thought disorders are usually protecting from suicide attempts [43, 149] while the literature on negative symptoms is contradictory [43, 58, 149]. Among our early onset schizophrenia subjects the most severely disordered cases with an earlier onset and prominent negative symptoms at first presentation, a very low exposure to illegal drugs and few social relations had a lower risk of suicide attempts. This is in agreement with the risk profile of suicide in schizophrenia pointing out young men with high levels of premorbid functioning and high expectations as being in a particularly high risk of suicide [35].

**Affective disorder**

Subjects with a lifetime diagnosis of affective psychotic disorder and a history of suicide attempts had few distinctions from the non-attempters. All pointed in the direction of increased severity of the disorder. A trend to more psychiatric admissions and to a lower degree of employment at follow-up was found among suicide attempters as well as a tendency to lower functioning and a trend to more cases with disability pension (44% versus 12%). Symptoms at follow-up were very few both among attempters and non-attempters. The most consistent finding associating number of episodes with suicide attempts [126, 156, 173, 175] was supported. We did not find any association between drug or alcohol abuse and suicide attempts. The rates of such abuse were surprisingly low.

**Nicotine dependence**

An unexpected finding was the strong association between nicotine dependence at follow-up and suicide attempts. This was not explained by any other factor i.e. depression at first episode or at follow-up and remained highly significant in the logistic regression analysis. Cigarette smoking also increased the odds of a suicide attempt in hospitalised adults with psychotic disorders but a regression analysis was not reported [127]. However, in another study of psychiatric in-patients smokers were twice as prone to suicide attempts and the association was significant after controlling for several confounding factors in a logistic regression [192]. In a study by Olsson and von Knorring (personal communication) there was a similar finding among adolescents with major depression where 44% of non-smokers with depression and 73.3% of smokers with depression (p<0.01) had a lifetime history of a suicide attempts. Cigarette smoking has been associated to suicide in adults [50, 81, 86, 159] and to suicide attempts
among females [23]. The mechanism associating smoking cigarettes and by that means possibly dependence on nicotine and suicide attempts or suicide has not been described. The secretion of neurotransmitters such as noradrenaline, serotonin, dopamine, acetylcholine, gamma-amino-butyric acid and glutamate is increased by the binding of nicotine to central nicotine receptors [82]. Smoking also improves processing of auditory stimuli (sensory gating) in patients with schizophrenia and may lessen negative symptoms [124]. In patients with schizophrenia treated with neuroleptics, increased cigarette smoking reduces adverse reactions to the drug therapy presumably because of an increase in the metabolism of neuroleptics [82]. Use of traditional antipsychotics, with a higher propensity to dopaminergic side-effects, results in patients smoking more [124]. There is some evidence that extrapyramidal side-effects, particularly akathisia and neuroleptic induced dysphoria, are associated with poor compliance and poor treatment outcome [63]. Patients treated with clozapine, with a lower propensity to dopaminergic side-effects, smoke less than patients treated with depot neuroleptics [164]. Nicotine dependency could thus be a way to cope with severe dopamine related side-effects of neuroleptics or reduce insufficiently treated symptoms of the disorder. However, most findings of increased suicide rate in smokers concerns people not suffering from psychotic disorders and not being treated with antipsychotics. Cigarette smoking withdrawal produces a range of symptoms including depression, aggressiveness and impulsivity [187]. Regular smokers exhibit greater variation in levels of stress and arousal (both higher and lower) as well as higher impulsivity than non-smokers [24]. Cigarette smokers with a history of depression were experiencing increasing symptoms of depression four weeks after smoking cessation as opposed to a decline in depressive symptoms among never depressed smokers [144]. Antidepressants can aid smoking cessation [95]. A stronger dependency on nicotine could thus be a marker of, or produce more severe depressive or impulsive traits resulting in both a failure to stop the dependency and to become suicidal.

Quality of life
Quality of life (QOL) measures were not at all uniformly associated to suicide attempts. An inverse association was observed for the domains religion, health, family relations and safety but not for satisfaction with finances, living, leisure, social relations and work or daily activities. However, the overall QOL measure was also inversely associated to suicide attempts. Previous reports linking quality of life assessments to suicidality [68, 109] did not adjust for concurrent symptoms of anxiety or depression. The overall QOL score and all domains except religion were not correlated to suicide attempts in our study after adjusting for symptoms of anxiety-
depression in the PANSS. The strongest association was seen for satisfaction with religious belief and it remained \((r = -0.30)\) after adjusting for concurrent symptoms of anxiety-depression. Further, the association between satisfaction with religious belief and attempted suicide remained on the verge of significance \((r = -0.26, p=0.053)\) after adjusting for both anxiety-depression and nicotine dependence. Young adult males in the U.S. state of Utah with low or no participation in the Christian church of Latter-day Saints were more likely to have committed suicide [88]. There was not any correlation between participation in religious activities during the last month and suicide attempts in our sample. On the contrary, there was a trend \((p=0.055)\) that subjects who did not belong to any religion were more content with their religious belief \((6.1 \text{ sd. } 0.9, n=16)\) than protestants \((5.4 \text{ sd. } 1.1, n=38)\) while other religions were too few to be analysed. Is this an artefact or is there some kind of satisfaction with a belief system regardless of religious belief that is protecting from suicide attempts? There is, to my knowledge, no other report linking the subjective satisfaction with religious belief to suicidality. Our very tentative findings suggest that satisfaction with religious belief could have an independent inverse correlation to suicide attempts. Satisfaction with health, family relations and safety might have some importance but the association between symptoms of anxiety-depression is probably a more important factor in determining the risk of future suicide attempts.

**Self-esteem**

Self-esteem was significantly lower in subjects with schizophrenia and a history of suicide attempts while the self-esteem was very good in all subjects with affective disorders regardless of previous suicide attempts or not. However, the correlation in the schizophrenia group was non-significant after adjusting for symptoms of anxiety-depression and also by just adjusting for the single item guilt feelings. Five of six subjects with schizophrenia and a pathological score on guilt feelings at follow-up, had attempted suicide.

**Quality of life (paper IV)**

In line with other studies [14, 110] individuals with schizophrenia or schizoaffective disorder were markedly impoverished in objective life conditions compared to those with psychotic mood disorders i.e. functional level, employment, need for disability pension, social contacts and in living independently.
Satisfaction in different domains

The EPSILON study [59] provides comparative QOL domain scores measured with the LQOLP for patients with schizophrenia from various parts of Europe. Patients from Copenhagen were in that study significantly more satisfied on the overall score. Our schizophrenia patients were similarly satisfied as those from neighbouring Copenhagen in spite of a lower functional level. The domains of greatest dissatisfaction among schizophrenia patients in Europe were work and finances. These domains did not cause dissatisfaction in the Copenhagen centre or in our schizophrenia group. These findings could be attributed to the more generous social welfare systems in the Scandinavian countries. The low satisfaction with social relations in our schizophrenia patients was similar to the findings in other European centers. On the contrary, our patients with a former episode of psychotic mood disorder were most dissatisfied with the domains work and finances. This finding can reflect the burden on the professional career and subsequent economical difficulties from episodes of mood disorder.

Comparison of satisfaction in schizophrenia versus affective psychosis

Individuals with schizophrenia or schizoaffective disorder experienced a significantly lower QOL in six of nine domains and in the perceived overall score compared to individuals with a lifetime diagnosis of bipolar disorder or major depression with psychotic features. Differences were most striking in the areas of leisure, health and overall score. This finding is in sharp contrast to earlier studies of chronic or hospitalised mood disordered patients [14, 39, 110, 168, 181]. Our subjects with an early onset of mood disorder were, at follow-up at age 26, mostly working or studying half to full time and only a small minority were supported by disability pension. They had a low symptom load and a remarkably high functional level. This positive clinical and functional outcome seems to have greatly improved subjective QOL in these individuals with a former episode of psychotic mood disorder. The areas where satisfaction was lower and no better then in subjects with schizophrenia, were work and finances.

Factors associated to quality of life

Schizophrenia

The QOL in the diagnostic groups were associated with a quite different set of factors. Clinical factors determined the largest variation in the schizophrenia group. This is in line with most earlier studies [16, 59, 77, 110, 224] but opposed to other [78, 168]. Half of the variation in global QOL and one third of the variation in satisfaction with health was explained by depressive mood. Subjects with schizophrenia suffered from a considerable
amount of depressive mood at follow-up. The anxiety symptom of somatic concern explained almost half of the variation in satisfaction with safety. These findings are in line with previous work [44, 49, 59, 78, 96, 97, 138, 168] on the importance of symptoms of depression and anxiety for the subjective appraisal of QOL in schizophrenia. Furthermore, two studies [97, 163] have reported a reduction in anxiety/depression to be the only significant correlation with a positive change in subjective QOL over time in patients with schizophrenia. We found an association between positive psychotic symptoms and satisfaction with work but not with perceived overall QOL. This could be due to the fact that our patients with schizophrenia did not suffer from as many positive symptoms as the patients in the study by Awad et al. [16]. Our sample was comparable in anxiety, depressive mood and psychotic symptoms to the EPSILON study [59], where the association to psychotic symptoms was weak and substantially smaller than the relation to anxiety/depression. The non-clinical factors of having a reliable friend and a frequent family contact did show an expected association to satisfaction with social contact and family relations but not in the perceived overall QOL. Our finding that depressive mood outweighed all other factors explaining perceived overall QOL could be attributed to the troublesome amount of depressive mood in our individuals with schizophrenia.

Affective psychotic disorder

QOL in the mood disordered group was generally associated to non-clinical factors. Individuals in the mood disordered group were almost free from psychiatric symptoms and even from symptoms of depression as assessed by the PANSS and reported in table 1. Thus, there was not much of a symptom load to possibly be associated to QOL. The striking finding of a strong association with degree of employment to both overall QOL and satisfaction with health suggests the importance of positive experiences from participation in society. The individuals with a psychotic mood disorder also rated their satisfaction with working and finances as the lowest. These findings indicates that the rehabilitation efforts for those with mood disorders should be focused on employment and education. However, as there was no comparison with normal controls we do not know if this finding really is dependent on the disorder. Another finding in mood disorders was the association between satisfaction with social relations and affective balance. The affective balance scale is made up of “soft” signs of depression (bored, lonely, easily upset, not proud etc.) which possibly did not emerge on the PANSS rating of depressive mood. There seems to be subsyndromal symptoms of depression that affects the subjective quality of social life of
the well functioning patients with a former episode of psychotic mood disorder.

Expressed Emotion (paper V)

The main finding in this study was that EE-FMSS assessed at hospital admission or after discharge was not related to one and two year relapse. This can very well be a type II statistical error as the numbers were too low to detect an expected difference in relapse. All absolute numbers were in the expected direction. As the FMSS is a more conservative measure [106] and the predictive power of FMSS was increased when borderline ratings were included in the high EE group [203] it seems reasonable to include the borderline ratings in the high EE group also in this study. In that case there was a trend to increased two year relapse rate in families with high EE during hospitalisation.

The EE measure was more often unstable than stable. It was in most cases a shift to low EE over time but an opposite shift was also seen. Other reports have noted a similar rate of shifts [26, 183]. Family burden was associated to continuously high or change to high family EE in these studies. This raises the question of predicting relapse from an aggregated high EE rather than the traditional admission EE.

In our data, there was a significant prediction of relapse at both one and two years when the aggregated measure of EE was used and the borderline ratings were included in the high EE group. Considering the lack of statistical power, the increased risk for relapse in a family high in EE at one point in the course of disorder could be regarded as substantial.

The moderate sensitivity and the high predictive power of EE-FMSS found in this study are in line with a study of adults with schizophrenia (18). In a review by Kavanagh [105] the specificity (ratio of low EE who did not relapse) of the CFI was 0.5 and 0.66 at one and two years while the sensitivity (ratio of high EE who relapsed) was 0.72 and 0.79 respectively. Thus, the CFI seems to delineate a larger group which is not as prone to relapse as the high-EE FMSS subjects in this study. The FMSS measure might better predict relapse if borderline ratings are included in the high EE group but still be more conservative than the CFI measure as few borderline-high did not relapse both in this study and in the study by Uehara [203].

When the post discharge high-EE were included in the high-EE group specificity remained high while sensitivity in finding the relapse prone patients increased to 0.8. This suggests that EE is not a trait but rather a state variable. The EE measure after discharge, and thus after returning to live in
the family, might have caught a different subset of high-EE interactions leading to relapse.

These results support the assumption that family EE is an important factor in determining relapse among outpatient adolescents with psychotic disorders. It is also possible that adolescents living in sub-threshold high-EE families may be prone to relapses. This may reflect their increased dependency and a higher degree of parental involvement and worrying. The FMSS may also delineate a more relapse prone group than the CFI. The four cases of low to high changes (from admission to discharge) indicate that EE is not a stable variable but rather a state variable.
CONCLUSIONS

1. A diagnostic split between schizophrenia spectrum psychosis and affective psychotic disorder is usually stable over time.
2. The main diagnostic shift is an influx to schizophrenia spectrum disorder of subjects with a better premorbid function and less insidious onset as compared to those with a stable schizophrenia diagnosis.
3. Early onset schizophrenia spectrum disorder usually has a poor functional outcome. Most subjects need support in the form of a disability pension. Early onset affective psychotic disorder usually has a good functional outcome. Most subjects work and enjoy regular friendships.
4. The functional level before onset of illness is the best predictor of future functional level in psychotic disorders. A family history of non-affective psychosis predicts worse function in schizophrenia. Frequent episodes and low intelligence predicts worse function in affective disorders.
5. The risk of suicide is increased about 30 times and males are at a much greater risk. Almost a third of subjects with early onset psychotic disorders attempt suicide. Females make more attempts.
6. Suicide attempts are related to more depressive symptoms but less negative symptoms at first episode, to readmissions and to dependence on nicotine. Suicide attempts are more strongly associated to symptoms of anxiety-depression than to quality of life.
7. At long-term follow-up, subjects with schizophrenia spectrum psychoses are less satisfied with life than those with a former episode of affective psychotic disorder. Subjective quality of life in schizophrenia is strongly associated to depressive mood, while in affective disorders it is associated to degree of employment.
8. Adolescents with psychosis in families rated high or borderline high in Expressed Emotion either during first episode or after discharge have an increased risk of relapse.
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REFERENCES

19 Beaustrais AL (2001), Suicides and serious suicide attempts: two populations or one? Psychol Med 31:837-845
26 Boye B, Bentsen H, Notland TH, Munkvold OG, Lersbryggen AB, Oskarsson KH, Ustein I, Bjorge H, Lingjaerde O, Malt UF (1999), What predicts the course of expressed emotion in relatives of patients with schizophrenia or related psychoses? Soc Psychiatry Psychiatr Epidemiol 34:35-43
33 Bullik CM, Carpenter LL, Kuper DJ, Frank E (1990), Features associated with suicide attempts in recurrent major depression. J Affect Disord 18:29-37
34 Butzlaff RL, Hooley JM (1998), Expressed emotion and psychiatric relapse: a meta-analysis. Arch Gen Psychiatry 55:547-552
35 Caldwell CB, Gottesman, II (1990), Schizophrenics kill themselves too: a review of risk factors for suicide. *Schizophr Bull* 16:571-589
42 Chen YW, Dilsaver SC (1996), Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. *Biol Psychiatry* 39:896-899
46 Dassori AM, Mezzich JE, Keshavan M (1990), Suicidal indicators in schizophrenia. *Acta Psychiatr Scand* 81:409-413
55 **Emminghaus H** (1887), Die Psychischen Störungen des Kindesalters. Tubingen: Verlag der H. Laup'schen Buchhandlung. pp. 293
70 **Goldstein MJ, Miklowitz DJ, Strachan AM, Doane JA, Nuechterlein KH, Feingold D** (1989), Patterns of expressed emotion and patient coping styles that characterise the families of recent onset schizophrenics. *Br J Psychiatry Suppl*:107-111
77. Hansson L, Eklund M, Bengtsson-Tops A (2001), The relationship of personality dimensions as measured by the temperament and character inventory and quality of life in individuals with schizophrenia or schizoaffective disorder living in the community. *Qual Life Res* 10:133-139
79. Harkavy-Friedman JM, Restifo K, Malaspina D, Kaufmann CA, Amador XF, Yale SA, Gorman JM (1999), Suicidal behavior in schizophrenia: characteristics of individuals who had and had not attempted suicide. *Am J Psychiatry* 156:1276-1278


Huppert JD, Weiss KA, Lim R, Pratt S, Smith TE (2001), Quality of life in schizophrenia: contributions of anxiety and depression. Schizophr Res 51:171-180


Joyce PR (1984), Age of onset in bipolar affective disorder and misdiagnosis as schizophrenia. Psychological Medicine 14:145-149


105 Kavanagh DJ (1992), Recent developments in expressed emotion and schizophrenia. *Br J Psychiatry* 160:601-620
108 Kendler KS, Tsuang MT (1988), Outcome and familial psychopathology in schizophrenia. *Arch Gen Psychiatry* 45:338-346
114 Kraepelin E (1896), Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. Leipzig: Barth
121 Lindström E, von Knorring L (1993), Principal component analysis in the Swedish version of the Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Nord J Psychiatry* 47:257-263
124 Lyon ER (1999), A review of the effects of nicotine on schizophrenia and antipsychotic medications. Psychiatr Serv 50:1346-1350
135 McGlashan TH (1984), The Chestnut Lodge follow-up study. II. Long-term outcome of schizophrenia and the affective disorders. Arch Gen Psychiatry 41:586-601
69


141 **Miklowitz DJ, Goldstein MJ, Nuechterlein KH, Snyder KS, Mintz J** (1988), Family factors and the course of bipolar affective disorder. *Arch Gen Psychiatry* 45:225-231

142 **Muldoon MF, Barger SD, Flory JD, Manuck SB** (1998), What are quality of life measurements measuring? *Bmj* 316:542-545

143 **Murray RM, Van Os J** (1998), Predictors of outcome in schizophrenia. *J Clin Psychopharmacol* 18:2S-4S


147 **Nicolson R, Rapoport JL** (1999), Childhood-onset schizophrenia: rare but worth studying. *Biological Psychiatry* 46:1418-1428

148 **Nineteen leading U.S. clinicians and researchers in early onset bipolar disorder** (2001), National Institute of Mental Health research roundtable on prepubertal bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 40:871-878


151 **Nuechterlein KH, Goldstein MJ, Ventura J, Dawson ME, Doane JA** (1989), Patient-environment relationships in schizophrenia. Information processing, communication deviance, autonomic arousal, and stressful life events. *Br J Psychiatry Suppl* 38;4-89

152 **Nyman AK, Jonsson H** (1986), Patterns of self-destructive behaviour in schizophrenia. *Acta Psychiatr Scand* 73:252-262


155 Olsen T (1961), Follow-up study of manic-depressive patients, whose first attack occurred before the age of 19 years. *Acta Psychiatrica Scandinavica Suppl.* 45-51


184 Schmidt M, Blanz B, Dippe A, Koppe T, Lay B (1995), Course of patients diagnosed as having schizophrenia during first episode occurring under age 18 years. European Archives of Psychiatry and Clinical Neuroscience 245:93-100
186 Skantze K, Malm U, Dencker SJ, May PR (1990), Quality of life in schizophrenia. Nord J Psychiatry 44:71-75

72
191 Strauss JS, Carpenter WT, Jr. (1972), The prediction of outcome in schizophrenia. I. Characteristics of outcome. Archives of General Psychiatry 27:739-746


197 Tollefson GD, Andersen SW (1999), Should we consider mood disturbance in schizophrenia as an important determinant of quality of life? J Clin Psychiatry 60:23-29; discussion 30


201 Tsuang MT, Dempsey GM (1979), Long-term outcome of major psychoses. II. Schizoaffective disorder compared with schizophrenia, affective disorders, and a surgical control group. Arch Gen Psychiatry 36:1302-1304


208 Ventura J (1993), J of Methods in Psychiatric Res 3:221-244
214 Werry JS, McClellan JM, Andrews LK, Ham M (1994), Clinical features and outcome of child and adolescent schizophrenia. Schizophr Bull 20:619-630
217 Westermeyer JF, Harrow M, Marengo JT (1991), Risk for suicide in schizophrenia and other psychotic and nonpsychotic disorders. J Nerv Ment Dis 179:259-266
224 Voruganti L, Heslegrave R, Awad AG, Seeman MV (1998), Quality of life measurement in schizophrenia: reconciling the quest for subjectivity with the question of reliability. Psychol Med 28:165-172
disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry* 34:867-876


