Outcomes of Early-Onset Schizophrenia

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OUTCOMES OF EARLY-ONSET SCHIZOPHRENIA

BY
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CV

I received my MA in psychology from Aarhus University in 2003. From 2004 – 2014, I was employed in the Department of Child and Adolescent Psychiatry at Aalborg University Hospital, mostly in the inpatient unit. During this time, I held a position as the head psychologist for three years. In 2014, I made a job change into my current position as the team leader of OPUS, an outpatient clinic for young adults with first-episode schizophrenia. I am authorized by the Danish Psychological Association and a certified psychologist with specialization in child and adolescent psychiatry.

Since the end of 2010, I have been enrolled as a PhD student part-time, doing research in early-onset schizophrenia. As part of the PhD, I have spent 6 months at The Zucker Hillside Hospital in New York, where I joined Professor Christoph Correll and his team in their projects. I have reviewed papers for BMC Psychiatry and Nordic Journal of Psychiatry, arranged research courses for psychologists in their specialist training and supervised projects. I have done oral presentations abroad at the Biennial meeting for the Schizophrenia International Research Society (SIRS) in Italy (2016), the Y-Mind conference for young researchers in Brazil (2013) and at the International Federation of Psychiatric Epidemiology in Germany (2013).

In 2015, I instigated an ongoing cohort research project in the OPUS clinic at Aalborg University Hospital with PhD, MD René Ernst Nielsen as co-primary investigator. I am a member of SIRS, ISPS, IFPE and the Danish society SPBU.

Ditte Lammers Vernal, August 2017

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I. Clemmensen L, Vernal DL & Steinhausen HC (shared first-authorship): A systematic review of the long-term outcome of EOS.
BMC Psychiatry 2012, 12:150[1].

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ABBREVIATIONS

Concepts	
AOP	Adult-onset psychosis
AOS	Adult-onset schizophrenia
COS	Childhood onset schizophrenia (<age 13)
DUP	Duration of untreated psychosis
EOP	Early-onset psychosis (usually in the schizophrenia spectrum)
EOS:	Early-onset schizophrenia
FEP	First-episode psychosis
GFS	General Functioning Scale (a term used in Study 1 for scales measuring global functioning, such as CGAS, GAF or GAS)
NPV	Negative predictive value (proportion of persons not diagnosed who are true negatives)
PPV	Positive predictive value (proportion of persons diagnosed which are true positives)
SSF	Study Specific Functioning outcome (a term used in Study 1)
VEOS	Very-early-onset schizophrenia

Registers and classification systems	
CRS	The Danish Civil Registration System
DPCRR	The Danish Psychiatric Central Research Register
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	The International Classification of Diseases - Classification of Mental and Behavioral Disorders
WHO	World Health Organization

Assessment measures	
CGAS	Children's Global Assessment Scale
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children (Present and Lifetime Version)
PSE	Present State Examination
QLS	Quality of Life Scale

SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for Assessment of Positive Symptoms

Studies

AESOP	Aetiology and Ethnicity in Schizophrenia and other Psychoses. Sample: Substance-induced psychotic disorders, schizophrenia spectrum disorders and affective psychoses (ICD-10: F1x.04; F1x.5; F1x.7; F20–29; F30–31.9; F32–33). Age: 16-64 years. Origin: UK
CAFEPS	The Child and Adolescent First-Episode Psychosis Study. Sample: First psychotic episode, including affective psychoses. Age: 9-17 years. Origin: Spain
EPPIC	The Early Psychosis Prevention and Intervention Centre. Sample: DSM-III-R/DSM-IV diagnosis of psychotic disorder. Age: 14-30 years. Origin: Australia
ISoS	International Study of Schizophrenia, 15-25 f-u). Sample: Schizophrenia and other psychotic disorders (analyzed as 1) all psychoses, 2) only schizophrenia, 3) other psychoses than schizophrenia. Age: Not specified, but adults. Origin: 14 culturally diverse cohorts.
NIMH-COS	Childhood Onset Schizophernia, study at National Institute of Mental Health. Sample: Only childhood onset schizophrenia. Age: 8-18, but onset of psychosis prior to age 13 years. Origin: USA
OPUS	Early intervention in patients with first-episode psychosis. Sample: Schizophrenia spectrum disorders, ICD-10 F20-29. Age range: 18-45 years. Origian: Denmark
TIPS	(‘Tidlig Oppdagelse og Behandling Av Psykoser’ = ‘Early recognition and treatment of psychoses’. Sample: DSM-IV schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic episode, delusional disorder, affective psychosis with mood-incongruent delusions or psychotic disorder not otherwise specified. Age: 15-65. Origin: Norway

Statistical abbreviations

CI:	95% Confidence interval
ZINB:	Zero-inflated negative binomial regression

TABLES, FIGURES AND APPENDICES

PREFACE

Since before I even started studying psychology, schizophrenia and psychotic disorders were among my primary field of interest. When I landed my dream position as a psychologist at the inpatient unit of child and adolescent psychiatry in Aalborg, my interest was further sparked in the meetings with young patients and their families.

I was and am interested in the patients and how they are affected by the disorder: the special sense of reality, their social relations and cognition, the long-term outcome and how they find their way, living with schizophrenia and perhaps recovering from it. Parents and patients often asked me what the future would look like and I was not always sure what to tell them.

The research unit of child and adolescent psychiatry in Aalborg is fairly young – it was established in 2008 by Professor Hans-Christoph Steinhausen. A journal club was established and as clinicians, we were invited to join research projects. With my interest in schizophrenia, I signed up to work on a review of the outcome of early-onset schizophrenia in the winter of 2009/10. Early in the stages of our collaboration, Hans-Christoph Steinhausen suggested that I should broaden the scope and do a full PhD study on the subject. Once the protocol was accepted at the university, my PhD journey began in December 2010.

During my time as a PhD student, I have held a joint position of part-time clinical work and part-time research. Owing to this combination, a job change - into a position as team leader in an outpatient clinic for young adults with schizophrenia - and the birth of my third child, the PhD has taken 6 years and 8 months. It has been a long and sometimes hard journey and I have been looking forward to the finish line. Never once, though, have I regretted going in to research – it has given me many wonderful experiences, collaborators, friends and newfound knowledge.

PROGRESSION OF THE PROJECT AND STUDY AIMS

The overarching theme of the PhD study is the outcomes of early-onset schizophrenia (EOS).

I started out by accumulating knowledge on the outcome of EOS into a systematic review (study 1[1]) in order to obtain optimal knowledge for studying the disorder in the nationwide Danish registers. Next, psychiatric records from patients diagnosed with schizophrenia in childhood or adolescence were collected from all child and adolescent psychiatric departments in Denmark in order to investigate the validity and accuracy of diagnoses in the Danish Psychiatric Central Research Register (DPCRR)[2] (study 2). The last part of my project consisted of a register study (study 3) and investigated the outcomes of EOS compared to adult-onset schizophrenia (AOS) in terms of both psychiatric outcome (inpatient days, hospitalizations, comorbid substance use and involuntary admissions) as well as outcomes related to functioning (educational level, primary source of income and institutionalization).

The thesis aims to answer the following research questions:

a) What do we currently know about the outcome of EOS and does it differ from adult-onset?

b) What is the validity of schizophrenia diagnoses from child and adolescent psychiatric departments in Denmark and how is the accuracy between a schizophrenia diagnosis in the DPCRR and the diagnosis written in the psychiatric record?

c) Based on Danish register-based data, are there differences between EOS and AOS in the following:

   - Number of inpatient days in short- and long-term outcome
   - Premorbid characteristics
   - Psychiatric outcome and measures of functioning

CONCEPTS AND DEFINITIONS

The definitions of EOS and very-early-onset schizophrenia (VEOS) varies [3-6]. In the current studies, EOS is defined as onset prior to 18 years of age and VEOS as onset prior to 13 years of age, which is in line with most studies[1]. AOS refers to adult-onset schizophrenia. Another term for early-onset is adolescent-onset, which is usually defined as onset between 13-17 years of age, where early-onset does not have a lower cut-off range. VEOS and childhood-onset schizophrenia (COS) are often used interchangeably with a tendency for VEOS to be the European term and COS used more in US studies. Prepubertal schizophrenia or pediatric schizophrenia are rarely used in contemporary research. In order to avoid terminology confusion, VEOS will be used consistently for studies regarding VEOS or COS throughout the thesis, with the exception of the large-scale COS study from the National Institute of Mental Health (NIMH), which is commonly referred to as the NIMH-COS cohort/sample[7].

EOS is used for early-onset schizophrenia (including childhood onset), VEOS for childhood-onset, EOP is used for early-onset psychosis, and AOP for adult-onset psychosis. FEP is used for first-episode psychosis.

OUTLINE OF THE THESIS

Chapter 1 is a general introduction to the field of EOS and the main areas of the thesis.

Chapter 2 describes the methods used in the three studies with regards to sample selection, methods, main focus and choice of statistical models.

Chapter 3 describes the results from the three studies.

Chapter 4 consists of a discussion of the studies and findings, strengths and limitations.

Chapter 5 is a perspective on which implications for the field and future research studies, we might draw from the thesis.

Chapter 6 is an epilogue on my thoughts on what to tell future patients and parents asking me about prognosis and outcome.

Chapter 7 is a conclusion with short, take-home messages in answers to the research questions outlined earlier.

English and Danish summary of the findings are available at the end of the thesis.

CHAPTER 1: INTRODUCTION

EARLY-ONSET SCHIZOPHRENIA IN A HISTORICAL CONTEXT

Psychotic disorders and madness have been described in children and adolescents as early as the 1800s [8]. Going back through historical archives, psychotic disorders are believed to have existed through the history of mankind with possible descriptions going back as far as Pharaonic Egypt, in the second millennium before Christ. The first clinical and academic descriptions of the disorder have been attributed to Emil Kraepelin, who, in 1887, described the disorder 'dementia praecox' in his classification of mental disorders, and also believed some children with mental handicaps to be suffering from this. Kraepelin regarded schizophrenia as a brain disease and understood it as a form of early dementia of the mind and a poor prognosis was an underlying principle[9]. Eugen Bleuler later coined the term 'schizophrenia' and 'the group of schizophrenias' in a lecture given in 1908 and opposed the notion put forth by Kraepelin that schizophrenia was necessarily a neuro-degenerative disease[9].

Some of the early descriptions of childhood schizophrenia resemble current knowledge; as early as 1926 August Homburger described that childhood schizophrenia was characterized by negativism, withdrawn, unpredictable and strange behavior[10]. He described three different types of premorbid features: children with normal development and IQ; children with premorbid mental retardation; and children with IQ in the normal range but character anomalies and strange behavior[10]. Onset could either be acute and catatonic or slow and hebephrenic with cognitive deterioration[10]. Jakob Lutz described childhood schizophrenia as separate from adult schizophrenia in the 1930s and a decade later, Leo Kanner and Hans Asperger outlined two types of autism from the group of childhood psychoses[10]. Kanner and Elwyn James Anthony later proposed three groups of psychoses with and without a relationship to schizophrenia: early infantile autism, childhood schizophrenia and disintegrative psychoses of childhood, the latter referring to psychoses related to brain damage and childhood dementia. These classifications later came to influence the International Classification of Diseases – Classification of Mental and Behaviorural Disorders (ICD) in ICD-9, and the Diagnostic and Statistical Manual of Mental Disorders (DSM) in DSM-III and DSM-III-R [10]. Lauretta Bender was interested in the clinical presentation of childhood psychoses and started her work in the 1940s at Bellevue Hospital in New York[8]. In 1958, she described schizophrenia in children as distinct from 'the pseudo-defective group', which resembled children with infantile autism; from 'pseudo-neurotic group' of children aged 3–5 with anxiety and the 'pseudo-psychopathic or antisocial' aged 10–11[8]. Bender also addressed diagnostic continuity and concluded that most children with schizophrenia would continue with the same disorder in adolescence and adulthood[8].

Throughout the twentieth century, the descriptions and classifications of schizophrenia in children and adolescents have been very heterogeneous with a lack of specificity. This is evident in the criteria of both the DSM-II and ICD-8. ICD-8 had one broad category of 'childhood psychoses', including disorders as diverse as psychoses, severe personality disorders and what we today would classify as infantile autism[8]. There was, at the time, no consensus regarding whether schizophrenia in children even existed[8].

Today, a series of papers on childhood psychoses from 1971 by Israel Kolvin and colleagues[11-16] are regarded as landmark papers, applying homogenous diagnostic criteria to early-onset psychoses and making it possible to distinguish autism and childhood schizophrenia by distinguishing between 'early-onset psychoses' (by age 3) and 'later-onset psychoses of childhood' (originating at age 5 or later) [11,17]. In their papers, they drew on prior work by Leo Kanner and Mildred Creak, in particular, of early psychoses, and on the work of B. Fish for late-onset psychotic disorders in childhood; however, they also described prior work by James Anthony, Lauretta Bender, Bernard Rimland and Michael Rutter as important with regard to moving towards a more operational way of classifying the psychoses in childhood[11].

In reading and interpreting clinical descriptions and outcome results of older studies, these shifts in concepts and descriptions are important to bear in mind[18]. The various concepts and descriptions of childhood psychoses and schizophrenia throughout history result in difficulties with using older studies of childhood psychoses for epidemiology purposes. The 42 year follow-up study by Remschmidt et. al.[10] serve as an example – the study included patients diagnosed between 1920 and 1961 with VEOS (including patients up to the age of 14 years) and re-evaluated all case records according to ICD-10 classification – only 50% of the original sample met ICD-10 criteria for schizophrenia and only 18% of the non-schizophrenia cases were even in the schizophrenia spectrum.

CLINICAL PRESENTATION AND CHARACTERISTICS OF EARLY-ONSET SCHIZOPHRENIA

Studies and reviews have found and described similarities between EOS and AOS in terms of the core symptoms of schizophrenia[19,20], but developmental variations in the clinical presentation must be considered[20,21]. Delusions in children are often vague and less elaborated than seen in adults[19,22], and it is important for the clinician to distinguish psychotic delusions from vivid imagination and developmental delay in reality testing[11]. Especially in VEOS, imaginary friends can be part of normal development[20,23]. Assessment of logic, loosening of associations and other formal thought disorders must also take maturity and IQ into account. Children's way of

expressing themselves can be different from adults' use of language in terms of cohesion, logic and symbolic use [20,23].

In terms of clinical characteristics, patients with EOS have been found to have more premorbid difficulties[24-27], potential higher genetic loading[28-31] and more cognitive dysfunctions [32-34] than patients with AOS. Furthermore, patients with EOS more often have insidious onset, and are more frequently profoundly affected by negative symptoms and disorganization[20]. With a long insidious onset in a young age, some children with early onset may interpret their symptoms as normal and ego-syntonic [19]. Children and adolescents often have longer duration of untreated psychosis (DUP) than adults [27,35], which also may be influenced by such ego-syntonic symptoms, not prompting the individuals to seek help.

Very-early-onset schizophrenia (VEOS) is by many considered a more severe disorder than both adolescent-onset schizophrenia and AOS, with both more intellectual deterioration, a more chronic long-term course characterized by negative symptoms and with a highly unfavorable outcome[17,36]. VEOS seems to be associated with greater heritability [17]. In contrast to adult- and adolescent-onset of the disorder, males are overrepresented in VEOS, with studies describing ratios of 3–5:1[10].

OUTCOME OF SCHIZOPHRENIA

Outcome of schizophrenia has been studied in adults for decades and several reviews of the outcome of first-episode schizophrenia or first-episode psychosis (FEP) exists[37-40].

Hegarty et al. reviewed 320 studies of adults with schizophrenia with a total of approximately 50,000 patients, published between 1895 and 1992 with a mean follow-up of 5.6 years and described considerable improvement in 40%[40]. Loss to follow-up across the cohorts ranged from 10& to 30%.

Menezes et al. included 37 studies and 4,100 patients with FEP in their meta-analysis of outcome, based on studies published between 1966 and 2003[37]. Mean follow-up was 3 years. Studies used different categorizations and definitions of outcome, but 'good' and 'poor' were common categories. Of the studies using these categories, good outcomes were reported in 42.2% and poor outcomes in 27.1%. The authors concluded that the outcome of FEP may be more favorable than previously reported and suggested that the reasons for this may be an over-representation of chronic, treatment-refractory patients in older studies, as well as patients with full recovery or otherwise good outcomes dropping out of the studies at a higher rate. Furthermore, they pointed to methodological differences in the pooling and comparison of data and suggested a globally used definition of outcome for future research. There was no

evidence of age at onset, DUP and diagnosis (schizophrenia vs. schizophreniform or affective psychosis) to be predictive in terms of outcome, which, as the authors state, was unexpected[37].

From the International Study of Schizophrenia (ISoS), Harrison et al. combined 14 incident cohort studies and four prevalence cohorts, totaling 1633 subjects[39], and demonstrated the initial 2-year course ('percentage of time spend experiencing psychotic symptoms') to be the strongest predictor of outcome at 15 and 25 years' follow-up. The rates of globally recovered were fairly high: 56% in the incidence cohorts and close to 50% in studies of AOS only[39].

Jobe and Harrow reviewed nine studies in 2005; the studies were from North America and ISoS, coordinated by the World Health Organization (WHO), all with a follow-up time of 10 years or longer[38]. Poorer outcomes were seen in schizophrenia as opposed to other psychotic disorders, as well as non-psychotic disorders; however, patients with extended periods of recovery were also seen in the schizophrenia groups and very few patients had a progressive, deteriorating course[38]. In total, 21–57% experienced good outcome.

In conclusion, the knowledge from adult studies on schizophrenia and schizophrenia spectrum disorders points to moderate-to-good outcomes in 21-50%, with most reporting rates around 40%, although outcome is worse in samples restricted to patients with schizophrenia. Studies vary considerable in methodology and outcome measures.

OUTCOME OF EOS AND VEOS

In EOS and VEOS, reviews have pointed to poorer outcomes compared to AOS[41-44]. Our review of outcome of EOS, which will be described more in detail throughout the thesis, was published in 2012 in BMC Psychiatry[1] (study 1). In the same year, Remschmidt and Theisen published a recapitulation with the current knowledge on EOS[36] and summarized the findings as a very poor prognosis in VEOS, with a typical course extending into adolescence and adulthood. Patients with acute onset and positive manifestations had better outcome as patients with insidious onset who more often have worsening impairment. Premorbid adjustment were stressed as important for the long-term outcome, and genetic predisposition likely worsened the outcome[36].

The largest follow-up study to date comparing outcome and age of onset was a register-based study conducted in Israel including 12,071 patients, with 1877 patients diagnosed prior to 19 years of age[45]. The study had a median follow-up of 10 years and up to 17 years of follow-up, and showed earlier age of first admission corresponded linearly to number of hospitalizations, using recursive portioning as the

primary statistical method[45]. Outcome was worse in patients diagnosed prior to 12 years of age. In total, 82.5% of patients diagnosed prior to the age of 17 had more than one admission, which decreased linearly with subsequent older-onset groups, as did the number of inpatient days during first admissions and number of annual admissions[45].

Some studies, including newer ones, have not been able to show a worse prognosis of EOP compared to AOP[35], and currently there are indications of a better prognosis for EOS and EOP than previously thought [46,47]. These studies have been conducted in combined treatment settings for early- and adult-onset. Such studies have been sparse, as children and adolescents are mostly treated in other facilities than adults, but comparing early-onset and adult-onset psychotic disorders from studies in different treatment settings can be problematic as study design, interventions and selection may differ[48]. Schimmelmann et al.'s study of patients in The Early Psychosis Prevention and Intervention Centre (EPPIC)[35] with EOP and adult-onset psychosis described minor difference in outcome between the two groups, which were mostly explained by confounders– patients with EOP had slightly worse premorbid functioning and higher DUP than patients with AOP (26 vs. 9 weeks), although DUPs were generally short in this study[35]. White et al.[49] also compared patients with EOP and AOP in the same sample and replicated the finding of longer DUP (125 weeks vs. 68 weeks) and found no differences in symptom severity. Joa et al.[50] compared patients with EOP and AOP patients from the TIPS ('Early recognition and treatment of psychoses') study in Norway and replicated the finding of longer DUP in patients with EOP. Furthermore, higher rates of lifetime suicidality (plans or attempts) were reported for patients with EOP. Thirty-five percent of the EOP sample was initially treated as outpatients versus only 16% in the AOP sample. The authors concluded that the clinical picture EOP may look like a milder form of schizophrenia due to a more insidious onset and less clear-cut psychotic symptoms. At the two-year follow-up the EOP and AOP patients in the TIPS study did not differ on suicidality, remission, substance use, number of patients on antipsychotic medication and hospitalization, social and occupational functioning[46].

Most studies reporting a better prognosis for patients with early-onset are not restricted to EOS but often include schizophrenia spectrum disorders. As schizophrenia is associated with worse outcomes than other psychotic disorders[1,38,39], this could bias studies. However, Immonen et al. published a meta-analysis in 2017 studying the effect of age of onset on outcome, by only including studies with patients with both EOS and AOS[48]; and samples were required to have at least 80% of patients with schizophrenia, schizophreniform, schizo-affective or delusional disorder. The conclusion from pooling data from 75 studies was that early age of onset had a negative effect on some outcomes (more hospitalizations with higher frequency, more relapses, negative symptoms, poorer social/occupational functioning and global outcome). All though these were important overall measures, all effect sizes were

small (<0.2) and the authors concluded that, on some outcomes, age of onset has a small but significant effect [48].

FACTORS RELATED TO PROGNOSIS

Premorbid functioning plays an important role in the course and prognosis of the disorder. It is well established that patients with a prior high level of functioning with regard to intellectual capacities and abilities for social functioning and integration have a better prognosis than children and adolescents who prior to onset of psychosis suffered from either intellectual impairment or poor social relations and communication skills[36]. Prognosis also seems to be worse if there is a family history of schizophrenia. DUP is a well-researched area, and reviews report longer DUP to be associated with poorer outcomes[51,52] and the ability to efficiently treat the psychotic symptoms[52,53].

Ballageer et al. conducted a study directly comparing clinical characteristics of EOS and AOS in patients aged 19–30 years, and showed many similarities in symptoms and clinical presentations between the two, but differences in several of the parameters that may predict a poorer outcome[27]. The sample consisted of patients with first-episode psychotic disorders (schizophrenia spectrums disorders, substance-induced psychoses, affective psychoses and other, non-affective psychoses) and 201 patients were included, of these 82 had early-onset psychosis (EOP). EOP was defined as the onset of psychotic symptoms between 15 and 18 years of age – a slightly older age cut-off than most studies of EOS/EOP – including the definition of EOS used in this thesis. Patients were thoroughly assessed by experienced psychiatrists and a master in psychology. Many similarities were found: premorbid functioning until the age of 15, adverse effects of medication, length of prodrome or duration of untreated illness (defined as onset of any psychiatric symptoms), measures of hallucinations, delusions, formal thought disorder or global scores on Scale for Assessment of Positive Symptoms (SAPS), and avolition, anhedonia, alogia, attention and global scores on Scale for Assessment of Negative Symptoms (SANS), proportion with substance use, anxiety or depression[27]. However, patients with EOP differed on measures specifically associated with poorer outcome – longer DUP (103 weeks vs 46 weeks, p=0.022), more bizarre behavior (76.5% vs. 60.5%, p=0.01 and the core negative symptom of affective flattening being more severe and affecting more patients (2.52 vs. 2.13, affecting 52.4% vs. 37%); and more EOP patients also had primary negative symptoms.

Furthermore, the efficacy of antipsychotic medication may be lower in EOS [54], and patients tend to be more sensitive to side effects that may occur more frequently [55].

In the past few years, two meta-analyses focused on predictors of outcome in EOS and EOP[26,56]. Stentebjerg-Olesen et al. conducted a systematic review of clinical characteristics and outcome predictors of EOP[57]. The review included 35 studies from 28 independent samples (n=1506) with a mean age <19 years at baseline, including primarily schizophrenia and schizophrenia spectrum disorders (89%), but also a smaller number of patients with affective, substance and organic psychoses. Mean follow-up was 17 months. Premorbid adjustment was positive correlated to outcome at 1–4 years with regards to social functioning, quality of life, global functioning and remission, and illness severity measured by CGI-S were lower and negative symptoms less prominent with better premorbid adjustment. Díaz-Caneja et al.[26] reviewed 75 studies of EOP in a systematic review using multivariate models. EOP was defined as psychotic illness in childhood or adolescence. In four of the studies, the upper age limit was >18 years of age, but the mean age was below 18. The focus of the review was not on the final outcome of EOP, but instead on predictors of outcome. Longer DUP was found to predict worse clinical, functional, and cognitive outcomes. The age of onset within these early-onset samples did not prove to be a consistent predictor of outcome in the multivariate models. Gender was also not consistently associated with outcome. Having a low IQ at baseline predicted worse functional outcome and higher likelihood of being diagnosed with schizophrenia. Remission was associated with acute onset or shorter DUP as well as higher baseline functioning. The authors summarize that patients with EOP with poorer premorbid adjustments and negative symptoms at baseline are at risk of poor outcomes.

DUP, premorbid functioning, intellectual functioning, mode of onset and family history of schizophrenia are found to be related to prognosis in both child-, adolescent- and adult-onset of schizophrenia[26,27,57,58].

Summarizing, from studies, meta-analyses and literature on EOS in general, there is agreement that the following are associated with worse outcomes in EOS / EOP: Longer DUP and insidious onset, profound negative symptomatology at baseline, genetic predisposition, poor premorbid adjustment, cognitive dysfunctions or low IQ and schizophrenia diagnosis compared to other disorders from the schizophrenia-spectrum, while remission, recovery and better outcomes were associated with acute onset. Effect of gender on outcome is not clear; some meta-analyses do not find a consistent association[26], while our review found poorer outcome for males[1], but the register-based study did not find a consistent association between sex and outcomes

After having outlined some of the literature and knowledge of EOS in terms of both clinical characteristics, outcome and factors related to outcome, I will now move on to the validity of schizophrenia diagnoses.

VALIDITY OF DIAGNOSES

Validity can be described and measured in several ways, common concepts are sensitivity, specificity, positive predictive value and negative predictive value, which all try to test proportions of positive and negative results, either focusing on the chance of being right or the risk of being wrong.

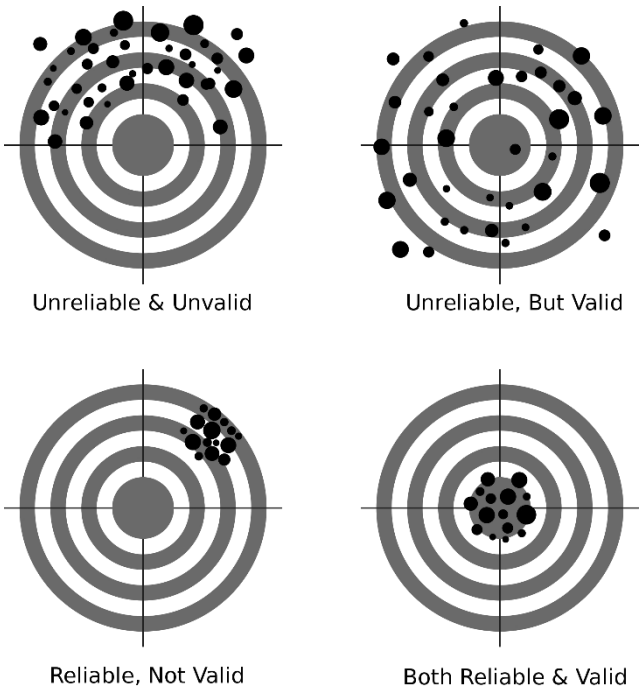
Sensitivity and specificity are statistical measures to assess performance of a binary test. Sensitivity measures the proportion of patients diagnosed correctly with the tested measure. Specificity measures the proportion of patients who do not have the disorder in question and are correctly identified as such.

Positive predictive value (PPV) and negative predictive value (NPV) are also measures of performance, but unlike sensitivity and specificity, PPV and NPV are affected by the prevalence; if the prevalence is high, PPV will be higher and vice versa. PPV is often used for diagnostic stability to measure the probability of the same diagnosis being given at follow-up.

The terms validity and reliability are sometimes, erroneously, used interchangeably. They are two different concepts, all though to find the best assessment tools, it is imperative that they correlate. Reliability measures consistency, while validity tells us if we are measuring what we think we are. It is often exemplified by darts, as in Figure 1.

For example, if someone had the idea that we could diagnose schizophrenia by measuring shoe size, the measurement would likely be extremely reliable – all ratings would be very close to each other and not require extensive training, and consistency close to perfection, at least in the adult population. However, the validity would be very low – even the general population would oppose this measurement of schizophrenia.

Figure 1: Validity and reliability exemplified.



Reliability refers to the degree to which the construct can be measured adequately. Interrater reliability refers to the degree different people will reach the same conclusions, and intrarater reliability, the degree to which one rater will reach the same conclusion if he/she were to measure the same construct on a different day. Reliability are also sometimes called precision or concordance.

The optimal method for assessment of schizophrenia would have both high validity and reliability – in such cases, it would be fairly easy to train clinicians to use a method that would enable them to arrive at the same conclusion (good reliability) and the conclusion would match the reality (good validity).

How to calculate sensitivity, specificity, PPV, NPV are shown in figure 2.

Figure 2: Diagnostic test evaluation

		Patients with a disease or disorder (as confirmed by gold-standard)*		
		Condition positive	**Condition negative**	
Screen test outcome	**Test positive**	*True positive* (TP) = 54	*False positive* (FP) = 8	**Positive predictive value** = TP / TP + FP) = 54 / (54 + 8) = 0.871 (87.1%)
	Test negative	*False negative* (FN) = 2	*True negative* (TN) = 9	**Negative predictive value** = TN / (FN + TN) = 8 / (2 + 8) = 0.818 (81.8%)
		Sensitivity = TP / (TP + FN) = 54 / (54+2) = 0.964 (96.4%)	**Specificity** = TN / (FP + TN) = 8 / (8+9) = 0.529 (52,9%)	

** The example is calculated from the findings in Makïkyro et al.'s study[59].*

DIAGNOSTIC VALIDITY OF SCHIZOPHRENIA IN REGISTERS

Internationally, as well as in Denmark, several mental disorders have been investigated in healthcare registers in order to assess accuracy of diagnostic registration as well as diagnostic validity[60-69]. The assessment of a register's usefulness for research studies should rely on two cornerstones:

1) The concordance between clinical and register diagnoses.
2) The validity of clinical diagnoses compared to diagnostic criteria.

The first is a matter of the preciseness and accuracy of the coding of diagnostic classification in the register. Some mistakes are unavoidable, but it should be investigated whether errors are random without any specific bias or if there are inherent misunderstandings in the coding or inexpedient local procedures. In the DPCRR the diagnostic codes are automatically generated from the psychiatric hospitals, so errors due to forgetfulness are avoided. The agreement between clinical and register diagnoses are fairly easy to assess; a review of the discharge summaries compared with DPCRR diagnoses would be sufficient.

The latter requirement of validity of clinical diagnoses is more difficult to assess as it involves an evaluation of the assessment conducted in the clinic. Adequate adherence to diagnostic criteria requires experience and competence by the clinician, as well as his/her willingness to follow the diagnostic classification system used at a certain time.

Byrne and colleagues investigated validity of the administrative data in the registers in a review of studies between 1966–2004[70]; 14 validity studies of register-data were found, with five focusing specifically on schizophrenia[59,61,64,69,71]. Generally, the studies drew positive conclusion about the validity. In the studies reporting solely on schizophrenia, a Swedish study described 86% true positives with a broad definition of schizophrenia and 76% with a narrow definition[69], a Danish study 66% true positives and sensitivity as 0.40[64], a Swedish older study as 76% true positives[61] , one Finnish study 48% false negatives, specificity of 1 and sensitivity of 0.52[71] , another Finnish study 93% true positives, a PPV of 0.87 and NPV value of 0.82 (exemplified in Figure 2)[59]. In studies examining several disorders, schizophrenia generally had better validity than the other disorders, with a Finnish study reporting accuracy of 99% in schizophrenia[72].

In Denmark, reliability of schizophrenia diagnoses have been investigated by Jakobsen et al. who documented high sensitivity (93%) and PPV (87%) of schizophrenia and for schizophrenia spectrum disorders as a broad entity (98%) in a study with 100 randomly sampled from a research biobank of which the majority were evaluated using both interview and medical record assessment[73]. Another study validated schizophrenia diagnoses registered in the DPCRR in 2009 by rating of psychiatric records and found the register diagnosis to be correct in 89.7–97.55% of the cases[62].

Prior to study 2 (submitted), only one study has validated EOS and EOP – the Swedish study by Dalman et al. published in 2002, validating schizophrenia diagnoses from the Swedish National Inpatient Register in patients diagnosed prior to age 20[69]. One-hundred patients with an ICD-9 diagnosis of schizophrenia syndrome (71 with narrow schizophrenia) were included, and 36 of them had EOS[69]. The validity between patients with EOS and AOS were similar (14% vs. 15% false positives).

All though no other methodological validity study of EOS seem to exist, the diagnostic process in the important work with the NIMH-COS cohort led by Judith Rapoport et al.[7] deserves mentioning.

In NIMH-COS, the investigators thoroughly reported their process of diagnosing and validating the referred patients, all of whom were referred with a tentative diagnosis of schizophrenia. If the initial screening process (telephone screening followed by clinical and structured interviews) yielded a provisional diagnosis of COS, the child would be admitted to a highly staffed inpatient unit for a medication-free period of up

to 3 weeks. Of all the patients referred, only 5% had the diagnosis confirmed[74]. Of the patients admitted with a provisional COS diagnosis, it was ruled out for almost 40%[25]. The researchers of the NIMH-COS cohort have underlined that diagnosing VEOS is a time-consuming process with high rates of false positives[25], which has also been confirmed by other studies[75].

DIAGNOSTIC STABILITY IN SCHIZOPHRENIA

A concept related to diagnostic validity, but not identical to, is diagnostic stability: the proportion of patients who retain the same diagnosis over time. For a disorder like schizophrenia, we would expect a high level of diagnostic stability as schizophrenia is known as a disorder with some chronicity, but we would not expect 100% diagnostic stability as some patients do have full remission, and a 100% stability measure might indicate that diagnoses are carried forward without new considerations or assessments.

Research confirms schizophrenia as a disorder with a high diagnostic stability over time, also known as a high PPV for long-term outcome[76]. In adult studies, Whitty et al. reported a long-time PPV of 96% – 72 in 75 patients with schizophrenia at baseline retained the diagnosis at follow-up after four years[77]. An older study by Amin et al. reported PPV of 83% in patients diagnosed with schizophrenia at onset measured at the three-year follow-up[78]. In early-onset samples, diagnostic stability have been reported in 66% and 100% of the patients[79-83]: Jarbin and Knorring[79] traced 68 former patients who had been diagnosed with a first-episode EOP 10.5 years previously; patients with a diagnosis with schizophrenia were all diagnosed with schizophrenia as a lifetime diagnosis at follow-up (PPV of 100%), and 28 of 29 in the schizophrenia spectrum retained a diagnosis in this spectrum at follow-up (PPV of 96.5%). Hollis and colleagues conducted a follow-up study on 110 patients with first-episode EOP, 51 of them with EOS. After 11.5 years, schizophrenia had a PPV of 80%[80]. In the Child and Adolescent First-Episode Psychosis Study (CAFEPS), the researchers used a prospective method for assessing diagnostic stability[82]. The participants, aged 9–17 years, all had EOP and were assessed with the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS)[84,85] at baseline and again after 2 years. The diagnostic stability of a diagnosis in the schizophrenia spectrum was 90% (n=40), and for schizophrenia 100% (n=5). A Polish study described diagnostic stability of 78% in EOS assessed after 8 years of follow-up[81]. Thomsen studied EOS in the Danish registers, including all patients (n=312) with EOS in the period 1970-1993[83]. Diagnostic stability was assessed for the patients with later admissions, and 33% had admissions for other disorders. In the subgroup who had at least 10 years of follow-up, schizophrenia was confirmed at a later admission in 64%[83].

Owing to the low incidence and prevalence of EOS, many clinicians in child and adolescent psychiatry are less experienced in diagnosing EOS. To exemplify,

approximately 100 patients are diagnosed with EOS each year in Denmark[86-88], a country with 5.7 million inhabitants, and although the number of patients with EOS has been increasing[89], it is still a small population compared with the larger group with AOS. The prevalence of VEOS is even smaller, as I will highlight in studies 2 and 3, to a degree that makes VEOS close to impossible to study quantitatively in a country as small as Denmark. To account for the low prevalence and therefore limited experience in regular clinics, as well as to establish a larger cohort for the purpose of research in assessment, clinical characteristics and treatment, the NIMH has supported a large-scale study in the USA – the aforementioned NIMH-COS cohort – in which children from across the country are assessed and treated in the same clinic. The NIMH-COS study has been enrolling patients since 1991 and is still ongoing. Despite the expertise level of assessment at the COS-Study clinic, inpatient assessment with a drug washout period is still warranted in many cases in order to avoid false-positive cases[90].

Despite the challenges of low prevalence and symptom presentation being influenced by developmental age, there is general agreement that schizophrenia can be reliably diagnosed in children and adolescents, but a thorough assessment by experienced clinicians is essential[20,25], especially for VEOS[25,90].

CHAPTER 2: METHODS

The thesis is based on three studies with three different types of study design and data selection:

- Study 1 is a literature review of the outcome of EOS, based on PRISMA guidelines for study selection, inclusion and design[91]. The study used quantitative measures to combine findings from the studies selected.
- Study 2 is a retrospective validation study based on psychiatric records of patients diagnosed with EOS. The study used experienced clinicians to rate the validity of the schizophrenia diagnosis based on the written material in the records. Interrater reliability was assessed. Concordance between register-diagnosis and clinical diagnosis in the records were assessed as well as validity of the clinical diagnoses as evaluated by the raters. Symptom distribution, clinical characteristics and rates of childhood adversities were described.
- Study 3 is a register-based study of outcomes of schizophrenia. The study included patients diagnosed with schizophrenia between 1996 and 2012 before the age of 40 years and compared patients with EOS and AOS on measures related to psychiatric outcome and outcomes of functioning. Descriptive analyses and regression models adjusting for confounding covariates were conducted.

The details of the methods used in each study are outlined below.

STUDY 1: SYSTEMATIC REVIEW OF OUTCOME OF EOS

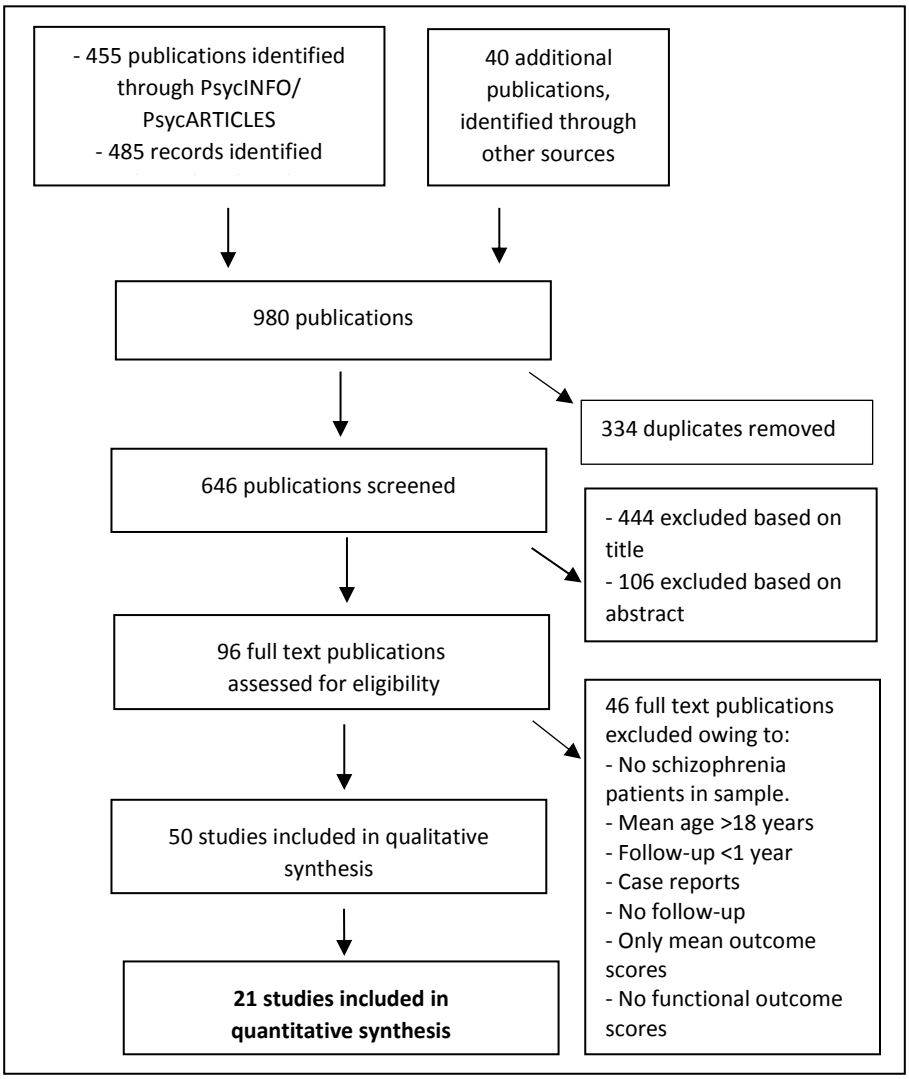
Study 1 is a systematic review of the outcome of EOS using quantitative measures. The literature search was conducted in PsycINFO, PSYCarticles and Pubmed, additional papers were included through hand-search. The search terms were the following present in title or abstract: adolescent onset schizophrenia, childhood onset schizophrenia, very early onset schizophrenia, early onset schizophrenia.

Inclusion criteria:
- Articles published after 1979 in the English language
- Sample consisted of patients with EOS or a combination of patients with EOS and EOP
- Mean age ≤18 years.

Exclusion criteria:
- Single case studies
- Studies without broad outcome measures, which could be classified as 'good', 'moderate' or 'poor'
- Studies only reporting a mean on outcome or with unclear outcome criteria
- Studies without internationally accepted diagnostic criteria (ICD or DSM)
- Studies with follow-up <1 year.

The literature search was conducted according to PRISMA guidelines[91] and a flowchart of the search process is presented below.

Figure 3: Flowchart of literature search



Outcome measures

The reported outcome of the studies were categorized into 'General Functioning Scale' (GFS) or Study-Specific Functioning outcome (SSF). GFS included Global Assessment of Functioning (GAF)[92], Children's Global Assessment Scale (CGAS)[93] or Global Assessment Scale (GAS)[94] with all scales running from 0 to 100. Poor outcome was classified as scores ≤ 50, moderate as scores 51–70 and good outcome as scores >70. SSF outcomes were outcomes defined in the specific study, either using a scale or categorical definition of outcome. SSF outcomes were also rated as poor, moderate and good based on their outcome measures. The three authors independently classified all studies into the three categories. In case of disagreement, a consensus decision was made.

We analyzed differences in studies including only patients with EOS versus studies including patients with schizophrenia as well as other psychotic disorders. Furthermore, five predicting variables were considered in the analyses for effect on outcome: drop-out rates, GFS/SSF measure of functioning, mean duration of follow-up categorized as ≤ 10 years and > 10 years, sex and time period of diagnosis.

Statistical analyses

Non-parametric tests were applied due to significant deviations from normal distribution. Analyses were conducted on adjusted sample sizes at follow-up assessment; weighted percentages were calculated for the reported rates to account for difference in sample size. Mann–Whitney tests with Bonferroni adjustments of *p*-values for multiple testing were conducted for the five predicting variables. A significant *p*-value was defined as 0.01 and highly significant at 0.002. Spearman's rho[95] was used for effect size (0.1-0.29 = small effect, 0.3-0.49 moderate effect, ≥0.5 = large effect). Data was analyses using SPSS version 20[96].

STUDY 2: VALIDATION STUDY OF EOS DIAGNOSIS

The study was a retrospective review of psychiatric records.

From ICD-10, codes F20.0-23.0, F20.6 and F20.9 were included, equivalent to paranoid schizophrenia, hebephrenic schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, schizophrenia simplex and schizophrenia unspecified. The decision to exclusively review schizophrenia records was based on available resources, as well as difficulties in blinding diagnostic decisions and considerations. Furthermore, no prior validation study of EOS diagnosis in the clinic or using the

DPCRR had ever been conducted in Denmark, so to evaluate as many files as possible was a priority.

Sample size

Psychiatric records from 200 patients diagnosed with schizophrenia before 18 years of age as registered in DPCRR. Sample size estimation with regard to adequate power was not conducted. This would have been difficult as there is only one study assessing validity of EOS which only included 36 patients with EOS[69]. The number of 200 was >20% of the total sample of patients with EOS for the time period; furthermore, it was manageable in terms of time and resources.

Collection of files

Based on a local pilot study at Aalborg Hospital in the North Denmark Region, the design of the study was initially based on discharge summaries. During that period, discharge summaries for severe mental disorders in child and adolescent psychiatry were often several pages long with a detailed description of symptoms leading up to diagnosis, symptoms after initiation of treatment and premorbid characteristics. Using only the discharge summary, a majority of the files could be rated with sufficient data.

The design of the study was changed after retrieval of the first psychiatric records from other regions as the degree of detail in the description of psychopathology varied too much and sometimes were not mentioned in the discharge summaries.

In order to have sufficient information for diagnostic classification, the following was collected when available: discharge summaries, case summaries, anamnestic material, conference notes, observations during inpatient admission and psychological assessment with cognitive or projective test material, and semi-structured interviews such as the Present State Examination (PSE)[97,98] or K-SADS / K-SADS-PL[84,85].

Several attempts were made to locate missing files and material – the search was extended to adult archives and other hospitals in the same geographic region.

Relevant materials were copied and securely stored at the research facility.

The raters

All six co-raters were child and adolescent psychiatrists with clinical experience in psychosis; additionally, the majority had either instigated or participated in research of early-onset psychotic disorders [23,99-105]. The mean number of years in child and adolescent psychiatry for the co-raters were 16.5 years (range 10–28 years). I have 10 years of experience in child and adolescent psychiatry and have psychologist

specialization in the field. Furthermore, since 2014, I have been managing an outpatient clinic (OPUS team) in adult psychiatry for younger adults with incident schizophrenia.

Data extraction

The material from the archives was initially read and evaluated by the primary rater (the PhD student, DLV), who selected relevant documents for the co-raters to assess.

Co-raters evaluated the diagnosis while recording data in a checklist, entailing all diagnostic criteria from ICD-10, as well as data regarding onset type, familial predisposition, DUP, loss of functioning, substance use, antipsychotic medication and whether a semi-structured interview had been used in the assessment (see appendix A). Along with the selected documents, the co-raters received a write-up detailing the following information if available: prior diagnoses and admissions, psychiatry predisposition and intellectual capacity.

As the primary rater of all files, I extracted demographic and anamnestic information, as well as details regarding assessment and functioning (see appendix B). Two psychology students re-evaluated the material to check for missing information and accuracy. Both psychology students were in their last year at university and had been working as psychology interns in a clinic for young adults with incident schizophrenia.

Ratings and extracted data from the psychiatric records were entered into a database using EpiData[106]. The data set was transferred to Stata 14 for analyses[107].

Validity measures

All records were rated as 'correct', 'maybe' or 'incorrect' based on criteria for an ICD-10 diagnosis of schizophrenia. Raters selected 'maybe' in cases with insufficient information, symptoms being described too vaguely, unclear duration to a diagnosis of schizophrenia or the presence of other diagnoses potentially explaining the symptomatology. Additional material from the psychiatric record was provided for the co-raters when possible, if needed to make a diagnostic decision. When the raters chose 'maybe', they would further specify if the diagnosis was leaning towards 'likely correct' or 'likely incorrect'. Finally, all categories were defined as confirmed ('correct' and 'likely correct') or not confirmed ('incorrect' and 'likely incorrect').

In case of disagreement between primary rater and co-rater, the details of the case were discussed openly to reach a consensus diagnostic decision. Another rater would be involved in case consensus could not be reached. Co-raters did not evaluate records from their own region of the country, while I rated all records except for one in which I had been involved in the patient's clinical assessment.

The term 'clinical schizophrenia' was used for cases in which the psychiatric record described the diagnosis as schizophrenia. Cases in which the DPCRR diagnosis of schizophrenia did not match the diagnosis described in the record, were defined as 'registration errors'. Validity for both clinical schizophrenia and DPCRR schizophrenia were evaluated.

Demographic variables and prior history

From the data extracted, developmental problems were rated as present if anamnestic data in the record described: delayed language or early interventions due to speech problems prior to 5 years of age, social developmental problems prior to age or delayed or markedly uncoordinated gross motor functions prior to 5 years of age. A formal ICD-10 diagnosis of developmental difficulties was not required. Childhood adverse events prior to schizophrenia included parental separation, parental death or parental substance use, change of school and unspecified adversities (e.g. witnessing domestic abuse, accidents, bullying, homelessness, immigration, parental crime or severe parental mental disorder). Presence of trauma included having experienced violence, sexual assault or other traumatic experience. Indicators of emotional and behavioral problems preceding schizophrenia included presence of self-harm, suicidal ideation, suicide attempts, aggressive behavior towards others, history of any criminal activity and problems with substance use.

Statistical analyses

Diagnostic concordance and validity of DPCRR and clinical schizophrenia were analyzed for all available records. Demographic data, psychosocial variables and symptom distribution were analyzed for all cases confirmed by raters, as well as those present in the clinical psychiatric record. Additionally, the patients were divided into cases of VEOS and patients with onset in adolescence (13–17 years). Post-hoc, an analysis of diagnostic concordance and validity of in- and outpatient diagnosed schizophrenia was undertaken.

For interrater reliability, Cohen's kappa (κ) was used with Landis and Koch's [108] scale for evaluating the results (κ <0 = no agreement, 0–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, 0.81–1 = almost perfect agreement). EpiData[106] was used to enter all data into a database; Stata 14[107] was used for analyses.

Permissions and ethics:

Permissions were obtained from Statistics Denmark, the Danish Data Protection Agency (journal no. 2013-331-0285), the Danish Board of Health (journal no. 3-3013-87/1) and the State Serum Institute (journal no. FSEID 00000359). All child and adolescent psychiatric departments in Denmark participated by giving access to their archives and psychiatric records.

STUDY 3: OUTCOME OF EOS IN THE REGISTERS

Register studies are one of the hallmarks of Danish research and, especially in medical and psychiatric research, Denmark is known worldwide for its registers[109-112]. Along with the other four Nordic countries (Finland, Sweden, Norway and Iceland), Denmark stands out with its extensive registers following every citizen from cradle to grave.

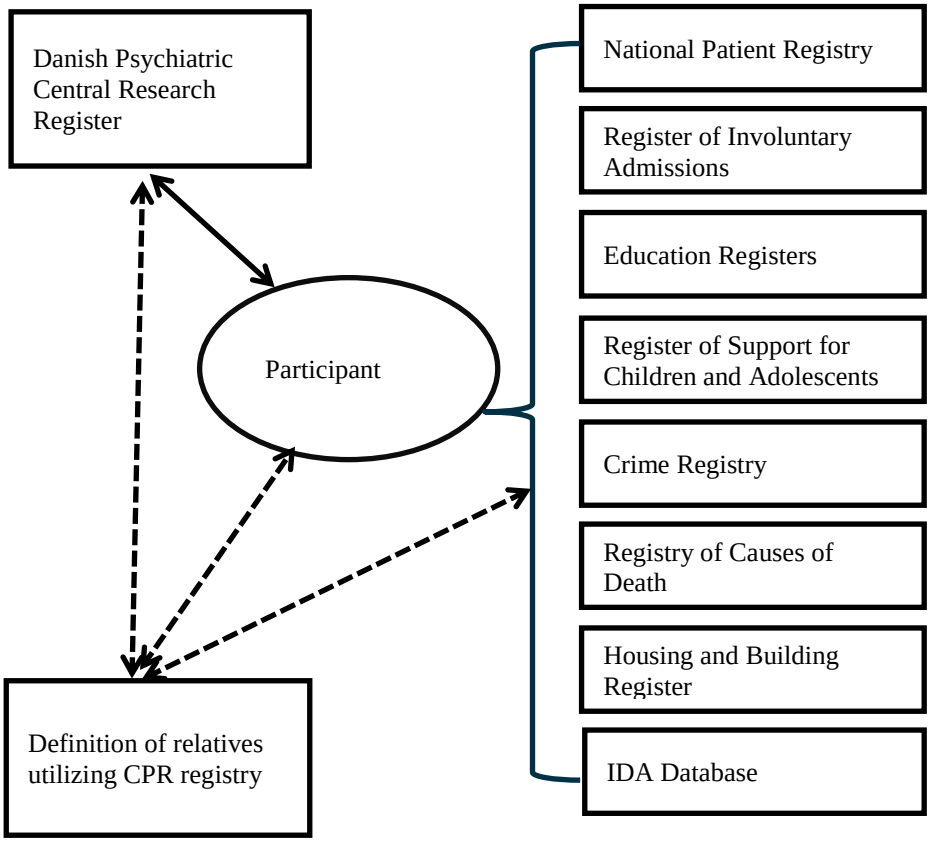
In the following paragraphs, an overview of the Danish registers will be provided before detailing the specifics of study 3.

THE DANISH REGISTERS, AN OVERVIEW

Denmark has extensive registers covering a lot of aspects of life. Each citizen born in or immigrated to Denmark has a personal registration number. This unique number is used in all contacts with the Danish public service, and necessary in daily life to open bank accounts, get appointments at the doctor or hospital, receive a library card, take out insurance, be employed, receive salaries and pay taxes. In the Danish registers, the personal registration number is converted into a unique ID-number to facilitate linkage between the registers without compromising data security and anonymity. Analyses are conducted via remote access to the server at Denmark's Statistic with a very high level of information security and regulations.

Figure 4 below provides an overview of the registers used in study 3 and the linkage between the registers.

Figure 4: Linking the Danish registers to participants in study 3



The Danish Civil Registration System (CRS) [113,114]

The Danish Civil Registration System (CRS) contains data on all Danish citizens born in Denmark or immigrated after 1st of April 1968 and permits accurate linkage in and between registers, as well as linkage of the individual to their family.

The Danish Psychiatric Central Research Register[2]

The Danish Psychiatric Central Research Register (DPCRR) was established in 1969 as an electronic database and contains data on all psychiatric admissions since 1969 and onwards. Outpatient contacts were included from 1st of January 1995. The coverage of DPCRR is believed to be almost complete. Diagnoses from private

practice, however, are not registered in DPCRR, including both private practitioners of general medicine, as well as psychiatrists working in private practice.

The Danish National Patient Register[115]

The Danish National Patient Register (NPR), established in 1977, covers all admissions to somatic hospitals including both in- and outpatient contacts and diagnostic codes from ICD-10. The diagnoses from the psychiatric hospitals have been included in the NPR since 1995.

The Danish Register of Involuntary Admissions and Treatment in Psychiatry

This register contains data of involuntary admissions and involuntary inpatient stays as well as situations where the patient have been restrained or given involuntary treatment.

Population Education Register at Statistics Denmark[116]

The Population Education Register at Statistics Denmark contains data on type and level of education with a coverage of 97% of Danish citizens born after 1945.

The Register of Support for Children and Adolescents[117]

This register contains information on all children placed out of the home, either with or without parental consent. The placement may be in foster care, institutions or orphanages and can be a result of problems in the home with violence, sexual abuse, substance use or severe mental disabilities or disorders, or the child having special needs or severe behavioral disturbance.

The Danish National Crime Register[118]

The Danish National Crime Register contains information on all convictions and incarcerations since 1980. The age of criminal responsibility in Denmark is 15 years.

The Danish Registry of Causes of Death

The Danish Registry of Causes of Death, established in 1969, provides data on time and cause of death according to the W.

The Housing and Building Register[119]

The Housing and Building Register was established in 1977 and notes the accommodation status of all inhabitants in the country. The register provides data on the type of housing, e.g. houses, apartments or institutions.

The IDA Database[120,121]

The IDA Database contains information about the total population of Denmark, including employment and primary source of income and activity.

The DPCRR[2] was used for sample selection as well as psychiatric data for both patients and their parents, the Danish Register of Involuntary Admissions and Treatment in Psychiatry was used to determine if the patients had experienced involuntary admissions and hospitalizations and the frequency, Population's Education Register at Statistics Denmark[116] was used to determine level of education for patients and their parents, The Danish Registry of Causes of Death[122] was used to determine premature end of follow-up, The Housing and Building Register[119] was used to collect data on institutionalization and parental separation, and the IDA Database[121] for data on primary source of income. Data on childhood adversities prior to a schizophrenia diagnosis were available from the Danish National Patient Register[115] in order to determine parental long admissions to somatic hospital, The Register of Support for Children and Adolescents[117] was used to determine rates of out-of-home care during childhood, The Danish National Crime Register was used to assess if parents had been incarcerated, The Danish Registry of Causes of Death to assess parental death and finally we assessed parental separation by use of The Housing and Building Register.

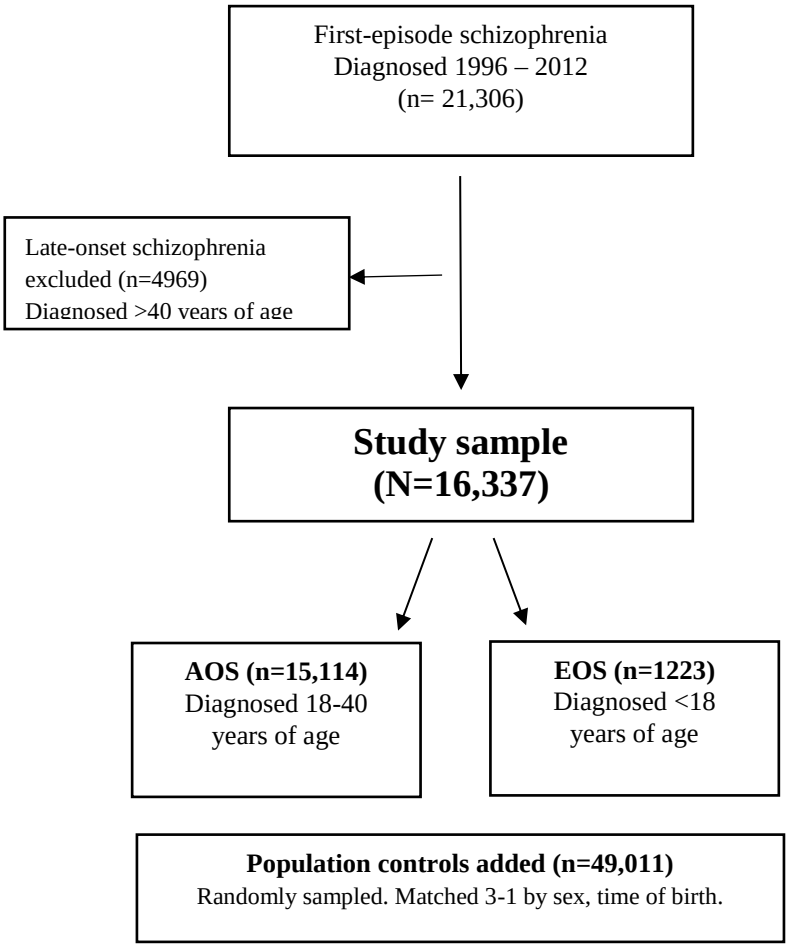
SAMPLE DEFINITION

The sample in study 3 was defined as patients with a first-episode ICD-10 diagnosis of schizophrenia in the DPCRR prior to age 40 in the period 1996–2012. The schizophrenia diagnostic codes included F20.0 paranoid schizophrenia, F20.1 hebephrenic schizophrenia, F20.2 catatonic schizophrenia, F20.3 undifferentiated schizophrenia, F20.6 simple schizophrenia and F20.9 schizophrenia, unspecified. Patients with a previous diagnosis of schizophrenia in ICD-8 were excluded. Emergency rooms diagnoses were excluded due to a reduced diagnostic reliability. Research has shown that the reliability of emergency room diagnoses is acceptable for broad diagnostic groups, such as depression, psychoses and alcoholism, but should be avoided for more specific subtypes such as schizophrenia[123].

The patients were followed in the registers until the end of 2014 or death, whichever came first. Age of onset was defined as the first day of the psychiatric in- or outpatient contact in which schizophrenia was diagnosed. The patients were divided into EOS or AOS, depending on diagnosis before or after age 18, see flowchart for sample selection, figure 5.

A control group was added in order to compare baseline and demographic variables. The control group was a random sample of the Danish population from the CRS, matched to the cases on birth year and alive at the time the case received the schizophrenia diagnosis. Three controls per case were matched. Controls were excluded if they developed schizophrenia but were allowed to have other psychiatric disorders, to achieve a sample representative of the general population. Matching was conducted utilizing the CRS[113,114] and the DPCRR[2,124].

Figure 5: Sample selection from DPCRR and CPR



OUTCOMES

The primary outcomes were number of inpatient days for the first 2 years after diagnosis and the annual number of inpatient days for the remaining follow-up time.

Secondary outcomes included the proportion of patients never admitted, number of readmissions among patients diagnosed as inpatients, annual number of admissions, length of first admission at or after schizophrenia diagnosis, mean length of admission, proportion of patients with heavy use of inpatient days defined as a mean of >40 annual inpatient days after the initial 2 years, and diagnosed substance use disorders during follow-up. Functioning outcomes consisted of having completed education at a level above law-mandated school, main source of income and living in an institution during the last year of follow-up. The functioning outcomes were restricted to patients with a minimum of 5 years of follow-up, and education and income measures furthermore restricted to patients aged 23 or older at the end of follow-up in order not to bias against the EOS sample.

Statistical methods

Primary outcomes of inpatient days for short- and long-term were analyzed using zero-inflated negative binominal (ZINB) analyses. This statistical model was appropriate due to an excess of patients with zero inpatient days, both in the short- and long-term analyses. Test of fitness in the data set were conducted utilizing the vuong zip option in Stata, which pointed to the ZINB model as being superior to the standard negative binomial model. Furthermore, the countfit option developed by Long & Freese[125] was conducted, and ZINB was preferred over the negative binomial regression model, Poisson regression and zero-inflated Poisson (p <0.001). Gender, year of diagnosis, placement out-of-home during childhood and substance use disorder during follow-up were used as covariates. Year of diagnosis is often used in register studies to control for structural changes, such as the shift from inpatient psychiatry to community-based outpatient treatment – the 'de-institutionalization' – with a substantial reduction in the number of psychiatry beds, a trend that has also been described in other countries [126-128]. Sensitivity analyses were conducted on four different subgroups to test the robustness of findings and control for possible misclassification.

Secondary outcome measures were analyzed with univariate statistics: *t*-test, chi-square and one-way ANOVA. Level of significance was defined as a p-level <0.05.

All analyses were conducted by remote access to Statistics Denmark's server, utilizing Stata [107]. The sampling was conducted with R using an algorithm to ensure the best possible match [129-131].

CHAPTER 3: RESULTS

STUDY 1: SYSTEMATIC REVIEW OF OUTCOME OF EOS

In total, for the quantitative synthesis in our systematic review[1], we included 21 studies[28,79,132-150], totaling 716 patients at follow-up with sample sizes between nine and 81 patients (mean 44.4, SD 19.4). Males were slightly overrepresented (56.5%). Among the studies, 13 consisted of only patients with EOS (n= 393) and eight consisted of EOS and other psychotic disorders (n = 323)*, mostly schizophrenia spectrum disorders, only one study also included affective psychoses[148]. Follow-up varied between 1.5 and 42 years (mean 14.4, SD 11.4). Mean age at onset was reported in 16 studies (mean 14.9, SD 1.5), but five studies only reported age ranges. The majority of the studies only included patients < 18 years of age; in six studies few older patients were included (maximum 20 years at the time). All studies had a mean age of onset <18 years. Ten studies used global functioning scales (GFS) and 11 used Study Specific Functioning (SSF) outcomes. Dropout rates were described in 17 studies and varied from 0% [135,147,150] to 59%[134].

The studies were heterogeneous in terms of design, sample size, duration of follow-up, type of evaluation and dropout rates. Since the studies were conducted across a wide time period (1920–2010), diagnostic classification changed considerably during follow-up.

Ratings of outcome

In the full sample, 17.2% had good outcome, 28.2% moderate and 54.6% poor outcome. In studies containing only patients with EOS, 15.4% had a good outcome, 24.5% a moderate outcome and 60.1% a poor outcome. In studies containing patients with both EOS and EOP, 19.6% had a good outcome, 33.6% had a moderate outcome and 46.8% had a poor outcome (p<0.001). The effect sizes between the EOS samples and the combined samples were moderate.

The three authors were in total agreement 19 of the 21 studies. For the remaining two studies, two of the authors agreed on the rating, which was considered as consensus.

Outcome by measures of functioning

* In the paper from study 1, the numbers are erroneously listed as EOS=422 and studies with mixed schizophrenia spectrum disorders=294.

In studies using GFS measures of functioning, more patients with moderate outcomes were found in EOS samples, whereas more patients in studies with mixed EOP and EOP had poor outcomes as measured by GFS. The effect sizes were small.

Duration of follow-up

Longer duration of follow-up was associated with worse outcomes in studies including only patients with EOS (poor outcome 67% vs. 51%; $p<0.001$). The effect sizes for the differences in good and poor outcomes depending on follow-up duration were moderate (0.43–0.45). In studies with mixed psychotic disorders, the findings were different – slightly more patients had good outcomes in studies with long follow-up (20.8% vs. 16.4%; $p=0.001$) and fewer patients with moderate outcomes (32.1 vs. 37.5%; $p<0.001$), however the effect sizes for the schizophrenia spectrum samples were small.

Sex

Only five studies reported separate results for males and females (n=190). In the analyses of these studies, males had more poor outcomes (59.2% vs. 39.5%; $p=0.002$), whereas females had more good outcomes (23.2% vs. 17.6%; $p<0.001$) and moderate outcomes (37.3% vs. 23.2%; $p<0.001$). Furthermore, we investigated sex proportions by comparing the six studies with <50% males to the 14 studies with >50% males and found the same results: the proportion with good and moderate outcomes were lower in studies with a male predominance, whereas these studies had a higher proportion of poor outcomes ($p\leq0.005$).

Drop-out rate

Seventeen studies reported how many patients dropped out during the studies. We dichotomized the attrition rates from the studies at the median and classified studies into having a high or low attrition rate (<28% and >28% drop-out rates, respectively). The rates of good outcome were the same, regardless of attrition rate, but more patients had poor outcomes in studies with high rates of drop out and more patients had moderate outcome in studies with low drop-out rates ($p<0.001$), the effect size was small.

Time period of diagnosis

Studies were dichotomized into studies including patients diagnosed before and after 1970 (n=234) and studies including only patients diagnosed in 1970 or later (n=461). Outcome appeared to improve in studies including patients diagnosed in a later time period, especially in studies with mixed psychotic disorders where the proportion of poor outcomes decreased from 78.5% in studies with patients diagnosed prior to 1970 (only one study, n=28) to 46.8% in studies with patients diagnosed after 1970

(p<0.001). In studies of patients with EOS only, the proportion of poor outcomes also decreased in newer studies (from 66.6% to 59.3%; p<0.001).

STUDY 2: VALIDATION STUDY OF EOS DIAGNOSIS

DIAGNOSTIC CONCORDANCE AND VALIDITY

Psychiatric records from 178 patients with a DPCRR diagnosis of EOS were retrieved (89%). The remaining 22 records were missing (11%). For the missing records, 12 were completely missing, but for 10 records it was clear schizophrenia was not a registration error.

Of the 178 records retrieved, the agreement between register-based and clinical diagnosis was 88.8%. In 20 records, the clinical diagnosis described in the record were not identical with the register-based schizophrenia diagnosis – these were registration errors. In 16 of the 20 registration errors, schizophrenia had been considered during the psychiatric contact, and the patient had been referred from out- to inpatient setting for further assessment to rule out schizophrenia, and the patients were later discharged without a schizophrenia diagnosis. In two of the registration errors, the raters actually confirmed the register-based diagnosis of schizophrenia to be correct.

In total, of the 178 register-based schizophrenia diagnoses, the raters confirmed 134 records as schizophrenia (75.3% validity), and 149 as in the schizophrenia spectrum (83.7%).

Among the 158 records with clinical schizophrenia – thus removing the registration errors – the raters confirmed 132 as schizophrenia (83.5%) and 145 as schizophrenia spectrum disorders (91.8%).

Inpatient vs. outpatient diagnoses

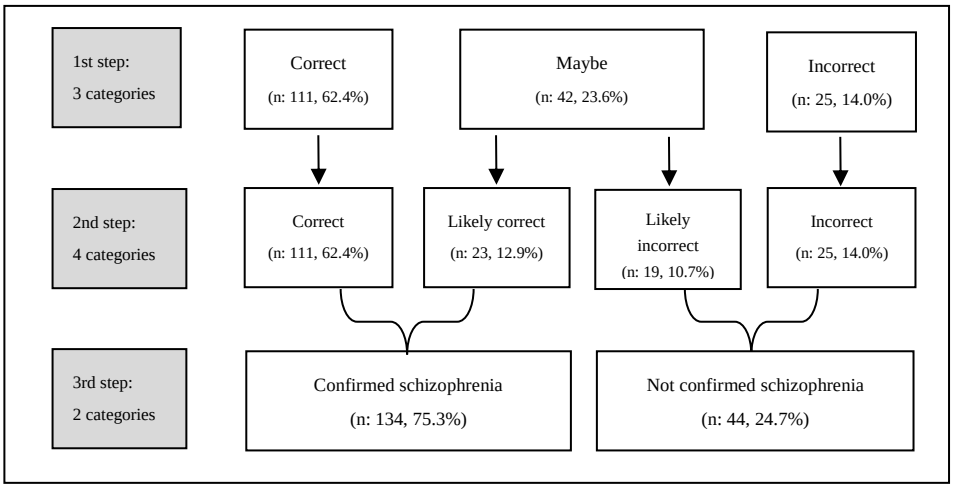
EOS diagnosed during inpatient treatment had a considerably higher validity than diagnoses from outpatient settings. Of the clinical EOS diagnoses, 71.9% were confirmed in patients diagnosed as outpatients and 91.5% in inpatients. Register-based schizophrenia had even lower validity in outpatient settings, owing to a higher rate of registration errors (19% vs. 5%). The raters confirmed only 59.5% of DPCRR EOS in outpatient setting vs. 87.9% from admissions (p<0.001).

Among the 26 clinical schizophrenia diagnoses that were not confirmed by raters, the raters diagnosed other disorders with psychotic symptoms in 100% of the non-confirmed records from inpatient settings (n=8), but only 55.6% of the outpatient settings (n=18).

Distribution of ratings and interrater reliability

The ratings are outlined in Figure 6, with three steps of validity classification: step 1: 'correct' – 'maybe' – 'incorrect', step 2: 'correct' – 'likely correct' – 'likely incorrect' – 'incorrect', and step 3: 'confirmed' – 'non-confirmed'.

Figure 6: Validation ratings of all retrieved psychiatric records (n: 178)



Cohen's kappa for interrater reliability was substantial, with weighted kappas for the three steps of validation categories of 0.78, 0.79 and 0.83, respectively. The raters were in complete agreement or able to reach consensus in all cases except for one, in which a third rater was involved, who read and rated the material blinded to the initial ratings.

DEMOGRAPHY AND PRIOR HISTORY OF CONFIRMED RECORDS

Among the 132 psychiatric records with both DPCRR schizophrenia, clinical schizophrenia and confirmation by raters, the mean age was 15.4 years (range 7–17, 95% confidence interval [CI] 15.0–18.8) and 53.8% were males. The majority had a predisposition to psychiatric disorders (85.8%) and approximately one-third had a predisposition to a psychotic disorder. With regard to developmental problems in childhood, difficulties with social development and interactions was the most common, affecting one-third of the sample. Most patients had indicators of emotional or behavioral problems prior to the diagnosis of schizophrenia (85.7%), exemplified by self-harm, suicidal ideation and attempts, aggressive behavior, substance use and criminal behavior.

Of patients with information about childhood adversities, almost half had experienced trauma (46.9%), either violence, sexual abuse or assault, or other traumatic occurrences, such as, for example, having escaped from war, witnessing violent deaths. Stressful or adverse life events such as change of school, being the victim of bullying, parental death, parental separation and parental substance use were also common, with 93.1% having experienced one or more (Table 1).

Table 1: Demography and prior history of confirmed cases (N = 132)

Variables	Number of records with data	n (%)
Male sex	132	71 (53.8)
Developmental problems with	93	40 (43.0)
- Speech and language development	93	16 (17.2)
- Social development	92	31 (33.7)
- Psychomotor development	95	10 (10.5)
Predispositions, any	120	103 (85.8)
- Schizophrenia spectrum	109	43 (39.5)
- Affective spectrum	112	58 (50.9)
- Anxiety disorders	110	25 (22.7)
- Other disorders	116	53 (45.7)
Adversities, any	130	121 (93.1)
Traumatic experiences (violence, sexual or other)	98	46 (46.9)
Change of school	115	82 (71.3)
Parental separation	124	64 (51.6)
Parental death	123	12 (9.8)
Parental substance disorder	108	30 (27.8)
Other adversities	120	85 (70.8)
Prior interventions or assessments outside psychiatry	117	97 (82.9)
Prior indicators for problems	126	108 (85.7)
Self-harm	92	46 (50.0)
Suicidal ideation	118	70 (59.3)
Suicide attempts	118	28 (23.7)
Aggressive behavior	109	39 (35.8)
Criminal behavior	114	15 (13.2)
Substance use	130	35 (26.9)

Assessment of confirmed cases[*]

Assessment with a semi-structured diagnostic interview was conducted in the clinic with 58 patients (52.7%), mostly using PSE/SCAN (41.8%)[97,98]. The vast majority had undergone somatic screening (n=125, 96.8%) and 95 (78.5%) were assessed using psychological tests of cognition. Insidious onset was most common and seen in 121 patients (93.8%). Functional decline or problems with self-care were described in 118 records (96.7%).

VERY EARLY ONSET SCHIZOPHRENIA

Few patients were diagnosed before the age of 13 (n=39) and only 35 records could be retrieved (89.7%).

More registration errors were present in VEOS compared to diagnoses at an older age (n=6, 17.1%), yielding a concordance between DPCRR schizophrenia and clinical schizophrenia of 82.9% vs. 90.2% in patients diagnosed at the age of 13–17 years. These registration errors affected the validity of DPCRR VEOS which was 71.4% compared to 76.2% in the older patients.

In the records with clinical schizophrenia, the validity of VEOS compared to adolescent onset did not differ.

Since the sample of confirmed VEOS diagnoses consisted of only 24 patients, very few statistically significant differences emerged between VEOS and schizophrenia diagnosed between 13 and 17 years of age when looking at premorbid history and clinical characteristics. A prior history of self-harm, suicidal ideation and substance abuse were all more common in patients with a later onset (all $p < 0.05$). There were tendencies which did not reach statistical significance for the following being more common in VEOS: male sex (70.8% vs. 50%), developmental problems (57.9% vs. 39.2%), aggressive behavior prior to diagnosis (52.6% vs. 32.2%), traumatic experiences (55% vs. 44.9%), and familial psychiatric predisposition (95% vs. 85%), especially for psychotic disorders (50% vs. 37.4%) and other disorders (62.2% vs. 42.3%).

[*] The results are based on the number of records with available information on assessment.

STUDY 3: LONG-TERM OUTCOME OF EOS

Sample

In study 3, we included 16,337 patients registered with a first-time schizophrenia diagnosis between 1996 and 2012, with 1223 (7.5%) classified as EOS. Mean ± SD age of onset among for the EOS group was 16.1 ± 1.7 years and 27.7 ± 6.3 years among patients with AOS. Mean ± SD follow-up was 9.5 ± 5.0 years (EOS 8.5 ± 4.5 years, AOS 9.6 ± 5.0 years; p <0.001). The majority of the sample had reached adulthood at the end of follow-up, with only 77 patients in the EOS group below the age of 18.

Primary outcome

Being in the EOS group was associated with an increased number of inpatient days in the short-term, defined as the first 2 years with schizophrenia (incidence rate ratio [IRR] 1.44, 95% CI 1.33–1.57; p <0.001). For the remaining period, mean annual inpatient days were similar for EOS and AOS (IRR 1.07, 95% CI 0.90–1.28; p=0.46). Sensitivity analyses were conducted on four different subgroups, which confirmed the pattern in three analyses: the youngest-onset group had more inpatient days in short-term outcome (p <0.005), with no differences shown in mean annual inpatient days in long-term follow-up. The exception was the sensitivity analysis comparing patients with AOS diagnosed at 18 years of age with those diagnosed with AOS at an older age, which found no difference in short-term outcome but more inpatient days in the remaining period for young adults.

Moderators of primary outcome

Comorbid substance use disorders were consistently associated with more inpatient days, both in the first 2 years (IRR 1.15, 95% CI 1.10–1.20; p <0.001) and in long-term follow-up (IRR 1.70, 95% CI 1.57–1.84). The sensitivity analyses confirmed the finding with the exception of short-term outcome in the analysis within the EOS group. Out-of-home placement during childhood showed the same pattern with increased inpatient days in both short-term (IRR 1.14, 95% CI 1.08–1.19; p <0.001) and long-term follow-up (IRR 1.32, 95% CI 1.22–1.44; p <0.001), this was also confirmed in the sensitivity analyses, with the exception of the sensitivity analyses including only patients with EOS.

The findings on sex were diverse; in the short-term outcome there was no effect of sex on inpatient days (IRR 1.04, 95% CI 0.94-0.95; p=0.086), whereas male sex were associated with an increased number of inpatient days during long-term follow-up (IRR 1.09, 95% CI 1.00-1.18; p=0.041). In the sensitivity analyses, there was no effect of sex in either short- or long-term outcome, except for two analyses showing a very small difference. In the EOS group, male sex was associated with a decreased number

of inpatient days in short-term outcome (0.75, 95% CI 0.67–0.84; p <0.001) and no effect on long-term outcome (1.01, 95% CI 0.78–1.32; p=0.95).

Secondary outcomes

Most outcomes related to psychiatric admissions were similar between patients with EOS and AOS (readmission rates, mean annual number of admissions, length of stay and heavy use of inpatient days and mean annual number of involuntary admissions), but patients with EOS were less likely to never be admitted during follow-up (17.2% vs. 20.1%; p=0.012), had a longer first admission (87.4 days vs. 74.6 days; p=0.005) and more patients with EOS had been involuntarily admitted or hospitalized (41.0% vs. 36.0%; p=0.002). More patients with AOS were diagnosed with substance use disorder (34.2% vs. 21.7%; p<0.001). For outcome related to functioning, there was no difference in institutionalization in the last year of follow-up (3.4% in AOS, 2.9% in EOS; p=0.49), but patients with AOS had completed a higher level of education (20.4% EOS vs. 42.1% in AOS; p<0.001), whereas more patients with AOS were living on social benefits as their primary income source (75.7% in EOS vs. 83.2% in AOS; p <0.001).

COMPARISONS WITH CONTROLS

Patients and controls differed on almost all measures concerning demography, prior history and outcome measures. Patients had more parental predisposition (26.3% vs. 12.4%; p<0.001), experienced more childhood adversities (all adversities; p <0.001), were more likely to have had prior psychiatric disorders and admissions (p <0.001), and their parents were less likely to be educated above law-mandated school level (65.3% vs. 71.5%; p <0.001), see Table 2.

At the end of follow-up, <3% of the control group had been admitted to a psychiatric hospital versus 80% among the patients, controls were less likely to be diagnosed with a substance use disorder (1.3% vs. 33.2%; p<0.001), less likely to institutionalized during last year of follow-up (0.2% vs. 3.3%; p <0.001). Controls had completed education above law-mandated school more often (79.9% vs. 40.9%; p <0.001) and were more likely to be in unsupported employment (80.6% vs. 15.6%; p <0.001).

Table 2: Demographic presentation of cases and population controls

Variable	AOS (n: 15114)	EOS (n: 1223)	*p-value*	Population Control (n: 49011) [1]
# male sex (N, %)	9557 (63.2)	602 (49.2)	<.001	30477 (62.2)
Age at onset (Mean years, SD)	27.7 (6.3)	16.1 (1.7)	<.001	-
Age at first psychiatric contact (Mean years SD)	24.9 (6.7)	15.0 (2.6)	<.001	25.9 (9.8) [4]
# Any parental predispositions (N, %)	3194 (26.2)	341 (27.9)	0.196	4992 (12.4)***
# Predisposition psychotic disorder (N, %)	760 (6.2)	71 (5.8)	0.62	647 (1.6)***
# Predisposition affective disorder (N, %)	1326 (10.9)	122 (10.0	0.36	2154 (5.4)***
# Predisposition substance disorder (N, %)	1022 (8.4)	103 (8.4)	0.96	1307 (3.2)***
# Predisposition other disorder (N, %)	2343 (19.2)	269 (22.0)	**0.021**	3465 (8.6)***
# Parental education above law-mandated school, any [2] (N, %)	8564 (64.2)	941 (78.5)	<.001	34496 (71.5)***
Childhood adversities[3]				
# Out-of-home care (N, %)	2913 (19.4)	263 (21.5)	0.072	1272 (4.7)***
# Parental death, any (N, %)	613 (4.1)	44 (3.6)	0.43	1335 (2.7)***
# Divorce (N, %)	1633 (56.8)	509 (53.6)	0.083	4425 (38.6)***
# Parent incarceration (N, %)	759 (12.7)	143 (11.9)	0.45	1307 (6.1)***
# Parental psychiatric admission (N, %)	1510 (12.4)	129 (10.6)	0.067	1942 (4.8)***
# Parent somatic admission >2 weeks (N, %)	1251 (16.0)	177 (14.5)	0.18	3469 (12.8)***
# Previous disorder, any (patient) (N, %)	10649 (70.5)	808 (66.1)	.001	2432 (5.0)***
# Premorbid psychotic disorder (N, %)	4620 (30.6)	372 (30.4)	0.91	110 (0.2)***
# Premorbid affective disorder (N, %)	2630 (17.4)	185 (15.1)	0.043	447 (0.9)***
# Premorbid substance use disorder (N, %)	3274 (21.7)	74 (6.1)	<.001	359 (0.7)***

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Variable	AOS (n: 15114)	EOS (n: 1223)	*p-value*	Population Control (n: 49011) [1]
# Premorbid other disorder (N, %)	7307 (48.4)	556 (45.5)	0.052	2093 (4.3)***
# Psychiatry prior to age 18 (N, %)	1828 (12.1)	1223(100)	<.001	1081 (2.2)***
Admissions and prior inpatient days prior to schizophrenia contact				
# No inpatient admissions prior (N, %)	6793 (45.0)	757 (61.9)	<0.001	47962 (97.8)***
Inpatient days (Mean, SD)[5]	141.5 (253.4)	99.0 (125.3)	<0.001	-
Inpatient admissions (Mean, SD)[5]	3.0 (4.0)	1.9 (2.6)	<.001	-

EOS: early-onset schizophrenia; AOS: adult-onset schizophrenia; SD: standard deviation
[1:] P-value for difference between schizophrenia cases and population controls, with *= p<0.05, **= p=<0.005 and ***=p <0.001. [2:] Parent with education above law-mandated school. Data from 1940s. Only patients with available data are included. [3] Childhood adversities: Registers were initiated at different times. Only patients born after initiation of the registers were included in these analyses: Parental psychiatric history: From 1969. Out-of-home care: 1977. Separation: 1986. Incarceration: 1980. Psychiatric hospital inpatient: 1969. Somatic hospital: 1977. [4:] Restricted to population controls with a psychiatric contact (n: 4949, 10.1%). [5:] Restricted to patients with prior admissions.

CHAPTER 4: DISCUSSION

OUTCOMES OF EOS, WHAT DO WE KNOW

Outcome of EOS was investigated in studies 1 and 3 from two different angles: a systematic literature-review using quantitative analyses and a register-based study of the full Danish EOS cohort compared to AOS.

In our review of outcome of EOS (study 1), we included 21 studies from English journals published between 1986 until 2010, totaling 716 patients. Good outcome was found in 17.2% of the full sample, moderate in 28.2% and poor outcome in 54.6%. The proportion with poor outcomes were higher for studies only including patients with EOS compared to studies including both EOS and other EOP (EOS = 15.4% good, 24.5% moderate, 60.1% poor vs. mixed psychotic disorders = 19.6% good, 33.6% moderate and 46.8% poor, $p<0.001$). Furthermore, the review described worse outcome for males, and a tendency for better outcomes in more recent time-periods. The review did not include studies on AOS, but compared to meta-analyses of AOS, we concluded that EOS carried a particular poor outcome.

By using Danish, nationwide registers we were able to conduct study 3 with 1,223 patients with EOS diagnosed between 1996 and 2012. Follow-up data was available for a mean of 8.5 years (SD 4.5, range 2-19 years) with almost no loss to follow-up. For comparison, an AOS sample of 15,114 patients diagnosed between 18 and 40 years of age during the same time period were added as well as a control sample from the general population. The register data allowed for comparison of EOS and AOS within the same study design and from the same general population, but still with the limitation of treatment in different settings (child and adolescent psychiatry vs. adult psychiatry). Number of inpatient days was the primary outcome in study 3, investigating both short- and long-term outcome. Short-term outcome of two years are used in many studies of schizophrenia outcomes [151-161]. Long-term prognosis is not always clear during the initial course [161], and to account for this we chose to treat the initial 2 years after diagnosis different from the long-term outcome. Inpatient days and admissions are universally understood as one way of measuring the severity of a mental disorder and important for administration and service planners as inpatient stays are an expensive part of treatment of mental disorders[162]. Patients with EOS had worse short-term outcome with more inpatients days, but the EOS and AOS groups were alike in long-term outcome after two years. Patients with EOS had longer first admission, were more likely to be involuntary admitted and less likely to never be admitted. The two groups were alike on readmission rates, annual number of admissions and involuntary admissions, heavy use of inpatient days and institutionalization. The AOS group had more substance use and were less likely to be in education at end of follow-up, but had accomplished a higher level of education than the EOS group.

Our readmission rate of 77% in patients with EOS diagnosed during inpatient admission, were similar to findings by Thomsen[83], who reported readmission rates of 66% in the first year of follow-up and 80% after two years.

We could not confirm more frequent, longer hospitalization and more relapses in patients with EOS in contrast to Immonen, but the differences described in the meta-analysis all had low effect sizes (Rosenthal's r between 0.11-0.17).

Substance use disorders and out-of-home care were the most consistent predictors of inpatient days across analyses in both short- and long-term outcome. Other studies have showed associations between substance use and relapses and worsening of psychotic symptoms in patients with psychotic disorders[163-167], and a frequent use of cannabis, especially of high potency, have also been found to trigger earlier onset of psychosis[168]. Study 3 found substance use disorders in 21.7% of patients with AOS and 6.1% with EOS were lower than other studies – an older review of psychotic disorders described cannabis use in 17-80% and alcohol in 21-86%[169]; a Scandinavian study found problems with alcohol and/or drug use problems in 33% [170], studies of a study of EOP reported cannabis use in 29% of the patients [171], another EOP study 14.6% for alcohol abuse and 32.1% for drug abuse[27]; an early detection program of FEP described drug-use in 17% of patients with EOP and in 28% of the patients with AOP[50], and finally, a review of EOP reported substance use disorders in 32% at baseline [57]. These numbers are more in line with our findings from study 2 where a history of illegal substance use was described in 33% of the patients with adolescent onset and 8% of the patients with VEOS. The lower numbers in study 3 might be explained by the use of register-based disorders instead of self-reports or interviews as register-based diagnoses for substance use disorders have been shown to have high specificity, but low sensitivity [172]. In contrast to most findings, including ours, a recent study by Rylander et al. found cannabis use to be associated with shorter inpatient stays and to have no difference with regard to 30-day re-admission rates [173], but only 20% of patients in the study had schizophrenia.

In Study 3, data concerning substance use during follow-up were calculated for the EOS and AOS group with descriptive analyses, using chi square to determine percentage of patients having had this outcome. The disadvantage of this method was leaving out the differences in length of follow-up between the groups as in the groups and thereby differences in time at risk. However, for substance use, such a method would also have some potential biases; 21.7% of the AOS population already had substance use by the time of diagnosis and thereby would be in greater risk from the outset, while the youngest in the EOS sample might not be in risk for substance use disorders from time of diagnosis.

Childhood adversities

The other covariate which were associated with inpatient days in most of our analyses was out-of-home placement during childhood prior to schizophrenia. Out-of-home placement is a by-proxy measure of childhood adversities which is a broad concept used to describe a wide range of difficult circumstances and experiences during childhood and adolescence. It can include severe trauma, violence, neglect, sexual assault, loss of or separation from parents, and being the victim of bullying, among others.

Placement out-of-home does not only constitute an adversity due to the separation from parents, but are also based on prior adversities. Whether voluntarily or with the parents' acceptance, placement of a child in foster care or an institution will only happen as a result of the child having grave behavioral or emotional difficulties, or special circumstances in the families, such as lack of basic parenting skills, substance abuse, neglect or severe mental disorders. A Danish study found children of mothers with schizophrenia to have a 40% risk of being placed in out-of-home care[117]. In study 3, 20% of the patients had previously been placed in out-of-home-care during childhood, which was four times more than the control sample. Furthermore, we found hospitalization to be increased in patients who had been placed in out-of-home care, even in long-term outcome. This could possibly be explained by a reduced social network, as well as reduced coping skills, including the ability to effective emotion regulation, an ability associated with stable childhood and secure attachment[174,175]. Furthermore, there is evidence that the involvement of family members has a positive effects on prognosis [176], and many children and adolescents placed in out-of-home care do not have the opportunity to benefit from healthy family involvement in their recovery.

Research of childhood adversities has increased significantly in the past decade[177], with several meta-analysis presenting consistent findings of high rates of adversities in patients with psychoses [178-181], in line with our findings from study 2. In a meta-analysis including studies published between 1980 and 2011, Varese et al. reported a significant association between childhood adversities and psychotic disorders; this association was not seen for parental death, but for both psychological, physical and sexual abuse, emotional and physical neglect and bullying (OR 2.4–3.4)[181]. Based on descriptions in the psychiatric records, we found that 47% of the patients with EOS had traumatic experiences and 93% had experienced adversities, also including more common experiences such as separation and school change.

Our finding in study 3 of a doubling of childhood adversities in patients compared to the experiences in the general population (placement in out-of-home care, parental incarceration and parental psychiatric admission) is in line with other studies: In an Australian study, 30% of patients with psychotic disorders had adverse experiences in childhood versus 15% in the general population [180], whereas a Danish study of early intervention in schizophrenias (OPUS) found 89% of the patients to have experienced childhood adversities compared to 37% in the matched control group[182].

Until recently, the etiological role of adversities in the development of psychoses has been unclear[183], but the evidence of a causal role at least for some people with psychotic disorders is growing strong[177,184,185]. Stilo et al. argue that the association between trauma and psychoses meets the the Bradford Hill criteria[186] regarding causation with the exception of specificity[185], see Table 3 for the full Bradford Hill criteria. Specificity is not met as childhood adversities increases the risk of several mental disorders and not just schizophrenia – other register studies have found childhood adversities to increase risk of, e.g., ADHD[187] and affective disorders. Childhood adversities seem to both increase risk of development of psychoses[177,184] and the outcome[184]. In our register study of inpatient days (study 3), out-of-home placement was considerably more common in the patients than in controls and also highly associated with inpatient treatment with regard to short-term and especially long-term outcome.

Table 3: Bradford Hill criteria[186,220]

- Strength: Strong associations are more likely to be causal than weak associations
- Consistency: If the same results can be found prospectively, retrospectively and in different populations
- Specificity: The case for a causal explanation is strengthened if an association is only found in specific groups with the same exposure
- Temporality: Necessary criterion that exposure most precede outcome
- Biological gradient: A causal association is more likely if a dose-response curve exist.
- Plausibility: A causal association is easier to adapt and believe if it seems plausible. However, Bradford Hill noted that this would depend on the current knowledge of biology.
- Experiment: If interventions or preventive actions can alter the frequency of the outcome, it gives strong support to a causation.
- Analogy: Analogies may add to evidence of associations otherwise weak.

Outcomes related to functioning

In study 3, we presented three outcome measures related to functioning at end of follow-up: institutionalization, primary source of income and having completed education past law-mandated school. Such measures are important in assessing outcome in patients with schizophrenia, as patients with remission in symptomatic outcome are still often struggling with impairments in social and vocational functioning, first reported in detail by Karow et al.'s studies[188]. Functional and symptomatic remission are often related, and better vocational outcome has been associated with higher rates of symptomatic remission and recovery and lower rates of relapse as well as a higher quality of life[189].

In the group of patients with AOS; 42% had completed an education above law-mandated school versus only 20.4% among the EOS patients. Both numbers were low

compared to the control group drawn from the general population, in which 79.9% had completed education, with slightly more in the younger group.

During the last year of follow-up, 3.3% of the patients had been living in an institution compared to 0.2% in the population controls. No difference between patients with EOS and AOS appeared. This number is lower than other studies of institutionalization among patients with schizophrenia[39,190]: In the ISoS study, 11.6% of the patients from the schizophrenia incidence cohort had spent the majority of the past 2 years in institutional settings at end of the 15-25 years follow-up[39]. Uggerby et al. included patients diagnosed with schizophrenia since 1969 and found 9.8% to be institutionalized in the year of 2006[190]. The OPUS-trial have reported proportion of institutionalization of 5-13% at different points of follow-up [191,192]. The reason for lower rates in our study is not clear. For older studies, such as the ISoS study, it may be explained by the aforementioned de-institutionalization. Also, compared to the ISoS study, we did not count hospitalization as institutionalization but reported both individually. The difference between our findings and the OPUS-trial may be based on selection, regional differences of use of institutionalization or time period of diagnosis – the OPUS-trial included 547 patients diagnosed in Copenhagen or Aarhus from 1998–2010, whereas study 3 included 16,337 patients diagnosed in all of Denmark between 1996 and 2012. In Uggerby et al's sample, their study selection included patients diagnosed since 1969 which may be part of the explanation for the different rates found. It was not explored in the design of study 3, if institutionalization in long-term follow-up differed with time of diagnosis.

In contrast to the meta-analysis by Immonen, our study could not confirm a generally poorer occupational functioning of EOS, with the exception of level of education[48]. A high number of patients in both groups were depending on public benefits at end of follow-up (EOS 75.7%, AOS = 83.2%), while only 16.4% were dependent on social benefits in the matched control group. These findings of dependence on social benefits and less than 20% employed in unsupported work are in line with other studies on FEP: in the AESOP-10 study of patients with FEP, only 22% of the patients were in paid employment at the ten year follow-up[193]; White et al. reported proportions of 19% in paid work[194], Jarbin and Hansson reported 89% in an EOS sample to be on disability at the 10 year follow-up[195], and in the Danish OPUS-study, functional recovery was met for 14% of the sample at the 10 year follow-up (n=304), defined ad engaged in work or study, GAF-F >60 at no psychiatric hospitalizations or living in supported accommodation for two years[196].

Some studies on schizophrenia have found more positive employment outcomes: The ISoS study with 502 patients with incident schizophrenia reported 37% to be in paid work and 20% to be engaged in relevant housework at end of follow-up, 15-25 years after diagnosis[39]. Interestingly, compared to our study, the ISoS had a higher proportion of patients institutionalized at end of follow-up, while at the same time the rate for employment in ISoS was almost doubled compared to the Danish register-

based findings[39] This difference is likely explained by difference in sample selection – the ISoS study included patients from 14 incident samples from very cultural diverse settings whereas all the patients in study 3 are patient diagnosed and treated in Denmark. It is thus possible that the higher rates of paid work in the ISoS may partly be owing to some societies with less opportunity for receiving social benefits than the Danish society. The authors of the ISoS findings underline that the variations across centers were wide [39]. However, findings from the EPPIC study are also more promising with regards to vocational outcome: at 7 year follow-up, 58.5% in the EOP group and 41.8% in the AOP group were either employed or studying, and another paper from reported full social and vocational recovery in 25% at the 7.5 year follow-up[197], including adequate interpersonal relationships and vocational functioning, measured by the Quality of Life Scale (QLS)[198].

Outcome of VEOS

Separate analyses of patients with VEOS cases were planned, both in studies 2 and 3. Only 39 patients with VEOS were registered in the period for study 2 (1996–2009), and only 52 in the period for study 3 (1996–2012). Study 2 found VEOS in the DPCRR had a higher rate of registration errors than schizophrenia diagnosed in adolescence (six of 35 collected records, 17.1% vs. 9.8% in the adolescent sample).

Statistical analyses of the selected VEOS group in study 3 was therefore not conducted owing to risk of false findings. In Study 2, we compared the 24 confirmed VEOS cases with the 108 confirmed cases with onset in adolescence, but few statistic significant findings emerged, likely due to sample size. Comparing adolescent onset and VEOS, only three indicators of problems prior to diagnosis reached statistical significance – all more common in adolescent onset: self-harm (56.3%& vs. 28.6%), suicidal ideation (65.3% vs. 30%), and substance use (31.1% vs. 8.3%). Premorbid difficulties, higher genetic load and a predominance of males have been described in other VEOS studies [21,83]. These characteristics were all present in the VEOS sample in study 2 in higher numbers than in the group of patients diagnosed in adolescence, but did not reach statistical significant levels, likely owing to the low number of VEOS patients (n=24 confirmed cases).

The low prevalence of VEOS, underscores the importance of a longitudinal study like NIMH-COS, including patients from a large geographical area to study this group of patients.

Summarizing the findings of outcome:

Similar to the meta-analysis by Immonen et al.[48] including both early and adult onset, the majority of outcomes investigated did not differ between early- and adult-onset in study 3. This conclusion is in line with findings from other studies [199]. Two studies from EPPIC including 366 patients with first-episode psychotic disorders and a

follow-up of approximately 7 years. Although the number of EOS and EOP patients were fairly low (n= 20 and 41, respectively), a significant difference between early- and adult-onset was found on several scales of psychopathology, functioning, occupation and quality of life, with patients with early-onset presenting with the most favorable outcomes in this study[199]. The AESOP study indirectly lends support to these findings: Lappin and colleagues compared 10 year outcomes of patients with non-affective psychoses and compared groups with different age cut-offs[200]. The outcome was similar for the groups diagnosed prior to or after age 25 as well as prior to or later than 35[200], leading to a recommendation that early intervention should not be restricted to certain age groups.

Based on the findings from study 3 as well as the current literature, I am in line with Immonen et al. in concluding that age of onset is not as important for outcome as previously thought[48].

VALIDATION STUDIES: DESIGNS AND CRITIQUE

In study 2, findings from a validation study of schizophrenia diagnoses in children and adolescents in the DPCRR were presented. Psychiatric records from 200 patients with EOS were randomly selected in the DPCRR, 178 could be retrieved (89%) and were all rated by two experienced clinicians. Of the retrieved records, 10.2% were registration errors in which the DPCRR schizophrenia diagnosis did not match the clinical diagnosis described in the records. The validity of the DPCRR schizophrenia was 75.3% for narrow schizophrenia and 83.7% for schizophrenia spectrum disorders. Of the 158 records with a clinical schizophrenia diagnosis, the raters confirmed 83.5% as schizophrenia and 91.8% as in the schizophrenia spectrum.

To my knowledge and in accordance with Byrne's review of validation studies from 2005, no gold standard exist for validating register data[70]. Byrne included 14 validation studies of register data published between 1966 and 2004; the results were briefly outlined in Chapter 1. Byrne and colleagues pointed out that most studies do not clearly define validity before analyzing their results[70]. Instead, Byrne and colleagues listed important parameters for the evaluation of quality in validation studies. In Table 4 below, the validation study is assessed using these parameters.

Table 4: Validation methods compared to Byrne's suggested standards[70]

Standard	Validation study of EOS
Sample	
Diagnoses	Only schizophrenia. No validity rating of comorbid diagnosis.
Sample size described	Yes (200 records, 178 collected)
Randomization used and described	Yes, all VEOS cases + random sample of EOS, matched by sex and geography to full sample
Study sample description	Yes (sex, age of onset and diagnosis, in- or outpatient setting, assessment in clinic, symptom distribution, duration, psychiatric predisposition, childhood characteristics and adversities)
Representativeness of the sample described	Yes. The register include close to all patients with schizophrenia in Denmark. The randomization make the study highly representative for patients with EOS in Denmark.
Assessment	
Assessment method	Yes (raters evaluated selected material from psychiatric records and used a pre-defined checklist with ICD-10 criteria). Concordance between clinical and register was assessed as well as validity of the clinical diagnosis according to raters.
Triangulation of assessment	No. Only psychiatric records were used. As patients were diagnosed 8-20 years ago there would be both recall-bias and ethical considerations if they should be contacted.
Methods	
Statistical analyses	Simple calculations of agreement between register diagnosis and psychiatric records as well as agreement between both and raters' diagnoses.
Blinding of diagnosis	No. The raters knew that all cases were registered with a schizophrenia diagnosis in DPCRR
Blinding of rater' evaluation	Yes. Two raters evaluated all records, blind to each other's rating. In case of disagreement, diagnosis was discussed to reach consensus.
Inter-rater reliability	Yes, by use of Cohen's kappa
Diagnostic reference standard used	Yes. All records were rated in accordance with ICD-10 criteria, using a check-list with all criteria described in detail.

Using these quality measures, the validation study fulfills most criteria. The main limitation of the study is the inclusion of only one diagnosis. Thereby, blinding of raters to diagnosis was not possible and the decision yielded an indication bias where the agreement could be an overestimate, as all raters knew the register-based and

clinical diagnoses. Furthermore, false-negative rates could not be estimated. It is likely that some children and adolescents are diagnosed with psychotic disorders in the DPCRR who, upon closer examination of the psychiatric records, would be reclassified as having schizophrenia. In a Finnish validation study of register diagnoses, including psychoses, personality disorders and substance abuse, 16% were false-negatives and met criteria for schizophrenia[71], a Swedish study found 10% false negatives in a study of psychotic disorders [60], and Fennig et al. reported a 15% false-negative diagnosis rate in a study comparing clinical and research diagnosis of psychotic disorders[201]. It is possible that the rate of false-negative diagnoses among other psychotic disorders in child and adolescent psychiatry would be even higher, as some clinicians may avoid or delay a diagnosis of schizophrenia in children and adolescents owing to either lack of experience or fear of the consequences of diagnostic labeling[8], which could be stigma from their surroundings or even the risk of stifling the adolescent's development as a result of the knowledge of having a serious mental disorder.

By using only psychiatric records, the study is also potentially biased by the selective recording of the clinician involved in the assessment. As Byrne points out, there will be a tendency to highlight symptoms and findings that fit your hypothesis rather than characteristics which may elicit doubt[70]. To overcome this bias, record assessment would have to be complemented by interviews of patients or observations. In the current study, we did not consider this solution feasible as it would entail recall bias. The patients would have to remember symptoms described 7–20 years previously and may be affected by how their disorder later progressed. Contacting patients many years after their diagnosis would also raise ethical considerations, and, finally, such a study would likely have a high rate of patients refusing to participate.

Our rating categorizations allowed a rating of 'maybe', which was then specified as 'likely correct' or 'likely incorrect'. As a third step, likely correct and correct were categorized as 'confirmed', and likely incorrect and incorrect as 'not confirmed'. It is suboptimal to categorize diagnoses deemed only 'likely correct' as a confirmed diagnosis. With regard to the terms of the study, we believe the chosen categorization was the best compromise: with a retrospective validation study, we could not administer additional assessments; furthermore, for some records, we did not have access to the full psychiatric record. The fact that 34% of the unconfirmed cases met the criteria for schizophrenia spectrum disorders (e.g. schizoaffective disorder, unspecified psychoses) underlines that 'likely correct' was not used to excess.

To some degree, this decision reflects real life in the clinics – sometimes the clinicians do not have access to all prior relevant data, the patient may refuse assessment, resources can be inadequate, or a patient might be seen at a time where the full symptomatic picture has not yet been developed; this stage can retrospectively be labeled prodromal schizophrenia. Finally, our classification systems are manmade to find similarities and differences between disorders and clusters, and guide us in

treatment choice. Changes in classifications and descriptions are made as more knowledge and evidence emerges. However, it is still just a system and not all will fit in the categories like shapes in a sorting cube.

In order to identify potential validation studies published after Byrne et al.'s review, the same search terms were used for publications from 2004 and onwards but adding 'schizophrenia' or 'psychoses' or 'psychotic' in the search. Additionally hand-search was conducted through inspection of references in other validation studies. One older studies not included in the original meta-analysis was found by hand-search: a study from Saskatchewan in Canada investigating the concordance between administrative hospital databases and psychiatric records, including 131 patients with schizophrenia in the register[202]. Rawson and colleagues reported diagnostic concordance of 77.1% using four-digit codes (schizophrenia subtypes) and 93.9% using three-digit codes. Furthermore, demographic and personal factors were accurate in more than 94%[202]. The diagnostic validity was not assessed, only concordance.

Since 2004, only four new studies on the validity of schizophrenia or psychotic disorders in registers was found; one Danish and three Finnish studies[62,63,203,204]. In one study, the interviewer was blind to the diagnosis, the other studies did not use blinding of raters or assessed interrater-reliability. Sample descriptions included gender and age in all three studies, and Uggerby et al. also described the symptoms distribution in the sample. Arajärvi et al. investigated register diagnoses of schizophrenia in an isolate population born between 1940 and 1969 using both psychiatric records for consensus diagnosis as well as diagnostic interview[204]. Consensus ratings of records were conducted for 164 patients and 131 of them also participated in interviews. The concordance of patients diagnoses with schizophrenia in both register, rating of records and in psychiatric interview was 55%. Among the 140 patients registered with a schizophrenia diagnosis in the register, 72.1% (n=101) was confirmed by ratings as schizophrenia, 87.9% (n=123) as in the schizophrenia spectrum and 97.1% (n=136) as disorders with psychosis.

Finally, a Danish study by Pedersen et al. has investigated the accuracy of documentation of psychiatric care for patients with schizophrenia in the medical records, by assessing the accuracy between the Danish National Indicator Project for schizophrenia and the psychiatric records[205]. They were unable to locate 12.4% of the psychiatric records. The psychiatric records had varying levels of missing information. For assessment of psychopathology, 37.5% records had missing information, while the completeness of antipsychotic treatment was high, with only 1% missing information.

Although no gold standard exist for validation studies and the papers report their findings in different ways, most papers provided information regarding number of correct cases in the register ("true positives"). The number of confirmed cases by raters varied from 50% to 100% in the 16 studies: 3 studies confirmed 50-66%[64,206,207],

5 studies (including ours) confirmed 72-78%[61,63,69,204], 3 confirmed 82.9 – 87.5%[59,73,208], and finally 5 studies confirmed as many as 93.9 – 100%[62,71,72,202,203] of the register-based diagnoses. With our number of 75.3% confirmation of register-based schizophrenia and of 83.5% as in the schizophrenia spectrum, the validity of the DPCRR for EOS is in the mid to lower range compared to most register-studies of schizophrenia, but the result is almost identical to the one other study investigating validity of EOS – Dalman confirmed 76% of the register-diagnoses as schizophrenia and 86% as in the schizophrenia spectrum[69] – indicating the EOS is a more difficult to diagnose accurately. The rate of registration errors were higher for EOS in DPCRR than described in the other studies. Removal of the registration errors, increased the validity in our study to 83.5% for schizophrenia and 91.8% for schizophrenia spectrum disorders.

STRENGHTS AND LIMITATIONS

In study 1, results from 21 studies were pooled and analyzed. To my understanding, our systematic review of EOS published in BMC Psychiatry in 2012[1] was the first review to use quantitative analyses to assess the outcome. However, heterogeneity was a challenge, as present in design of the 21 studies in terms of the diagnostic classification used (ICD-9, ICD-10, DSM-III, DSM-III-R, DSM-IV), outcome measures (global functioning scales, employment, social disability and living situation, course of the disorder), length of follow-up (2–42 years), retrospective or prospective and sampling. The challenge of heterogeneity has also been described in other meta-analyses of outcome[26,57].

In study 3 – using the full cohort of all patients in Denmark diagnosed with EOS in a certain period – many of the potential challenges and biases from comparing different study designs were eliminated. However, register-based studies over long periods still have bias in terms of changes in organizational structure such as the de-institutionalization in psychiatry, and using calendar-year of diagnosis as a co-variate in the regression analyses was added to correct for this.

Prospective cohort studies, as well as randomized controlled trials, are difficult to conduct in EOS owing to the low incidence and prevalence of the disorder resulting in small sample sizes. Long-term prospective studies are even harder to conduct, as larger samples are needed owing to high attrition rates in these studies. In study 1, the mean sample size was 44 (range 9 – 81 patients), and even in meta-analyses of EOS or EOP, the total number of patients is relatively low (n = 716 in our review of 21 studies, n = 773 in Stentebjerg et al.'s review of 28 studies[209]). These methodological difficulties calls for research with other study designs to investigate the course and outcome of EOS.

By using the nationwide Danish registers, we were able to follow-up a cohort of 1,223 patients with EOS and comparing them to a large group of patients with AOS in study 3. To the best of our knowledge, this is the largest study to date of patients with EOS. The patients were followed for 2–19 years of follow-up, with a mean of 8.5 years in the EOS group.

Register studies have an advantage in epidemiological research, as it is possible to perform large-scale studies with data that have already collected. In a country with free access to health care and no private psychiatric hospitals, register-based studies can be conducted with little selection bias. Schizophrenia studies and psychiatric research in general often have a high attrition rate ('dropouts'), in studies of psychosocial treatment, pharmacological trials [210,211] and outcome studies [212]. It is not clearly established if dropout is associated with a specific outcome. In our systematic review of 21 early-onset studies, (study 2), the median attrition rate was 28% and in three of the studies, it was > 50% [1]. In the studies with a high number of dropouts, the outcome tended to be worse. This is in line with some other studies: an Indian study reported that > 60% of patients completely lost to follow-up had been in a state of remission when last seen [213], whereas another study described higher dropout rates in patients with a severe course[214]. Menezes et al., who described a reasonably favorable course in their meta-analysis of 4100 patients with first-episode AOP, suggested selection bias and attrition bias might be part of prior findings with a more severe prognosis. Patients in recovery or with good outcomes may be lost to follow-up[37].

By using registers to assess the outcome of schizophrenia, we could circumvent the bias of dropout. It is a great advantage of study 3 that there was virtually no loss to follow-up. With extensive registers for employment, housing, hospital treatment, education, medication, mortality and crime as is the case in Denmark and other Nordic countries, there is virtually no loss to follow-up. People will only leave the registers if they either leave the country or if they are not in contact with any public services, including social benefits, emergency rooms, healthcare etc. Since data are collected automatically, there should be no collection bias. Selection bias is reduced as all patients are included, thus not restricting to a certain geographic area or socio-economic group. Some selection bias remain as our patient sample can only include patients who were in contact with the health system and diagnosed – this bias is also present in most clinical studies.

LIMITATIONS BY REGISTER-BASED STUDIES

Defining EOS and AOS by use of the registers is different from clinical studies. In clinical studies with assessment of patients or information from close relatives, age of onset is mostly defined as age of the first clear psychotic symptoms. This method is not possible in register research as there is no access to data in the psychiatric records

or from specific assessment instruments, and no contact with patients. The most commonly used method in register studies is index date (first day of first hospital contact with the diagnosis, either as an in- or outpatient)[215,216]. Another possible method in register-based studies would be to use first day of first antipsychotic treatment or first day in inpatient treatment, whichever comes first. However, some patients are treated with antipsychotic medication prior to true psychotic symptoms as a means to aid better sleep or less chaotic thinking.

By using the index data as the time of onset, there will be large variations between the time of index date, the time of onset of first psychotic symptoms and the time the clinician decide on the diagnosis and to initiate treatment. Some patients have had psychotic symptoms over diagnostic threshold for years prior to seeking help, others present with high-risk symptoms which may later turn out to be prodromal, and still others seek help for depressive disorders, suicidal thoughts, anorexia, etc., where the disorders may progress to schizophrenia during the psychiatric course. In all probability – based on studies of DUP – age of onset defined by index date will be later than the age of onset defined by onset of psychotic symptoms. This corresponds to the findings in study 2, where estimated age of first psychotic symptoms were more than 1.5 years prior to the schizophrenia contact. Quality research of the Danish assessment and treatment of schizophrenia has shown that DUP is > 6 months for approximately half of patients in both EOS and AOS[86-88,217]. It is therefore possible that part of the patients with AOS have had early-onset. In study 3, a sensitivity analyses was conducted, comparing patients with EOS to AOS patients diagnosed after the age of 25 to address this bias, and we confirmed the same findings as in the main analyses.

Accuracy and coverage of register data are not always known which is another limitation of register studies. Compared to the extensiveness of register data, only a fraction of the data or even the data variables have been assessed. As described previously, most studies of diagnostic validity report adequate to high quality data, however most studies have not assessed the accuracy of all the other data reported to the register, such as dates for visits and comorbid disorders or quality of care[205]. Admission dates have been found to be reliable in register studies from other countries[59,208], dates from visits to outpatient facilities are probably more uncertain[208].

Finally, register-based research have a challenge in the endless possibilities. Research should always be driven by hypothesis and not 'data-fishing'. The magnitude of data in the registers are so large that almost anything will be able to elicit a result, with *p*-values pointing to a true difference. Furthermore, as with clinical studies, researchers should always be wary of statistical differences that may point to a true difference with regard to *p*-value but where the effect, power or numerical relevant is so low that it is clinically irrelevant. With regard to the secondary outcomes of study 3, we found some outcomes to be different between EOS and AOS but with a fairly small difference. Five percent more patients with EOS had been involuntary admitted, and

3% fewer patients with EOS had never been admitted, whereas other outcomes were more convincing of a clinically relevant difference – e.g. half as many patients with EOS as those with AOS had completed above law-mandated education and 13% more patients with AOS were diagnosed with substance use disorders. Those are the differences that we should attempt to address through targeted interventions.

CHAPTER 5: IMPLICATIONS FOR THE FIELD AND FUTURE RESEARCH

Perspectives for clinical practice from the validation study

For disorders with a likelihood of a long psychiatric course, it is desirable to be able to go back and evaluate the premise of the diagnosis for the first episode. Even in records where we had access to all material from the original assessment, the raters were sometimes in doubt due to vague clinical descriptions.

Our findings suggest that clinical practice can be improved concerning descriptions, as it was sometimes not possible to decide whether the symptom reached a clinical threshold (e.g. no impact/distress; very short duration; only happened 1–2 times). Some descriptions would be as short as 'patient has bizarre delusions', which is insufficient, especially given the fact that clinicians are not always in agreement with regard to definitions of 'bizarre'. Furthermore, it was not always clear if potential differential diagnoses had been considered.

In Chapter 4, the role of trauma in psychosis was discussed, highlighting the findings from studies 2 and 3, both pointing to a high number of patients having experienced trauma or adversities as also known from other studies. While the presence of trauma is not necessary for a schizophrenia diagnosis, trauma and adverse events are important for future treatment planning and understanding the individual patient where traumatic experiences from the past may influence the specific delusions or hallucinations, as well as reduce the coping abilities of the patient. The subject of trauma should be addressed at an appropriate time during the assessment phase. The presence of psychopathology does not influence the likelihood of reporting abuse, and reports are fairly consistent over time, also in patients with psychotic disorders, and underreporting of trauma is more probable than false accounts[218]. The patient may not be ready to talk about it at this point, but by addressing the issue, the clinician conveys that this is a subject that can be talked about. Studies have found that clinicians often either do not ask about trauma or do not document if a trauma history have been taken[218,219]. This tendency were also seen in study 2 where patients and caregivers were often not asked about traumatic or stressful events in the initial assessments, and in >25% of the records, I could not find any descriptions of trauma or adversities being considered.

Finally, we discovered what seems to be a systematic bias in the outpatient schizophrenia diagnoses in the DPCRR: of the 79 schizophrenia diagnosed given in outpatient settings, 15 were misclassifications (19%) and the majority of these were owing to the same type of error: The patient was seen in the outpatient clinic, a suspicion of schizophrenia emerged and the patient was referred to an inpatient facility

for further treatment. A final diagnosis of schizophrenia had not been made, yet the outpatient contact was coded as such. This systematic error could be eliminated by coding a psychiatric contact as unspecified psychosis (F29 in ICD-10) as long as the assessment for schizophrenia is still ongoing.

Implications for register studies:

Based on our finding of higher validity of inpatient schizophrenia diagnoses, future register studies of EOS could restrict their sample to patients diagnosed as inpatients. However, such restrictions would also depend on the nature of the study as an exclusion of patients with no admissions would exclude some of the patients with the best prognosis. Another way to limit the risk of registration errors would be to require at least two contacts with schizophrenia. In study 3, we chose to conduct sensitivity analyses with different subgroups of the sample and in this way confirmed the overall findings without biasing towards a more severe sample.

Proposition: Systematic and frequent validation studies

Denmark has a valuable research source in its registers, but to uphold the scientific value of the registers, the data must be of high quality regarding both concordance and clinical quality in classification.

Far from all psychiatric diagnoses in the DPCRR have been through quality assurance in terms of validity and concordance studies, and some diagnoses have mostly or only been investigated in adults or children/adolescents (attention-deficit hyperactivity disorder, autism). McConville and Walker investigated the reliability of diagnoses in Scotland's psychiatric register and found varying reliability and frequency of misclassifications across the diagnoses[207]. On the basis of their study, McConville and Walker recommended investigations of all diagnoses individually in terms of reliability[207]. I agree with this conclusion and would suggest a more organized structure of frequent and systematic validation studies of diagnoses in the DPCRR.

Systematic and frequent validation studies of all major mental disorders would benefit the clinicians in Danish child, adolescents and adult psychiatry. Furthermore, it would be valuable for psychiatric research due to the many register studies coming from Denmark. Today, all psychiatric departments have electronic patient records, which would make the study process much easier than studies conducted in time periods with paper records (including study 2).

Such a step would require an organizational set-up. Currently, validation studies of register data are mostly conducted by researchers prior to a register-based study where an investigation of the data quality is needed. The validation study is thus designed to meet the specific requirements of the future register study. By continuing this path, some disorders may never be validated and others will only be validated for subgroups of people or for a certain period of time. By having a better organizational practice in place, studies could be designed with appropriate time intervals, with a design allowing comparisons between studies, and they could be designed to include registration errors, clinical as well as register-based validity, sensitivity and specificity. Furthermore, it would be possible to carry out the studies close to the time of diagnosis with the organizational structure in place; permissions and data collection procedures would be more efficient and the framework already laid out. Conducting register-based studies may seem like an easy process, but without an organizational structure, there are several logistic challenges and extensive data-management.

As an added bonus, systematized validation studies would be beneficial for the training of younger doctors and psychologists, by offering a current update on diagnostic tendencies, administrative practice leading to registration errors etc.

Last but not least, the patients: By continuously educating ourselves and maintaining high quality assessment, the chances are higher that the individual patients will receive the most correct assessment of his current state.

CHAPTER 6: WHAT DO WE TELL THE PATIENTS?

After having studied the outcome of early onset schizophrenia – and owing to the research design of the project, also educated myself and others on the outcome of AOS in the process – I have often asked myself whether this would alter the way I answer questions from my patients.

'Will this pass?'

'Do I have to take medication forever?'

'Will she ever be able to take care of herself again?'

The questions are many, and the torment and despair often evident in the acute phase of the disorder. Once it passes, and the patients fare better, the fear of becoming psychotic again is often present.

I entered research with to a desire to be able to answer these questions more in depth and confidently. I knew the common numbers; we as clinicians often tell our patients: '*20–25% have complete remission, 50% will have a moderate outcome with half having episodes but feeling well in between, and 25% will continue to experience psychotic symptoms'*, but at the same time I knew that child and adolescent onset had a particularly poor prognosis. When I started the PhD project and gave my first poster presentation at a Danish conference, I had a therapy session with one of my regular patients scheduled shortly thereafter. My poster was right outside my office in the hallway – the poster highlighted all the findings from our review on the prognosis of EOS (study 1). In particular, the conclusion '*In contrast to the adult manifestation, the early manifestation of schizophrenia in childhood and adolescence still carries a particularly poor prognosis*' stood out to me, along with the very chaotic and tormented picture I had picked to go along with it. I took the poster down before my patient came.

Along the way of the PhD, I have often thought back to this incident and again posed the questions to myself along with reflections on what to tell patients. A few times I even thought to myself that I would rather have picked a different area of research, just to have more good stories to share.

Now, with all the results ready, I think I am ready to answer the questions truthfully and honestly, while at the same time considering what things I would like my treating clinician to pinpoint if the situation were reversed.

Everybody needs to retain some hope. In situations where we are down on our luck, feeling despair and powerlessness, we need a chance to believe that it will get better. It does not mean we should all be 'happy-go-lucky' preachers and only share optimism and recovery tales. For some patients, that would be overlooking their despair and turmoil.

But even though the research points to more severe outcomes for schizophrenia than most other mental disorders, it also points to remission for some, benign outcomes for others and improvement for the majority. Even in EOS, the prognosis do not seem as poor as previously believed. Twenty percent in our register-based EOS sample were never admitted to hospital during follow-up.

So, when speaking to my patients, I will share my knowledge of the field. But it will not be all gloom-and-doom talk. As for child and adolescent schizophrenia, I will let them know that it is has been associated with a more severe outcome than what is known from AOS – but that some studies, including my own of all cases diagnosed in Denmark over almost two decades, does not confirm this difference for the long-term outcomes on most measures. Perhaps some of the negative findings from prior studies were due to very high number of drop-outs or selection bias from only investigating patients in specialized settings. Then, I will move away from all the percentages, the ORs, confounders, 'significant findings' and *p*-values. And I will bring back the talk to the individual patient – talk about his/her personal strengths and assets, how his/her surroundings, life events and support system may benefit him/her towards a better outcome, towards a personal recovery. How he/she can reduce the risk factors and stressors. And I will remember that as a clinical and also as a researcher sometimes my job is just to listen and help facilitate while people find their own way. And at times, they will need me or someone else to carry the flashlight.

CHAPTER 7: CONCLUSION

Having investigated EOS from several different angles; reviews of other studies; validation of schizophrenia diagnoses in Denmark; and register studies of outcome, I will now summarize the findings related to the initial research questions:

a) What do we currently know about the outcome of EOS and does it differ from adult onset?
    - Although prior studies have pointed to a more severe course of EOS, this Danish nationwide register-based study of a large EOS sample could not confirm a difference on the majority of outcomes. In line with Immonen's meta-analysis[48] and studies from EPPIC[47] and ÆSOP[200], our results point to age of onset being less predictive for outcome than previously thought.

b) What is the validity of schizophrenia diagnoses from child and adolescent psychiatric departments in Denmark and are the diagnoses correctly registered in the DPCRR?
    - Ten percent of schizophrenia diagnoses in children and adolescents are misclassifications; however, the vast majority of the misclassifications are still in the schizophrenia spectrum. Of the cases diagnosed with schizophrenia in the clinic, experienced raters evaluated 83.5% to be correct and 91.8% as being in the schizophrenia spectrum. Although EOS can be diagnostically challenging, we were in line with other studies in concluding that it can be reliably diagnosed by experienced clinicians conducting thorough assessments.

c) Based on Danish register-based data, are there differences between EOS and AOS in the following:

    - Number of inpatient days in short- and long-term outcome?

    With regard to short-term outcome, defined as the first 2 years of diagnosis, patients with EOS spend more days in hospital than those with AOS, but for long-term outcome the number of annual inpatient days did not differ. Our sensitivity analyses point to the initial difference as a potential effect of different treatment patterns in child and adolescent psychiatry versus adult psychiatry. Childhood adversities and co-morbid substance use disorder were more associated with inpatient days than early- vs. adult-onset.

- Premorbid characteristics

In study 3, patients with EOS and AOS were strikingly similar with regard to premorbid characteristics as measured in the register (disorders prior to schizophrenia and a number of parental variables: predisposition, divorce, death, substance use disorder, incarceration, psychiatric admission and longer somatic admission). Only premorbid substance use disorder in patients reached a significant and clinically relevant difference, possibly owing to the age difference. It is important to bear in mind that we were not able to measure the degree of premorbid developmental difficulties in the patients or their cognitive function as these measures are not available in the registers. In the validation study, 43% of the patients with EOS had experienced problems with speech and language development, social development or psychomotor development during childhood.

- Psychiatric outcome and measures of psycho-social functioning

For psychiatric outcomes, EOS and AOS were similar with regard to long-term admissions, inpatient days and heavy use of inpatient days. Three differences emerged: fewer patients with EOS patients were never admitted and more patients with EOS had experienced an involuntary admission; both differences were minor ($\leq 5\%$). Finally, more patients with AOS had a diagnosis of substance use disorder, which may be attributed to their older age.

For psychosocial outcomes, patients with EOS were less likely to have completed education above law-mandated school, even 5 years into adulthood. Though this difference was large between the two groups, many patients with AOS would have reached this level of education before the development of schizophrenia. More patients with EOS were in unsupported work or education at end of follow-up.

The thesis do not touch upon all aspect of outcomes of EOS and other important issues remain, e.g. suicide rates and all-cause mortality as well as more detailed studies of education and vocational outcomes would be highly relevant to investigate further in the large cohort of EOS patients identified by the DPCRR.

Still, looking ahead, more emphasis should be placed on risk factors for poor outcome, some of which can be prevented or at least reduced, and the knowledge of such risk markers can help us identify them in the individual patient in order to intervene more efficiently.

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ENGLISH SUMMARY

Early-onset schizophrenia (EOS), usually defined as onset of symptoms prior to the age of 18 years, has been associated with poor outcomes for several decades. Less than 10% of all patients with schizophrenia are diagnosed in childhood and adolescence. The low prevalence makes it difficult to conduct large-scale studies investigating EOS, and studies are often biased by high drop-out rates as well as selection bias. In the past few years, a number of studies has been published pointing to EOS being more similar to AOS than previously thought in terms of outcome, with some even suggesting a better prognosis for early-onset psychotic disorders.

This thesis investigates the outcome of EOS through a systematic review and with data from the Danish, nationwide registers. Furthermore, a validation study of the schizophrenia diagnoses registered in children and adolescents in the Danish Psychiatric Central Research Register (DPCRR) was conducted to assess the concordance between the diagnosis described in the psychiatric records and the register-based diagnosis as well as to evaluate the quality of the clinical diagnosis of schizophrenia by rating psychiatric records.

The systematic review of long-term outcome of EOS included studies in English-language journals published after 1980 with at least one year of follow-up. Twenty-one studies were included with a total of 716 patients. Studies were included if a majority had EOS, but approximately half of the studies also included other psychotic disorders. Patients were followed for a mean of 13 years with a range of 1.5-42 years. Mean age of onset was 14.9. In the studies of patients with EOS only, 15.4% had a good outcome, 24.5% a moderate outcome, and 60.1% a poor outcome. In the full sample, also including some patients with other psychotic disorders, 17.2% had good outcome, 28.2% moderate, and 54.6% poor outcome.

In the validation study, 178 psychiatric records of a random sample of 200 children and adolescents diagnosed with schizophrenia in the period 1994–2009 were retrieved. Eleven percent of the DPCRR registered schizophrenia diagnoses were registration errors, and the diagnostic validity of DPCRR registered schizophrenia was 75.3% for schizophrenia, with 83.5% of the records in the schizophrenia spectrum. Of the clinically diagnosed schizophrenia, the raters confirmed 83.5% to be correct, with 91.8% meeting criteria for schizophrenia spectrum disorders. Schizophrenia diagnosed during an inpatient contact had higher validity and fewer registration errors. In conclusion, EOS diagnoses in DPCRR are valid for register research, but diagnostic accuracy can be improved by including only patients diagnosed during hospitalization.

The third study included 16,337 patients registered with a schizophrenia diagnosis in the DPCRR between 1996 and 2012 before the age of 40 years, 1,223 of the sample

had early-onset. Mean age of onset in the patients with EOS was 16.1 ± 1.7 years and 27.7 ± 6.3 years among patients with AOS. Duration of follow-up was 8.5 ± 4.5 years for patients with EOS and 9.6 ± 5.0 years in the AOS group). The majority of the sample were adults at the end of follow-up, with only 77 patients in the EOS group below the age of 18 (6.3% of EOS). The primary outcome measure was inpatient days during short- and long-term outcome. In the short-term outcome, the patients with EOS had more inpatient days, but after the initial two years, there was no difference between the two groups. Substance use disorders and being placed in out-of-home care during childhood were stronger associated with inpatient days in long-term follow-up than age of onset. For the secondary outcomes, there were many similarities between patients with EOS and AOS, but EOS had a longer length of first admission, were less likely to never be admitted and more likely to have experienced involuntary admission and fewer had achieved an educational level above law-mandated school, even when restricting analyses to patients at least 23 years of age. Patients with AOS were more likely to have comorbid substance use disorders and at the end of follow-up, more patients with AOS were dependent on social benefits as primary source of income.

To conclude, the outcome of EOS may be more similar to outcome of AOS than previous studies have suggested, and the register-data could not confirm a particular poor prognosis for patients with EOS. The thesis have not assessed all outcomes of EOS and several topics would be worth exploring further by use of the large sample of patients with EOS identified by the DPCRR, in particular mortality and suicide-risk as well more detailed studies of educational and vocational outcomes. Other factors not related to age may be more important for prognosis, such as substance use and childhood adversities, which must be considered when addressing preventive strategies as well as intervention strategies.

DANSK RESUME

Tidlig skizofreni defineres som debut før det 18. år og er forbundet med en dårlig prognose. Færre end 10% med skizofreni, diagnosticeres med tidlig skizofreni. Den lave prævalens gør det vanskeligt at undersøge forløbet af tidlig skizofreni, og der er ofte stort frafald ved longitudinelle studier. De seneste år er der publiceret studier, der peger på, at prognosen ved tidlig skizofreni er mere lig skizofreni med debut i voksenalderen, og nogle finder bedre forløb ved tidlig skizofreni.

Afhandlingen undersøger forløbet af tidlig skizofreni gennem et systematisk litteratur-studie samt via data fra de landsdækkende, danske registre. Derudover består afhandlingen af et validerings-studie af skizofreni-diagnosen registreret hos børn og unge i det Danske Psykiatriske Centrale Forsknings Register (DPCRR). Valideringsstudiet fokuserer på overensstemmelsen mellem register-diagnosen og diagnosen, der er noteret i journalen og på, om diagnosen er stillet efter de diagnostiske kriterier i henhold til ICD-10 og således vurderes fagligt valid.

Det systematiske litteratur-studie inkluderede studier fra engelsksprogede artikler udgivet efter 1980 med mindst et års follow-up, hvor hovedparten af patienterne havde tidlig skizofreni. 21 studier med i alt 716 patienter blev inkluderet, knap halvdelen af studierne inkluderede også patienter med tidlig debut af andre psykotiske lidelser, primært inden for skizofreni-spektret. Den gennemlige opfølgningstid var 13 år, og den gennemsnitlige alder for debut af psykotiske symptomer var 14,9 år. Forløbet af skizofreni var kategoriseret i ”mildt”, ”moderat” og ”svært”. I studier af patienter med tidlig skizofreni havde 15,4% et mildt forløb, 24,5% et moderat forløb og ca. 60,1% et svært forløb. Blandt hele gruppen, inklusiv patienter med andre psykotiske lidelser, havde 17,2% et mildt forløb, 28,2% et moderat forløb og 54,6% et svært forløb.

I valideringsstudiet lykkedes det at lokalisere 178 psykiatriske journaler ud af et tilfældigt udtræk på 200 børn og unge, der var registreret i DPCRR med en skizofreni-diagnose i perioden 1994 – 2009. Elleve procent af diagnoserne var registreringsfejl, hvor patienten ifølge journalen ikke var blevet diagnosticeret med skizofreni. Blandt register-diagnoserne blev 75,3% bekræftet af raterne som skizofreni og 83,5% som indenfor skizofreni-spektret. Blandt de kliniske skizofreni-diagnoser bekræftede raterne 83,5% af diagnoserne som skizofreni og 91,8% som inden for det skizofrene-spektrum. Diagnoser foretaget under indlæggelse havde en højere validitet pga. færre registreringsfejl. Det konkluderes, at skizofreni-diagnoser fra DPCRR kan bruges til register-forskning, og at diagnostisk præcision kan øges ved at fokusere på patienter diagnosticeret under indlæggelse eller med flere forløb.

Registerstudiet af forløbet ved skizofreni inkluderede 16,337 patienter med skizofreni registeret i DPCRR mellem 1996 og 2012, der var diagnosticeret før de fyldte 40 år, af disse var 1223 diagnosticeret før det 18. år og udgjorde gruppen med tidlig

skizofreni. Gennemsnitsalder for diagnose ved tidlig skizofreni var 16.1 ± 1.7 år og ved voksen-debut 27.7 ± 6.3 år. Patienterne blev gennemsnitligt fulgt i registrene i 9,5 år (tidlig skizofreni 8.5 ± 4.5 år, voksen-debut 9.6 ± 5.0 år). Indlæggelsesdage var det primære outcome-mål. Patienter med tidlig skizofreni havde flere indlæggelsesdage i de første to år efter diagnosen, men herefter var der ingen forskel på de to grupper, mens komorbide misbrugsdiagnoser samt anbringelser i løbet af barndommen var stærkere associeret til indlæggelsesdage. Forskellen i starten af forløbet kan muligvis forklares med anderledes indlæggelsesmønstre i børne- og ungdomspsykiatrien i forhold til voksenpsykiatrien. På de øvrige mål for forløb lignede de to grupper hinanden på mange områder, men patienter med tidlig debut havde længere varighed af første indlæggelse, færre blev aldrig indlagt og flere oplevede at blive tvangsindlagt. Endvidere opnåede færre med tidlig debut at færdiggøre en uddannelse udover folkeskolen, selv ved det fyldte 23. år. Patienter med debut i voksen-alderen havde hyppigere en komorbid misbrugsdiagnose og var oftere på offentlig forsørgelse som den primære indtægtskilde ved afslutning af follow-up. Antallet af patienter med EOS i registerstudiet er, så vidt vides, den største gruppe med EOS undersøgt til dato.

På baggrund af afhandlingens resultater konkluderes, at forløbet af tidlig skizofreni ligner forløbet af skizofreni med debut i voksen-alderen mere end tidligere antaget, og vi har ikke kunnet påvise gennem register-data, at skizofreni hos børn og unge har en værre prognose. Afhandlingen har ikke afdækket alle områder af tidlig skizofreni, og der er områder, det vil være meget relevant at belyse gennem det store sample identificeret gennem DPCRR – det kunne f.eks. være mortalitet og selvmordsadfærd, ligesom uddannelse- og arbejdstilknytning kan undersøges i et mere detaljeret design.

Der bør også være fokus på, at der er andre faktorer, der ikke har at gøre med debutalder, der kan være væsentlige for prognose og forløb, så som stof- og alkoholmisbrug samt belastninger og traumer i barndommen. Disse faktorer må adresseres både i forebyggelsesøjemed samt i forhold til interventionsindsats.

APPENDIX A: CO-RATER CHECKLIST FOR VALIDATION STUDY

Rater assignment

1. The rater is provided with a printed check-list (see next page) and material from the psychiatric record (e.g. discharge summary, diagnostic interview, observations, anamnestic information, psychological assessment)
2. The rater must tick the relevant spaces ___ and write comments where it is requested, marked with _____.
3. After filling out the form, the rater must use the information to evaluate the likeliness of correct schizophrenia diagnosis on the following scale:

___ 1) Correct ___ 2) Maybe ___ 3) Not correct

If the rater ticks 'maybe', the reason should be specified (e.g. insufficient information, vague description of symptoms, unclear duration of symptoms required to classify schizophrenia or presence of other diagnoses potentially explaining the symptomatology). If insufficient information, contact DLV to see if additional record material is available.

If the rater ticks 'maybe', an arrow should indicate if the rating is leaning towards correct or incorrect.

How to fill out the checklist

1. **Name & ID:** Provide patients initials and study-assigned ID.
2. **Start & end date of this contact: Is already coded (**Specify first date of this contact (admittance date or date of first contact in out-patient facility) and the date the patient was discharged from hospital or out-patient facility)
3. **Cognitive decline:** Tick 'yes' if it is described that the patient does not have the same cognitive or educational capacities as previously. The knowledge may stem from psychological testing or could be based on school information. Tick 'no' if it is described that there is no such decline and tick 'not mentioned' if the record does not give information regarding possible decline.
4. **Family disposition for schizophrenia:** Tick 'yes, 1st degree relatives' if father/mother/full sibling or offspring has schizophrenia, tick 'yes, 2nd degree relatives' if a relative with whom the patient shares 25% of genes has schizophrenia (grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling), tick 'no disposition' if it is explicitly stated that there is no known disposition, tick 'not mentioned' if the material does not mention dispositions. Tick 'other disposition' and write which if patient is disposed to other psychiatric illness than schizophrenia.

5. **Drug use:** Specify if drug use has been present or is present and specify drug of choice.
6. **Onset type:** Insidious vs. acute: Tick 'insidious' if presence of neurodevelopmental difficulties and attenuated/sub-syndromal symptoms for > 1 month preceding full psychosis. Tick 'acute' if preceding symptoms and difficulties have been absent or present for less than 1 month prior to full psychosis.
7. **Duration of untreated psychosis:** Specify length of duration of untreated psychosis. The first date that the patient is offered antipsychotic medication is defined as the last day of untreated psychosis. Thus, if the patient has had psychotic symptoms for 1 year before being offered medication, the duration is 1 year. Tick 'not mentioned' if the record does not give information on this.
8. **Anti-psychotic medication prescribed:** Tick yes and write prescription (type and dose). Tick 'no' if the patient is not on medication at discharge and tick 'not mentioned' if the record gives no information on this.
9. **Diagnostic interview used for diagnosis:** Tick 'yes' if an interview format is mentioned and if possible, specify which one. If the record does not specify the type of interview but mentions the use of a diagnostic interview, tick yes and write 'not mentioned' under 'which'. If the record states that a diagnostic interview has not been used, tick 'no'..

The smaller checklist in the square consists of the diagnostic requirements for a schizophrenia diagnosis in the ICD-10:

10. **1st rank symptoms:** Tick 'yes', 'no' or 'not mentioned' according to which information is given in record. If 'yes', tick which 1st rank symptom or 'not mentioned' if this is not specified
11. **Other symptoms of schizophrenia:** Tick 'yes', 'no' or 'not mentioned' according to which information is given in the material. If 'yes' tick also which symptom or 'not mentioned'.
12. **Duration of illness:** Specify <1 month, >1 month or 'not mentioned'. If <1 month, specify if this could be due to medication.
13. **Finally, the rater should evaluate the likelihood of schizophrenia based on the information available.** Even if it is not possible to have all the information needed for diagnosis, the rater must state whether he/she feels confident that the examination has been thorough and the diagnosis given is thought to be a best estimate. The rating 'maybe' is available for cases when the rater is in doubt. Remember it is possible to request additional information as DLV has selected parts of the full record for the rater to use.

ID_nr: [_] [_] [_] -- [_] [_] [_] **Initials** [_] [_] [_]

Period for rating (month/yr – month/yr): _____ – _____

Cognitive / educational decline:

___ Yes
___ No
___ Not described

Familiære dispositioner

___ Yes, 1st degree schizophrenia
___ Yes, 2nd degree schizophrenia
___ Yes, other: _____
___ No familiar predisposition
___ Not described

Substance use

___ Yes, throughout the course of the disorder
Elaborate _____
___ Yes, previously: _____
___ No drug-use now or previosly
___ Not described

Type of onset

___ Insidious
___ Acute (<1 mo)
___ Not described

DUP

___ Specify duration _____
___ Not described

Anti-psychotic medication prescribed

___ Yes, elaborate type
_____
___ No
___ Not described

Semistructured interview used

___ Yes: _____
___ No
___ Not described

ID_nr: [_] [_] [_] -- [_] [_] [_] **Initials** [_] [_] [_]

ICD-10 criteria for schizophrenia (F20.x)		
1st rank symptoms *(not necessary for diagnosis, but sufficient for diagnosis if at least one clear FRS))*	___ Yes *Tick the relevant below* ___ Thought echo, -insertion, -withdrawal or -broadcasting ___ Delusion of control or delusional perception ___ Voices giving running commentary, discussing patient among themselves or stemming from patient's body ___ Bizarre delusions ___Not mentioned which 1st rank symptom **(see detailed description in the appendix)**	___ No ___ Not mentioned
Other symptoms of schizophrenia *(at least 2 if no FRS)*	___ Yes *Tick the relevant below* ___ Persistent hallucinations without affective content, often accompanied by half-formed delusions ___ Thought/language disturbance (incoherent or irrelevant speech, neologisms, blocking, etc.) ___ Catatonic behavior ___ Negative symptoms (anhedonia, asociality, affective flattening, alogia, amotivation – not due to depression) ___ Not mentioned which symptoms **(see detailed description in the appendix)**	___ No ___ Not mentioned
Duration of illness	___ < 1 month Due to medication __ ___ > 1 month Specify duration: _____weeks, months, years (circle which)	___ No ___ Not mentioned

Rater's evaluation of the patients' diagnosis of schizophrenia based on record material:

___ 1) Correct ___ 2) Maybe ____ 3) Incorrect

(reasons for maybe: insufficient information, vague description of symptoms, unclear duration of symptoms required to classify schizophrenia or presence of other diagnoses potentially explaining the symptomatology).

When rating maybe, specify if the rating is leaning towards 'correct' or 'incorrect'.

Raters' best-estimate diagnosis: _____

Use back page for comments.

Definitions from the 'The ICD-10 Classification of Mental & Behavioral Disorders, Clinical descriptions and diagnostic guidelines'.

1st rank symptoms:

A. Thought echo, thought insertion or withdrawal, and thought broadcasting;
B. Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception;
C. Hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body;
D. Persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g. being able to control the weather, or being in communication with aliens from another world);

Other symptoms (at least 2 needed for diagnosis):

E. Persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end;
F. Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms;
G. Catatonic behavior, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor;
H. Negative symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or to neuroleptic medication;
I. A significant and consistent change in the overall quality of some aspects of personal behavior, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal. **In Danish psychiatry, this item is listed as 'negative symptoms' also.**

ID _____ Birth Mo/Year _____

Sex		Hospital, Region	
Siblings, number x/N			
Household (parents, divorced, mom/dad, other)			
Mom current work			
Dad current work			
Birth complications y/n		if y, desc:	
Birth preterm y/n		Gestation wks	
Birth weight		Birth lenght	
Language devl. normal y/n		if n, desc	
Social devl normal y/n		if n, desc	
Motor devl normal y/n		if n, desc	
Ageapp relations y/n		if n, desc	
Dispositions y/n			
SZ		if y, who	
Bipolar		if y, who	
Depression		if y, who	
Anxiety		if y, who	
Other		if y, who	
Intelligence test y/n		if y, year/type	
Total IQ		details	
Trauma y/n		**if y, cont.**	
Sexual		if y, type	
Violent		if y, type	
Other		if y, type	
Belastninger y/n		**if y, cont**	
School change		if y, N	
Parental separation		if y, type	
Parental death		if y, type	
Parental substance abuse		if y, type	
Victim of bullying		if y, type	
Other		if y, type	
Previous interventions		**if y, continue**	
PPR (school/kindergarten intervention		if y, type	
Social services		if y, type	
Private psychologist		if y, type	
Other		if y, type	

ID _____ Birth Mo/Year _____

Previous suicidal ideation		Suicidal idea during psyc.	
Previous attempts, y/n		Attempts dur psyc.co	
Previous agg. Impulses y/n		Agg. dur psyc.co	
Previous crime y/n		Crime dur psyc.co	
Previous selfharm y/n		Selfharm dur psyc.co	
Loss of function, school y/n		if y, desc.	
Loss of function, social y/n		if y, desc.	
Loss of function, cognitive y/n		if y, desc.	
Psychiatry prior to SZ:			
1st dx			
2nd dx			
3rd dx			
4th dx			
Admissions prior or during		**X admission at time of SZ**	
1st adm x year and lenght			
2nd adm year and lenght			
3rd adm year and lenght			
			X medication
Medication prior or during			**at time of SZ**
1st AP			
2nd AP			
3rd AP			
4rd AP			
Polypharma y/n			
Max nr of AP			
Weight gain during AP, kg		period:	
Antidepressive medication			
Anxio			
Other			
Noncompliance y/n			
MEDICATION AT DISCHARGE:			
Notes on medication			

ID _____ Birth Mo/Year _____

Age first psychiatric contact		**Age SZ contact**	
Age at SZ onset			
Referal dx at SZ contact			
Dx at IP / OP		if IP, frivil y/n	
Onset type (insi, acute, sub-acu) **ICD-10 criteria**		DUP, wks	
DX Diagnostisk interview y/n		**if y, type**	
DX_first rank y/n		if y, cont.	
DX Control delu y/n		DX Bizz delus y/n	
DX Body delusions y/n		DX Delusional perception y/n	
DX FRS thought disorders y/n			
DX Non-aff. Hall. y/n		if y, cont.	
DX Auditory y/n		Føle hall, y/n	
DX visual y/n		Taste / olfactory y/n	
DX Thought distu y/n			
DX catatonia y/n			
DX negative symp y/n DX duration, wks		if y, type	
DX somatic screen, y/n			
DX Drug-use currently y/n		if y, type	
Drug-use previously y/n		if y, type	
Discharge diagnoses:			
Miss-classifications in DPCR, y/n			
SZ diagnosis valid Y/N/MAYBE			
Dx by rater	_____		
Notes on symptoms			
Notes on file			

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RESEARCH ARTICLE Open Access

A systematic review of the long-term outcome of early onset schizophrenia

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Abstract

Background: The current review analyzes the long-term outcome and prognosis of early onset schizophrenia based on previously published studies in 1980.

Methods: A systematic search of articles published in the English-language literature after 1980 identified a total of 21 studies, which included 716 patients who were either suffering from early onset schizophrenia (EOS) or both EOS and other psychotic disorders (MIX). The authors of the current review scored the outcome as either "good," "moderate," or "poor." The mean age of onset in these studies was <18 years.

Results: In general, the outcome in studies with EOS is worse than the outcome in MIX studies. Only 15.4% of the patients in EOS studies versus 19.6% of the patients in MIX studies experienced a "good" outcome. In contrast, 24.5% of the patients in EOS studies versus 33.6% in MIX studies experienced a "moderate" outcome, and 60.1% in EOS studies versus 46.8% in MIX studies experienced a "poor" outcome. The authors identified various significant effects on outcome. In EOS, the findings were significantly affected by sample attrition, indicating that in studies with a high dropout rate, fewer patients experienced a "moderate" outcome, and more patients experienced a "poor" outcome; however, the effect sizes were small. Furthermore, the effects were also small and more favourable for specific functioning measures, as opposed to more global measures, small to moderate in terms of worse outcomes for follow-up periods >10 years, small to moderate for more unfavourable outcomes in males, and small to large for worse outcomes in studies including patients diagnosed before 1970.

Conclusions: In contrast to the adult manifestation, the early manifestation of schizophrenia in childhood and adolescence still carries a particularly poor prognosis. According to these aggregated data analyses, longer follow-up periods, male sex, and patients having been diagnosed before 1970 contribute predominantly to the rather poor course of EOS.

Keywords: Early onset schizophrenia, Childhood onset schizophrenia, Long-term course, Outcome, Prognosis

Background

Traditionally, schizophrenia has been perceived as a disorder with high rates of chronicity and deterioration over time. Some recent studies have shown better prognosis of the disorder [1,2]. Typically, the onset is in early adulthood with less frequent manifestation in adolescence and rare onset in childhood. In the literature, the definition of early onset schizophrenia (EOS), or adolescent onset schizophrenia, varies with studies defining it as onset before age 17–21 [1,3-18].

Quite similarly, the age of onset in very early onset schizophrenia (VEOS), or childhood onset schizophrenia (COS) also varies across studies with definitions before 12–15 years of age [3,9,15,17,19-25]. The most common definition of EOS is onset before age 18, and the most common definition of VEOS is onset before age 13.

While adult onset schizophrenia (AOS) has been studied in great detail for many decades, research on EOS and VEOS is still more limited, partly due to its low prevalence and the fact that EOS was not recognized in the diagnostic systems before the introduction of DSM-III. The prevalence of schizophrenia in children and

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adolescents is rather low, with estimates of VEOS varying between 1 in 10.000 [21], 1 in 30.000 in children before age 13 [13], and 1.4 in 10.000 before age 15 [26]. Among patients with schizophrenia, a Finnish study found that 4.7% had onset at or before age 18 [27].

The nosological status of schizophrenia in children has been discussed for many years. In the DSM-II, the category of childhood schizophrenia referred to both psychotic and autistic disorders; however, the eminent studies by Kolvin et al. [28] made clear that schizophrenia in children had to be differentiated from autistic disorders. Since the appearance of the DSM-III, children with schizophrenia have been diagnosed with the same criteria as adults [23,29-31]. Both the stability and reliability of the diagnosis of EOS [31-35] as well as the validity of the diagnosis in children and adolescents are firmly established [1,36-39].

In 2005, more than 800 studies focused on the outcome of schizophrenia, irrespective of age at onset [40]; however, the majority looked at adult onset. Most studies on outcome of EOS have been restricted to small samples and/or short follow-up periods. The results are inconclusive across studies with some showing a prognosis resembling that of AOS but most reporting poorer prognosis [21,23,34,38,41]; only a few studies do not concur with this trend [42-44].

One of the more recent cohorts was studied at the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne, Australia [45]. This cohort contained patients with mixed early and adult onset psychosis. At a rather short mean follow-up of 18 months, the study found no significant difference between early and adult onset on outcome variables related to remission. In a more recent analysis, the follow-up period in the EOS subsample was extended to a mean of 6.9 years; the authors claimed that there was a better outcome in the EOS group compared to the adult onset group [42].

It has been suggested that differences in outcome across studies may be more to the degree of disability than in the rate of recovery [30]. Generally, there is agreement that the course of schizophrenia is rather heterogeneous among both adults and children [41,46,47]. Various predictors of outcome have been studied with no clear picture emerging due to a lack of replication studies. However, there is evidence that the diagnosis of VEOS predicts lower educational achievement, less independence both economically and emotionally, lower rates of employment, poor social relationships, and a continuing need of psychiatric care [21].

The current systematic review is focused on the analysis of the entire existing literature on the long-term outcome of EOS published since 1980 in English-

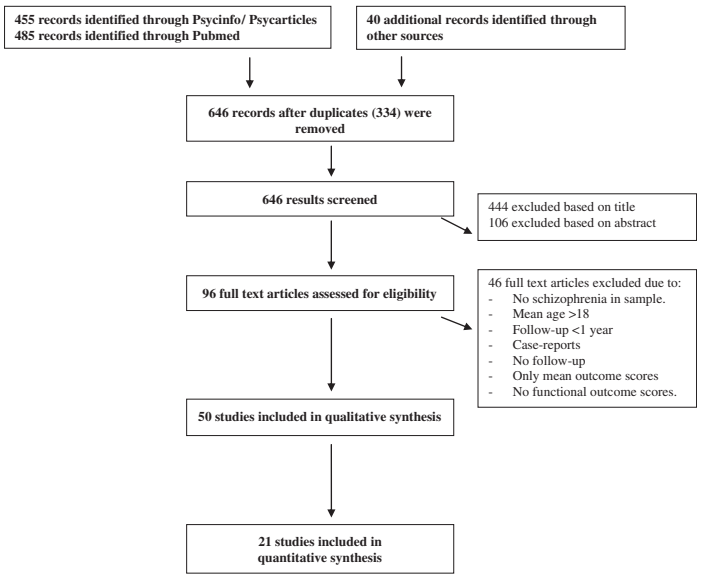

Figure 1 Flowchart of the literature search.

language journals. We have chosen not to include studies published before 1980 because, regardless of their scientific validity at the time, they focused primarily on symptoms, they did not report on functional outcome in a standardized way, and they did not express shortcomings in terms of the studies' participants. In addition to detailed descriptions, the current analysis is based on inferential statistical tests of aggregated data across studies in order to study both effects and prognostic factors. The report was written in accordance with the guidelines of the PRISMA statement [48].

Methods

Identification of studies

The literature search was carried out using the following databases: PsycINFO, Pubmed, and PSYCarticles. A search in Psycinfo and PSYCarticles for English-language articles published since 1980 using the criteria "AB = adolescent onset schizophrenia," OR "childhood onset schizophrenia," OR "very early onset schizophrenia," OR "early onset schizophrenia" yielded 455 results. A search of publication titles and abstracts in PubMed based on the same terms and limitations yielded a total of 485 articles; 96 articles were chosen for further inspection. In addition, studies mentioned in previous review articles were also considered. The process of the literature search is shown in Figure 1.

Due to the interest in performing quantitative analyses based on inferential statistical tests, the following exclusion criteria were used: single case studies, studies reporting only on single or specific parameters (e.g., IQ or mortality) but no overall broad outcome measures allowing a classification into "good," "moderate," or "poor" outcome (see below), studies only reporting on mean outcome parameters, studies not based on internationally accepted diagnostic criteria (as reflected in the ICD and the DSM), studies with follow-up time <1 year, and studies with poor description of outcome criteria (e.g., no global functioning scores). In the case of duplicate publishing, data from the sample were included only once in the data set with the study that included the latest selected assessment. The analysis included both retrospective and prospective studies.

A mean age of ≤18 years was required. The majority of the studies only included patients aged <18 years with just a few studies also including 18 year olds [5,11,49,50], one study including patients aged 19 years [6], and one study [32] including a few patients aged 20 years at the time of onset; however the latter study was included because of a mean age at onset of 16.8 years. Studies reporting data on pure EOS and studies reporting combined data on EOS and other psychotic illnesses (MIX) were included in the analyses.

A total number of 21 studies were suitable for analysis [1,5,6,8,11,15,18,23,29,32,38-41,49-55].

Outcome measures and effect variables

All data was collected from published material only. The studies were categorized as reporting outcome by use of either a General Functioning Scale (GFS, including Global Assessment of Functioning (GAF, [56])), Children`s Global Assessment Scale (CGAS, [57]), and Global Assessment Scale (GAS, [58]) or Study-Specific Functioning (SSF) outcomes. All GFS studies used scales running from 0 to 100. A total of 10 studies used GFS scales [5,23,32,39,40,50-53,55]. The GFS studies were categorized as a "poor" outcome (score ≤ 50), "moderate" outcome (score 51–70), or "good" outcome (score >70). Out of these ten studies, five had deviating definitions of the three outcome categories. As described in Table 1, four studies used other cut-offs for "poor," "moderate," and "good" [5,23,40,52]. One study [51] even divided the more generally used class of "poor" outcome into deteriorated (< 30) and minimal improvement (30–50). These two groups were combined into "poor" outcome (< 50), whereas all other deviating ratings were taken directly into the analysis.

The SSF outcomes were also rated as "poor," "moderate," or "good" depending on the outcome as defined in these studies and shown in Table 1. In two studies [6,29] ratings were based on outcome scales, whereas the ratings in the remaining nine studies [1,8,11,15,18,38,41,49,54] were based on categorical outcome measures. Based on the above-mentioned three categories of outcome and using the same cut-off scores, the three authors of the current study performed the ratings independently in each study. There was full consensus among the three authors in the independent ratings of 19 studies, and after two authors agreed in the remaining two studies, full consensus was also reached for these remaining two ratings.

Dropout rates were comprehensively described in 17 studies and ranged from a minimum of 0% [6,23,55] to a maximum of 59% [15]. Reasons for dropout included untraceable subjects, subjects refusing to participate, death, moving out of the area, and suicide. One study, however, included suicide as a measure of outcome [50], but since most studies did not do so, suicides were subtracted from the data in this particular case in order to have consistent criteria for all ratings.

A total of five predicting variables were considered in the analyses as to their effect on the outcome measures: drop-out rate, type of measures of functioning, duration of follow-up, sex, and time period when patients had been diagnosed. Duration of follow-up was grouped into 1–10 and >10 years. The cut-off was chosen to obtain comparable sample sizes. If the duration of follow-up did not fit into one of these two outcome groups due to varying

Table 1 Overview of the 21 Studies

Authors	Diagnosis	Period of Diagnosis	N	Dropout N (%)	Age at onset (yrs.)	Sex		Duration of follow-up (yrs.)	Outcome criteria	Original outcome ratings	Outcome (%)		
						Female N (%)	Male N (%)				Good	Moderate	Poor
Hassan et.al (2011)	SZ, psychosis NOS	2003-2010	37	14 (27)	Mean = 12.2	23 (62)	14 (38)	Mean =3.2	CGAS: Good: ≥ 70 Moderate 40-70 Poor: ≤ 40 and partial or no remission.		27.0	48.7	24.3
Ledda et al. (2009)	SZ	1992-2002	15	2 (12)	Mean = 15.1	9 (53)*	8 (47)*	5	GAF*		11.8	60.0	27.6
Reichert et al. (2008)	SZ & SZ-AFF	1990-2000	27	59 (80)	Mean = 15.5	8 (30)	19 (70)	Mean = 13.4	Employment	3,7% university study 18,6% regular work 48,1 sheltered work 25,9% unable to work 3,7% unemployed	22.2	51.8	25.9
Remschmidt et al. (2007)	SZ	1920-1961	38	0 (0)	5-14	23 (61)	15 (39)	Mean = 42	GAS: Good >71 Moderate: 41-70 Poor: <40		5.8	23.7	60.5
Fleischhaker et al. (2005)	SZ	1983-1988	81	20 (20)	11-18	36 (44)	45 (56)	4-11	GAF: Poor: <40 Moderate: 41-70 Good >71		19.80	38.20	42.00
Helgeland et al. (2005)	SZ	1963-1978	9	N.A	13-17	1 (11)	8 (89)	Mean = 28,1	Social disability (medication, means of income, living situation)	All on antipsychotic medication at follow-up, all on disablement benefits, none living in an ordinary home	0,00	0.0	100.00
Röpcke et al. (2005)	SZ, SZ-AFF, schizo-phreni-form disorder	1979-1988	39	16 (29)	Mean = 16	19 (49)	20 (51)	10.2-21.2	GAS: Good >60 Moderate: 51-60 Poor: <51		21.00	28.00	51.00
Jarbin (2003a)	SZ	1982-1993	30	58 (66)	11.8 - 18.7	11 (37)	19 (63)	5.1-18.2	GAF (or employment if GAF not available)	79% very poor 18% poor 3% good	3.00	0.00	97.00

Table 1 Overview of the 21 Studies *(Continued)*

Hollis, (2000b)	SZ	1973-1991	51	17 (25)	Mean = 14.0	22 (43)	29 (57)	4-22	Remission at follow-up		12.00	40.00	48.00
Lay et al. (2000)	SZ & SZ-AFF (ICD-9)	1976-1987	65	31 (32)	11,5-17,9	38 (59)	27 (41)	10	Social disability (DAS-scale and global evaluation on a 6-points scale)	12,5% no dysfunction, 7,8% minimum, 14,1% obvious, 29,7% serious, 31,3% very serious, 4,7% maximum dysfunction	20.00	44.00	36.00
McClellan et al. (1999)	SZ		11	7 (39)	11-16	3 (27)	8 (73)	2	Course of illness and description of impairment		0.0	9.00	91.00
Aarkrog (1999)	SZ, SZ-AFF	1968-1976	28	N.A.	12-20 (M = 16.8)	7 (25)	21 (75)	17-26	GAS		3.6	17.9	78.5
Eggers et al. (1997)	SZ (DSM-III-R)	1925-1961	44	27 (38)	6-14	25 (57)	19 (43)	Mean = 42	Social disability (Eggers social scale)	1-2: Good remission GAS >70 3-4: Moderate remission < GAS 51 5-6: Poor remission - < GAS 40	25.00	25.00	50.00
Maziade et al. (1996)	SZ (DSM-III-R)	1968-1990	40	37 (48)	10-17	13 (33)	28 (67)	14.8	GAS		5.00	15.00	80.00
Werry et al. (1994)	SZ, Schizo-phreni-form disorder	1968-1990	53	41 (36)	7-17	22 (42)	31 (58)	4.3	Living situation		20.7	17.00	62.30
Rund 1994	SZ (ICD-9)	1980-1990	24	0 (0)	13,1-17,9 (Mean = 16)	8 (33)	16 (67)	2	GAS		0	21.0	79.0
Cawthron et al., 1994	SZ (ICD-9)	1975-1986	9	10 (53)	14-18	-	-	2-13	Adult Personality Functioning Assessment	Seven (78%) continuously ill. None of these employed or married; extremely poor social functioning. The two recovered patients (22%) were ill for only 2% of the follow-up period.	22.00	0.00	78.00

Table 1 Overview of the 21 Studies *(Continued)*

Asarnow et al. (1994)	SZ	1980-?	18	3 (14)	6-11,3	5 (24)	13 (76)	2-7	CGAS >60 = good 51-60 = moderate <51 = poor	28% good outcome CGAS >60, 28% moderate improvement CGAS 51–60, 28% minimal improvement CGAS <51, 17% deteriorating CGAS <41	28.00	28.00	44.00
Gillberg et al. (1993)	SZ (DSM-III / ICD 9)	Born 1960–1982.	23	0 (0)	13-19	9 (39)	14 (61)	11-17	Overall register data outcome	13% overall possibly good 9% intermediate outcome 78% extremely poor	13.00	9.00	78.00
Krausz et al. (1993)	SZ, mood disorders, psychoses (PSE)	1972-1978	55	6 (10)	14-18	28 (51)	27 (49)	11-16	Mental and social handicaps rated according to Brown (1966),	20% inpatient, 26% seriously handicapped 16% handicapped but employed 26% not handicapped 12% no findings	29.6	18.5	51.9
Inoue et al. (1986)	EOS and acute psychotic episode (DSM-III)	1971-1981	19	N.A.	10-17	9 (47)	10 (53)	3	Ability to work	47% unable to work 16% limited work ability 21% working at a lower level than previously, 16% working as before	16.00	37.00	47.00

If not otherwise specified: GAF: Global Assessment of Functioning >70 = Good; 70-51 = Moderate; <51 = poor. SZ: Schizophrenia. SZ-AFF: Schizoaffective disorder. CGAS: Children Global Assesment of Functioning Scale. GAS: Global Assessment Scale. N.A. = Not assessed. PSE = Present State Examination. *Based on N at baseline.

Table 2 Outcome by diagnoses based on 21 studies (N = 716)

Outcome variable	Percentages of subjects by diagnosis										Analysis			
	EOS				Mixed									
	Mean	SD	Range	Median	Mean Rank	Mean	SD	Range	Median	Mean Rank	U	z	p	rho
	N = 422				N = 294									
Good	15.4	7.7	0-28	15.8	300.05	19.6	9.1	0-29	21.0	442.40	37368	−9.08	<.001	0.34
Moderate	24.5	14.6	0-60	23.7	299.75	33.6	12.9	18-52	37.0	442.83	37241	−9.13	<.001	0.34
Poor	60.1	18.9	27-100	60.5	410.59	46.8	17.8	24-79	47.0	283.73	40051	−8.09	<.001	0.30

length of follow-up within the sample, the mean duration was used for classifying the study [5,38,49,51].

In one study, there was no information on sex distribution [49], and only a minority of studies reported outcomes stratified for sex [1,11,41,52]. Multiple studies noted sex differences without reporting stratified data. Time period of diagnosis considered studies including patients diagnosed before and after 1970 (<1970+) [1,6,18,23,29,32,49] and studies with all patients diagnosed in 1970 and later (≥1970) [5,8,11,15,34,36,38,40,41,52,53,55].

Finally, diagnoses were considered by dividing the data-set into studies containing only patients with EOS and studies including both patients with schizophrenia and patients with other psychotic disorders, i.e., psychosis (MIX).

Statistical analyses

The three categories of "good", "moderate", and "poor" were calculated in percentages and rounded to the nearest decimal. In order to take into account the large variation in sample sizes, weighted percentages were calculated by weighting each reported rate with the size of the study group. All analyses were based on adjusted sample sizes at follow-up assessments rather than actual sample sizes after patient recruitment.

Due to consistent and significant deviation of the data from the normal distribution, non-parametric tests were used in the analyses. The effects of the four predicting variables mentioned above on the three outcome measures were analyzed using the Mann Whitney test with Bonferroni adjustments of p-values correcting for multiple testing. Considering five tests, findings were significant at the $p = 0.01$ level and highly significant at $p = 0.002$. In addition, effect sizes were calculated using the formula of $rho = z/\sqrt{N}$), where 0.1 is indicating a small effect, 0.3 a moderate effect, and 0.5 a large effect. Data analyses were performed by use of the SPSS 20 (SPSS, Chicago).

Results

Study characteristics

The current review is based on 21 studies containing 716 patients at follow-up. Detailed information on study characteristics and outcome findings is provided in Table 1. The sample sizes ranged from 9 to 81 patients with a mean group size of 44.4 (SD = 19.4). There were considerable differences in design, group size, methods, duration of follow-up, type of evaluation, and missing data. Diagnostic classification changed considerably over the period in which the studies were conducted given the fact that patients had been diagnosed over a wide time period ranging from 1920 to 2010. Since the 1990s, there has been an increasing reliance on DSM-IV and ICD-10 criteria. In 16 studies consisting of 592 patients, the mean age at onset was 14.9 (SD = 1.6) years; five studies reported only age ranges [6,8,11,49,51].

The mean duration of follow-up varied between 1.5 and 42.0 years (mean = 14.4; SD = 11.4). In 20 studies based on 707 patients, a total of 394 males (56.5%) were included. Repeated follow-up assessments were based on six samples and findings were described in nine articles [8,11,29,35,41,53,54,59,60]. Unfortunately, the data from these studies are not suited for repeated measurement analysis because both the sample sizes between follow-up periods (except [11]) and the duration of follow-up differed considerably. The total group of studies (N = 21) was divided into a group of EOS studies (N = 422) and a group of MIX studies (N = 294).

Table 3 Outcome by attrition rate based on 18 studies (N = 660)

Outcome variable	Percentages of subjects by dropout rate								Analysis			
	Low dropout (<28%)				High dropout (>28%)							
	Mean	SD	Median	Mean Rank	Mean	SD	Median	Mean Rank	U	z	p	rho
	N = 342				N = 318							
Good	18.8	8.2	19.8	324.72	17.0	8.0	20.7	340.77	52400.000	−1.081	n.s.	0.04
Moderate	32.0	12.8	38.2	370.67	25.2	15.6	25.0	291.96	42007.500	−5.301	<.001	0.21
Poor	49.1	15.3	48.0	293.44	57.7	21.3	51.0	373.99	41703.500	−5.423	<.001	0.21

Table 4 Outcome by measures of functioning based on 21 studies (N = 716)

Outcome variable	Percentages of subjects by measures of functioning											
	GFS				SSF				Analysis			
	Mean	SD	Median	Mean Rank	Mean	SD	Median	Mean Rank	U	z	p	rho
EOS	**N = 222**				**N = 200**							
Good	14.3	7.8	15.8	185.75	16.6	7.5	20.7	240.07	16486	−4.60	<.001	0.22
Moderate	27.0	12.8	28.0	220.02	21.7	12.8	17.0	202.05	20309	−1.52	n.s.	0.07
Poor	58.7	15.3	44.0	186.00	61.7	15.3	62.3	239.80	16540	−4.56	<.001	0.22
MIX	**N = 128**				**N = 166**							
Good	15.0	11.1	21.0	122.18	23.1	0.4	20.0	167.02	7383	−4.54	<.001	0.22
Moderate	30.5	12.1	28.0	131.75	36.0	1.0	44.0	159.64	8606	−2.82	.005	0.14
Poor	54.5	22.6	51.0	165.75	40.9	0.7	30.0	133.42	8287	−3.27	.001	0.16

In addition to the various descriptive parameters, Table 1 contains columns reporting the outcome criteria used in the various studies, the original outcome ratings, and the outcome (in%) divided into the three categories of "good," "moderate," and "poor," as calculated and rated by the us, which we based on the data in the preceding column containing the original outcome ratings.

Outcome in samples of pure EOS vs. mixed psychotic disorders

As shown in Table 2, studies only containing EOS patients came up with a rate of 15.4% with a "good" outcome, whereas 24.5% experienced a "moderate" outcome, and 60.1% experienced a "poor" outcome. In the MIX samples, the figures were 19.6% with "good" outcome, whereas 33.6% experienced a "moderate" outcome, and 46.8% experienced a "poor" outcome. In each outcome category, though, the variation across studies proved to be remarkably high.

There were significant differences in outcome between the EOS and the MIX samples. A significantly greater proportion of the MIX samples experienced a "good" or "moderate" outcome compared to the pure EOS samples. Consequently, the percentage of patients with a poor outcome was smaller in the MIX samples than in the EOS samples. All effect sizes were moderate.

Effects of drop-out rates in the samples

Dropout rates in 17 studies ranged between a minimum of 0% and a maximum of 59%. This distribution was dichotomized at the median, and studies were classified as having a high (>28%) or a low (<28%) dropout rate. The effect of the attrition on the three outcome parameters was assessed by Mann Whitney tests and showed highly significant differences in the "moderate" and "poor" outcome groups but not in the "good" outcome groups (see Table 3). The rate of "moderate" outcomes was significantly higher in the low attrition samples compared to the high attrition samples, whereas the opposite was the case in the "poor" outcome group with a higher rate of poor outcomes in the high attrition samples; however, the effect sizes were small. In contrast, the three studies with a dropout rate of 0% all experienced high numbers of "poor" outcome [6,23,55], ranging from 60.5% to 79%.

Table 5 Outcome by duration of follow-up based on 21 studies (N = 716)

Outcome variable	Percentages of subjects by duration of follow-up											
	<10 yrs				>10 yrs				Analysis			
	Mean	SD	Median	Mean Rank	Mean	SD	Median	Mean Rank	U	z	p	rho
EOS	**N = 187**				**N = 235**							
Good	19.2	5.9	19.8	269.28	12.4	7.6	12.0	165.52	11167.5	−8.74	<.001	0.43
Moderate	29.4	14.8	38.2	243.08	20.6	13.3	23.7	186.37	16067.0	−4.78	<.001	0.23
Poor	51.4	15.8	42.0	150.18	67.0	18.4	60.5	260.30	10505.5	−9.28	<.001	0.45
MIX	**N = 80**				**N = 214**							
Good	16.4	11.6	16.0	120.69	20.8	7.7	21.0	157.51	6415.0	−3.35	.001	0.20
Moderate	37.5	11.7	37.0	180.86	32.1	13.0	28.0	135.03	5891.0	−4.16	<.001	0.24
Poor	46.1	23.5	47.0	126.55	47.1	15.3	51.0	155.33	6884.0	−2.61	.009	0.15

Table 6 Outcome by sex based on 5 studies (N = 190)

Outcome variable	Percentages of subjects by sex											
	Males				Females				Analysis			
	Mean	SD	Median	Mean Rank	Mean	SD	Median	Mean Rank	U	z	p	rho
	N = 92				N = 98							
Good	17.6	10.6	24.0	82.41	23.2	11.7	30.4	107.79	3304.0	−3.22	<.001	0.23
Moderate	23.2	19.3	25.0	68.80	37.3	37.3	46.0	120.56	2052.0	−6.56	<.001	0.48
Poor	59.2	23.2	74.0	107.78	39.5	39.5	36.0	83.97	3378.	−3.03	.002	0.22

Effects of the measures of functioning

In order to assess the effect of measures of functioning, studies based on GFS were compared to those using SSF measures. As shown in Table 4, there were highly significant differences in the outcomes based on these two measures of functioning in the "good" and "poor" outcome groups of the EOS samples and the MIX samples. In the latter sample, the outcome also differed significantly for the "moderate" outcome group. In the EOS samples, there were lower rates of "good" and "poor" outcomes in studies based on GFS compared to SSF outcomes. This was also true for the "moderate" outcome groups of the MIX samples. The effect sizes were small for all comparisons. In the 5 studies reporting a mean GFS in EOS patients at follow up based on a total of 199 patients [5,39,50,51,53], the grand mean weighted for sample sizes of these studies was 47.0.

Effects of duration of follow-up

Findings that deal with the effect of duration of follow-up are presented in Table 5. In the EOS samples, the effect was highly significant for all three outcome groups. Moreover, there was a moderate effect size indicating that follow-up longer than 10 years was associated with a smaller proportion of patients with a "good" and "moderate" outcome and a larger proportion of patients with a "poor" outcome. In the MIX samples, differences for "good" and "moderate" outcomes were highly significant, and differences were significant for poor outcomes; however, the effect sizes were small. In these samples, the rate of both "good" and "poor" outcomes was increasing with longer follow-up periods, whereas the rate of "moderate" outcome was declining.

Sex effects

Direct calculations could only be made on the basis of five studies reporting separate results for males and females (4 with MIX and 1 with EOS patients). As Table 6 shows, highly significant differences were found for "good," "moderate," and "poor" outcome. These results indicate a generally less favourable outcome for males who less frequently than females experienced a "good" or "moderate" outcome and more frequently experienced a "poor" outcome. The effect sizes were small to moderate.

To further investigate the effect of sex in a larger sample, we compared 6 studies with <50% males to 14 studies with >50% males; findings are shown in Table 7. Differences were significant to highly significant on the various levels of outcome. There is a clear indication that both EOS and MIX studies containing a majority of males generally experienced a less favourable outcome. The proportion of "good" and "moderate" outcomes was lower in studies based on a male predominance, whereas the proportion was higher in the "poor" outcome groups.

Effects of time period of diagnosis

The data-set allowed a dichotomization into two groups of studies, namely, those including patients diagnosed

Table 7 Outcome by sex proportions based on 20 studies (N = 707)

Outcome variable	Percentages of subjects											
	<50% males				>50% males				Analysis			
	Mean	SD	Median	Mean Rank	Mean	SD	Median	Mean Rank	U	z	p	rho
EOS	N = 97				N = 316							
Good	19.4	5.3	15.8	262.34	13.9	7.9	13.0	190.01	9958	−5.26	<.001	0.26
Moderate	29.9	12.9	25.0	238.20	23.6	14.4	17.0	197.42	12300	−2.97	.003	0.15
Poor	50.7	11.0	50.0	175.80	62.5	19.9	62.3	216.58	12300	−2.96	.003	0.15
MIX	N = 157				N = 137							
Good	25.0	4.3	27.0	188.68	13.3	9.2	16.0	100.31	4290	−8.99	<.001	0.52
Moderate	36.1	13.1	44.0	160.27	30.7	12.1	28.0	132.86	8749	−2.79	.005	0.16
Poor	38.9	10.7	36.0	119.96	56.0	19.9	51.0	179.07	6340	−6.02	<.001	0.35

before and after 1970 and those where all patients in the sample were diagnosed in 1970 or later. Table 8 provides a comparison of the outcome of these two groups. In the EOS samples, there is a highly significant decline of "good" outcomes in all patients diagnosed in or after 1970; however, the effect is only small. In contrast, there are large effects indicating that the proportion of "moderate" outcomes increased significantly, and the proportion of "poor" outcomes decreased significantly over time. Taking all three levels into account, the overall outcome improved significantly over time.

There was only one MIX study containing patients diagnosed before 1970. On the other hand, there were clear moderate time period effects indicating highly significant improvements with increasing proportions of "good" and "moderate" outcomes and decreasing proportions of "poor" outcomes.

Discussion

This is the first systematic review on the outcome of EOS that is covering all suitable studies published in the English-language literature since 1980. The analyses were based on statistical tests measuring both the general outcome and the effects of clearly defined predictors. The review focuses on general trends; one has to consider that the studies report rather diverse findings, though in part, this diversity may be explained by the pronounced heterogeneity of the schizophrenia syndrome itself [61,62]. Furthermore, the distributions of the main outcome variables of "good," "moderate," and "poor" differ depending on the measurements and definitions used in the various studies.

The main findings are the following: (a) the outcome for EOS is relatively poor and less favourable than in MIX samples; (b) samples with high dropout rates report less "moderate" and more "poor" outcomes, even though the effect sizes are small; (c) the effect sizes of measures of functioning are also small, which can be attributed to the fact that in EOS samples global measures of functioning are associated with less "good" and "poor" outcomes than specific measures of functioning; however, in the MIX samples, specific measures of functioning are associated with better outcomes on all three levels; (d) in EOS, the effect of duration of follow-up shows less favourable outcomes after more than 10 years of follow-up, whereas in MIX samples, the longer follow-up is associated with more "good," less "moderate," and more "poor" outcomes; (e) the outcome in both EOS and MIX samples is less favourable in males; and (f) the outcome is better in patients who had been diagnosed in more recent decades. In the subsequent paragraphs, these major findings will be put into perspective.

General outcome

In the current review, we discovered that 15.4% of EOS patients experienced a "good" outcome, 24.5% experienced a "moderate" outcome, and 60.1% experienced a "poor" outcome. Clearly, these findings indicate that EOS is still a mental illness with a rather unfavourable prognosis; this conclusion is in accordance with previous reviews [5,7,12,21,31,63,64]. On the other hand, these previous reviews were based on non-aggregated data, and they did not employ rigorous data analyses as the authors do in the current review.

Furthermore, from the current analyses, it became evident that studies of patients with EOS show a worse prognosis than studies containing both patients with EOS and patients with other psychotic disorders (MIX). Unfortunately, separate analyses of the outcome of the various psychotic disorders were not feasible. In addition, differences in time points of measurement in the two samples may have been operant. Nevertheless, the different outcome in the two groups may serve as some indirect evidence that other psychotic disorders, i.e., schizoaffective disorders, schizophreniform or bipolar disorders with psychotic features, take a less serious

Table 8 Outcome by time period of diagnosis (N = 705)

Outcome variable	Percentages of subjects by period of diagnosis											
	<1970+				≥1970				Analysis			
	Mean	SD	Median	Mean Rank	Mean	SD	Median	Mean Rank	U	z	p	rho
EOS	**N = 216**				**N = 195**							
Good	16.2	7.6	15.8	228.03	15.8	7.1	19.8	181.60	16302.0	−3.987	<0.001	0.19
Moderate	17.2	7.3	17.0	137.25	24.9	15.8	38.2	282.15	6210.0	−12.452	<0.001	0.61
Poor	66.6	12.9	62.3	274.75	59.3	20.3	44.0	129.85	6210.0	−12.447	<0.001	0.61
MIX	**N = 28**				**N = 266**							
Good	3.6	0.0	3.6	38.50	19.6	7.9	21.0	158.97	672.0	−7.220	<0.001	0.42
Moderate	17.9	0.0	17.9	14.50	33.6	12.5	37.0	161.50	.0	−8.810	<0.001	0.51
Poor	78.5	0.0	78.5	256.50	46.8	15.3	47.0	133.03	672.0	−7.220	<0.001	0.42

Note: <1970+: studies including patients diagnosed before and after 1970.
≥1970: Studies containing patients diagnosed in 1970 and later.

course in terms of chronicity and functioning because all analyses based on the mixed psychotic samples showed a less severe outcome than the pure EOS samples. This finding is in accordance with similar studies in adults [2,65].

When considering the impact of dropout rates, the general findings on outcome may be only slightly different than one would expect without any attrition in the samples. In samples with high attrition rates, patients with a "moderate" course of the disorder were less likely to be followed up, and those with a "poor" outcome were more likely to show up at follow-up assessments at the various sites, whereas there was no attrition effect on the rate of "good" outcomes. In contrast, it is unclear whether the rate of "poor" outcomes would be different. On the one hand, our analyses showed that the rate of "poor" outcomes declined significantly with low attrition rates. On the other hand, three studies without any attrition showed an increased rate of "poor" outcomes. However, one has to keep in mind that the effect sizes for attrition were only small. High dropout rates are very common in psychiatric services with estimated rates ranging from 20 to 60% [66], which proves to be in line with the findings in the current review with dropout rates between 0 and 59% and a median of 29%.

Impact of age at onset

In contrast to EOS, the outcome in studies of adult patients is generally more favourable [5]. Hegarty et al. [67] reviewed 320 adult studies from 1895 to 1992 (more than 50,000 patients in total) and found that approximately 40% improved considerably during follow-up. Jobe & Harrow [2] reviewed nine North American studies and the WHO-coordinated International Study of Schizophrenia (ISoS), all with a follow-up period of 10 years or longer, and concluded that, although adult patients with schizophrenia as a group have a worse outcome than other psychiatric patients, only a few patients show a progressive deteriorating course; depending on the strictness of the criteria used for diagnosis, 21-57% experience a "good" outcome. The ISoS compared long-term follow-up studies (10–15 years) from 14 culturally diversely treated incidence cohorts and four prevalence cohorts, totaling 1633 subjects, and found that approximately 50% experience a "good" outcome [65].

A recent international study that examined outcome after three years of follow-up in adult outpatient schizophrenia (N = 11.078 from 37 countries) found that 66% achieved clinical remission measured with the CGI, whereas only 25.4% achieved functional remission defined as good social functioning for 6 months in terms of occupational/vocational status, independent living and active social interactions [68]. There were large regional differences in the study. Patients in Europe were less likely to achieve clinical remission but were doing better in regards to functional remission. The general outcome both in the EOS group and the mixed psychotic group in the current review clearly shows that schizophrenia and psychosis originating in childhood and adolescence on average follows a worse course than AOS. In comparison to other disorders originating in childhood or adolescence, EOS stands out by way of its particularly poor course. For instance, the outcome seen with eating disorders is much better as is shown by similar types of analyses by the senior author [69,70].

This conclusion is also supported by a recent large cohort study from Israel with 12.071 participants. This study found that earlier onset corresponds linearly with the severity of the course of the disorder and appears to have some prognostic impact [71]. Young age at onset might have a detrimental effect on outcome because of impact at very crucial times of development and neurobiological maturation in childhood and adolescence, which prove to have more lasting effects in terms of both cognitive and psychosocial impairments [1,32,35,72].

So far, unfortunately, there are only a small number of outcome studies based on VEOS patients only, with an over-representation of females, whereas there are more studies with a varying range of age at onset within the defined EOS age range. Furthermore, there is not a single study based exclusively on patients with adolescent onset schizophrenia; thus, there are no real solid data for a comparison of the outcome of VEOS. Clearly, more detailed analyses will be needed. Given the low prevalence rates of VEOS, only collaborative studies across several sites could arrive at sample sizes needed for a differential look at the effects of age, sex, clinical features, or treatment effects on the outcome of VEOS.

The impact of the measures of functioning

The current study is the first to make use of analyzing the impact of specific measures of functioning. Not surprisingly, the advent of global measures of functioning since the seventies also had an effect on the studies of the outcome of EOS. In contrast, a few studies continued with an older tradition to define study-specific functioning outcomes. Thus, a comparison of these two different traditions became possible. In the pure EOS studies, there were relatively small effect sizes, indicating that studies based on the more recent GFS arrived at slightly lower rates of both "good" and "poor" outcomes and no differentiation in the "moderate" outcomes than studies based on SSF outcomes. Accordingly, in EOS the overall pattern is clearly not more favourable for one of these two types of outcome. In the MIX studies, the effects were also small though more clearly showing a general pattern of less favourable outcomes based on GFS rather than on SSF assessments. Thus, the two

analyses point to different findings in the two types of studies. In other words, the heterogeneity of the MIX samples favour the SFS outcomes in which the measurement might have tipped closer to the differences in the diagnostic composition of the samples.

However, this interpretation is only an assumption that needs further examination. Particularly, both the validity and the reliability of these measures need to be studied in greater detail. So far, this has been tested only in parts for some of the GFS measures in general child and adolescent psychiatry patients [73] but not specifically in patients suffering from schizophrenia. In particular, the GAF confounds symptoms and functioning with lower ratings driven by symptoms, so someone who is symptomatic but functional will receive a misleadingly low rating.

The impact of intervention

In general, there is very little information on the impact of intervention on the outcome in EOS, even though all patient samples were seen clinically and received treatment. With the exception of a single study [72], all studies provided treatment as usual. In a recent intervention study with follow-up based on the Australian Early Psychosis Prevention and Intervention Centre (EPPIC) study, the authors found an increase in GAF score with a mean GAF score of 64 at follow-up [42]. By comparison, Oie et al. [74] found a mean GAS score of 47.7 in their EOS group containing 15 patients assessed when they were clinically stable on antipsychotic medication and followed up for 13 years. Moreover, Kao et al. [75] found a mean GAF score of 47 in 19 EOS patients after 1 year follow-up, and Gochman et al. [76] found a mean CGAS score of 43.6 after at least 8 years of follow-up. In the single intervention study included in the current review, the mean GAF score was 35 in the intervention group and 24 in the control group [55]. Only Ledda et al. [53] found a mean CGAS score of 62.1, which is quite comparable to the finding of the EPPIC study [42].

Nevertheless, in the latter study [42], the attrition rate was large (22/63) in the total EOS group and well explained only in a single person who committed suicide. It is unclear whether the 21 other patients that were not followed-up represent a subgroup with less favourable outcome because the authors did not provide a thorough attrition analysis. Thus, the claim of the authors that their outcome findings are superior to previous outcomes is not yet substantiated.

The impact of duration of follow-up

The current analyses revealed, with small to moderate effect sizes, that across the three levels, the outcome deteriorated with longer follow-up periods (>10 years) in the EOS samples, but the association was rather curvilinear in the MIX samples with both "good" and "poor" outcomes increasing at the expense of "moderate" outcomes with longer follow-up periods. These differences again point to the already noted different course of the other psychoses, apart from schizophrenia. Nevertheless, the present findings need to be interpreted with caution because the two follow-up periods of ≤10 and >10 years are rather broad and reflect limitations of the data not allowing a more fine-grained analysis. Furthermore, the analysis was based on a series of cross-sectional rather than longitudinal studies. Unfortunately, among the 21 outcome studies of the present analysis, there are only six samples that were assessed repeatedly for follow-up and were described in 9 articles [8,11,29,35,41,53,54,59,60]. The study by Krausz and Müller-Thomsen [11] showed an increase in the proportion of "good" outcome from the first follow-up at 5 years to the second follow-up at 11 years (19 to 31%), whereas the rate of "poor" outcomes declined (74 to 59%) with a rather constant proportion of "moderate" outcomes (7 to 10%). These findings are in contrast to the findings of the current review. Lay et al. [41]) studied a mixed psychotic group that had been previously followed-up [35]. Unfortunately, approximately one third of the group had dropped out in between the two assessments, so it is unclear whether or not the slight shift from "moderate" to "poor" outcome (from 32 to 36%) is a valid finding. None of these longitudinal studies made use of inferential statistical tests of any significant change of the course of the disorder over time.

The impact of sex

The current review supports the notion that male sex carries a less favourable prognosis in EOS but also in MIX samples. Nevertheless, as described in the methods section, there were profound limitations in the data for a proper analysis of sex effects. With a few exceptions [1,11,41,52,55], the vast majority of studies did not stratify outcome by sex; thus, two rather restricted types of analyses had to be performed. The direct comparisons of a small subsample suitable for direct comparisons clearly favoured females in terms of having a better outcome. The supplementary analysis based on a larger sample compared the outcomes of samples with either less or more than half of the samples being comprised of males. The findings were in line with the previous results indicating that male sex is a negative prognostic factor.

When looking at the various studies considered in the current review, one may see that some studies reported a tendency for worse outcome for males [1,5,6,8,11,15], but only two of these provided statistically significant differences [5,8]. One study found a specific "poor" outcome in females which proved to be not statistically

significant [49]. In contrast, most of the 20 studies either reported no prognostic impact of sex [39,40] or did not specify or mention sex in relation to outcome measures [18,23,29,32,38,41,51,53,54]. One study noted that the risk of suicide was increased about 30 times in males [50].

In the 21 studies listing the distribution of sex, the average proportion of males was only 55%, a surprising discovery given that schizophrenia usually has an earlier onset among males than among females [17] and that late onset after age 45 is more common among females [24]. Especially with regard to VEOS onset, the literature points to a male predominance [12] with a ratio of approximately 2–2.5:1 [17,24,64]; however, in the two studies of VEOS, female sex was dominant in both series of patients [23,29]. In conclusion, there is some indication of a potential sex bias in the outcome studies in terms of containing more females than expected. Potential explanations include a higher dropout rate of males from outcome assessments due to less compliance and/or a higher mortality rate.

The impact of time period of diagnosis

The time span of the original diagnosis of the patients varied enormously between 1920 and 2010. During this period, major changes in the understanding of schizophrenia including the nosological classification, assessment, and intervention took place. Thus, our analysis took potential time period effects into account. The data-set was dichotomized into studies containing patients diagnosed before or after 1970 and patients all diagnosed in 1970 or later. This grouping was not ideal because it was still based on considerable heterogeneity in terms of the time when the patients were diagnosed. Nevertheless, it represented a feasible and pragmatic approach and reflected the fact that some major changes in the classification of schizophrenia both in the ICD and the DSM took place in the seventies.

The findings indicated that the overall outcome in EOS and even more clearly in MIX samples improved over time; thus, one may argue that the progress in treatment and rehabilitation of schizophrenia might have had a beneficial effect for those who were born and diagnosed later. In summary, one may also conclude that the overall relatively poor long-term outcome of EOS is, in part, due to the inclusion of studies containing patients who had been diagnosed many decades ago.

Limitations

First, we decided to include only studies published after 1980, assuming that these studies would reflect a rather common international frame of understanding of the nosology of schizophrenia and psychoses. Even with this restriction, though, there was a large time span over which patients had been diagnosed. Even more importantly, there may have been general problems with the recruitments of the samples. There might have been a bias both at the time of the first clinical presentation and of follow-up assessments. The less severely affected patients with a rapid remission of symptoms may not have been included at the beginning of the studies. Furthermore, it is not fully clear which effect no attrition might have had in particular on the rate of "poor" outcomes.

In the current review, we have used the categories of "good," "moderate," and "poor" outcome. These categories are commonly used in the outcome literature of various mental disorders. While the three authors of the current review showed excellent convergence in the outcome ratings of the various studies regarding this classification, one may argue that the cut-offs of these three outcome groups are debatable. Nevertheless, our cut-offs (>70 = good, 51–70 = moderate, and <50 = poor) imply some face validity because they are clearly demarcating major thresholds in functioning on GFS measures. Six GFS studies were based exactly on these definitions, whereas five studies used slightly different definitions. Two studies [40,51] used a lower cut-off of >60 rather than >70 for the definition of "good" outcomes, whereas three studies [5,23,52] requested a lower cut-off of <40 for "poor" outcomes. Thus, these differences imply a less strict definition of the outcome, so our findings might have been slightly better if we had accepted these definitions. Even among these five studies, though, there is no fully congruent set of definitions. Thus, our procedure was not only plausible in terms of the construction of the various GFS measures but also served as a good compromise considering the heterogeneity of definitions of "good," "moderate," and "poor" outcomes.

Some of the limitations in reviews of schizophrenia, as stated by Jobe & Harrow [2] and Castle and Morgan [77], are also relevant for the current analyses. The comparability of follow-up studies is compromised by differing criteria for diagnosis and outcome variables, sample selection (i.e., bias between inpatient and outpatient indexing), varying duration of follow-up, differences in the American and European tradition of diagnostic approaches, and prospective and retrospective designs leading to different preciseness of data acquisition. Furthermore, many studies have used different assessments for diagnosis and outcome. Various studies have lost patients due to suicide, which were counted as dropouts; however, one could argue that suicide in terms of outcome should be listed in the "poor" outcome group, as suggested by Jarbin [50].

Furthermore, the lack of any clear data on mortality rates in EOS and VEOS is a shortcoming of outcome studies that should be addressed in future studies. Since EOS and VEOS are very rare, patients often come from

a large geographic area to the specialist research units; thus, some patients travel far to be part of the study. This might be a bias in terms of only the most affected individuals will travel this far to be part of a study, which also indicates that the patients who have the best outcome might drop out.

Finally, no firm conclusions can be made thus far as to the effects of interventions, and it is unclear whether the large variation is due to different interventions, varying clinical manifestations, or an interaction of both. As with the study of other disorders, research on the effects of intervention on course and outcome is most neglected. Further studies are clearly needed.

Conclusions

This exhaustive analysis of the available evidence on the outcome of EOS and VEOS points to the still rather poor prognosis of early manifestations of schizophrenia. The outcome of schizophrenia is worse than for other psychotic disorders, which applies to both adult and early onset schizophrenia. In both AOS and in EOS, though, there are many individual differences and so the course and outcome of schizophrenia is rather heterogeneous. Further insight into the long-term course of EOS might result from refinements in the design of future studies. Most particularly, the course of the individual patient will ultimately profit from a better understanding of the causes and refined treatment of this serious disorder.

Future studies on the long-term outcome of EOS might benefit from the following: (a) commonly used diagnostic criteria and standardized assessments; (b) detailed description of sample characteristics; (c) low attrition rates of the sample; (d) repeated and long-term follow-up assessments with standardized instruments covering clinical symptoms and functioning; (e) detailed information on type and duration of interventions including their effects on outcome; and (f) the use of large aggregated samples. These samples might be identified in national registers so that a potential sample bias caused by local hospital recruitment might be avoided.

Abbreviations

EOS: Early onset schizophrenia; VEOS: Very early onset schizophrenia; AOS: Adult onset schizophrenia; MIX: Studies including both EOS and other psychotic disorders; GFS: General functioning scale; SSF: Study-specific functioning; GAF: Global assessment of functioning; CGAS: Children's global assessment scale; GAS: Global assessment scale.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LC carried out all statistical analyses, DL was responsible for the literature search, HCS was responsible for the design of the study. All three authors performed the ratings of the outcomes and contributed equally to the writing of the manuscript. All authors read and approved the final manuscript.

Authors' information

Both LC and DL are psychologists and are currently working on dissertation projects dealing with various clinical aspects of early onset schizophrenia. Both are specializing in clinical child and adolescent psychology within child and adolescent psychiatry departments in Denmark. HCS is a research professor in child and adolescent psychiatry, a professor emeritus in child and adolescent psychiatry, and an honorary professor in clinical child and adolescent psychology.

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STUDY 1:

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STUDY 2

Vernal, DL; Stenstrom, AD; Staal, N; Christensen, AM; Ebbesen, C; Pagsberg, AK; Nielsen, RE; Correll, CU; Lauritsen, MB: Early-Onset Schizophrenia: Validation Study of the Early-Onset Schizophrenia Diagnosis in the Danish Psychiatric Central Research Register

The paper has been submitted in August 2017. The paper has been available for the assessment committee.

STUDY 3

Vernal, DL; Boldsen, SK; Lauritsen, MB; Correll, CU; Nielsen, RE: Long-term Outcome of Early-Onset Schizophrenia: A Nationwide Danish Register Study over 19 years.

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