**Early-Onset Schizophrenia Spectrum
Disorders:
Cognitive Function, Clinical Characteristics and Obstetric
Complications**

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Paper I-III

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Summary

Cognitive deficits are a core feature of schizophrenia and appear with increased severity in early-onset schizophrenia (EOS). EOS is defined as onset of symptoms before 18 years of age. Affected youths often experience increased symptom severity compared to those with later onset, in addition to a more severe clinical course and outcome. The interaction between biological and psychosocial factors seems to determine the incidence and expression of schizophrenia, but the way in which they interact is uncertain. Evidence indicates that the disease reflects underlying deviations in early brain development, and that fetal exposure to obstetric complications (OC) is a risk factor for developing the illness and may also affect cognitive deficits in schizophrenia.

Research questions that remain unexamined are whether cognitive deficits in EOS may derive from exposure to OC, and if so, how the individual OC affect different areas of cognition. Also, there is still uncertainty about the longitudinal cognitive course in EOS; some suggest neurodegeneration after illness onset, while others claim a stable cognitive course after onset. Another question is the extent to which the cognitive course in EOS is influenced by clinical characteristics during the early illness period, such as psychotic and general symptoms and duration of untreated psychosis.

The aim of Paper I was to investigate a relationship between OC and cognitive deficits in EOS. Our first research hypothesis was that we expected to find a higher frequency of OC among EOS patients than among healthy controls. Secondly, we wanted to examine if OC affect the overall cognition in EOS. Our results gave no indication of group differences in OC in EOS and healthy controls. When examining the relationship between OC and cognition, a shorter gestational length in the EOS group led to significant decreases in the overall cognitive composite score, and in processing speed. Our results suggest that the cognitive deficits in EOS may be partly attributable to the length of gestation. Cognitive dysfunctions did not appear among controls, so gestational length had a different impact on the two groups. Hence, a shorter gestational length did not increase the risk for early psychoses, but did significantly affect the cognitive difficulties in this group.

In Paper II, we first reported how the cognitive composite score develops over time in EOS, compared to healthy controls, but the primary aim of the paper was to investigate to what extent the cognitive course in EOS was influenced by clinical characteristics during the early

illness period (symptoms, duration of untreated psychosis (DUP), remission, suicide attempts and hospitalizations). Our results indicated that generalized cognition follows a stable course over the first years of the disease in EOS, though at a significantly lower level in EOS compared to the control group. Some baseline clinical characteristics (psychotic symptoms, DUP, remission and hospitalization) had no influence on cognition during the first two years of illness. In contrast, higher levels of general symptoms and a history of suicide attempts at baseline were identified as more potent risk factors of a deteriorating cognitive course than the psychotic-specific symptoms.

In Paper III, our aim was to examine the association between perinatal complications and executive function in EOS, compared to healthy controls. Research shows extensive brain maturation in newborns, suggesting them to be particularly vulnerable for perinatal insults. Executive function is mainly mediated by the prefrontal cortex, an area that matures last during pregnancy. Thus, exposure to perinatal complications may influence executive dysfunction in EOS. All participants were assessed with the Wisconsin Card Sorting Test (WCST) and the D-KEFS Color Word Interference Test (CWIT). Results suggested that exposure to perinatal complications and particularly shorter gestational length, was associated with increased executive difficulties in EOS. Exposed healthy controls did not exhibit similar executive difficulties. Hence, the EOS patients seemed especially vulnerable for executive deficits due to perinatal insults. The findings indicate that EOS youths learn more slowly and experience more difficulty with problem-solving, which carry important implications for clinical practice. Lower Apgar 5-minutes scores were associated with executive dysfunction in both groups, thus, may be an indicator of executive difficulties among adolescents in general.

Abbreviations

ARMS	At risk mental state
AOS	Adult onset schizophrenia
CDD	Calculated daily doses
Composite score	A sum score of the six first tests in the MCCB (see below)
CWIT	D-KEFS Color Word Interference Test
DUP	Duration of untreated psychosis
EF	Executive function
EOS	Early-onset schizophrenia spectrum disorders
MCCB	The MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery
NMBR	The Norwegian Birth Registry
OC	Obstetric complications
PANSS	The Positive and Negative Syndrome Scale
PANSS general	The general scale of the PANNS
PCS	Prefrontal Cortex System
SCID-I	The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), modules A-D
SDD	Schizophrenia spectrum disorders
Split-GAF	The Global Assessment of Functioning-Split version (symptoms and function)
WCST	The Wisconsin Card Sorting Test

List of papers

The present thesis is based upon the papers listed below.

Paper I:

Gestational length affects neurocognition in early-onset schizophrenia

Teigset, C. M., Mohn, C., Rund, B. R. *Psychiatry Research*. 2016; 244: 78-85. doi: 10.1016/j.psychres.2016.07.017. Epub 2016 Jul 12.

Paper II:

Do clinical characteristics predict the cognitive course in early-onset schizophrenia-spectrum disorders?

Teigset, C. M., Mohn, C., Brunborg, C., Juuhl-Langseth, M., Holmen, A., Rund, B. R., 2018; *Journal of Child Psychology and Psychiatry*. 2018 Mar 24. doi: 10.1111/jcpp.12896.

Paper III:

Perinatal complications and executive dysfunction in early-onset schizophrenia

Teigset, C. M., Mohn, C., Rund, B. R. (submitted)

1 INTRODUCTION

Schizophrenia spectrum disorders describe a group of mental disorders that causes extensive burdens to those who affected. Throughout the last decades, our comprehension of the developmental components of the pathogenesis of schizophrenia has substantially evolved. It has been suggested that as much as 80 % of the likelihood of developing schizophrenia is explained by genetic factors (Crow, 2007; Sullivan et al., 2003). The interaction between biological and psychosocial factors seems to determine the incidence and expression of the illness, but the way in which they interact is uncertain (Preti and Wilson, 2011; Tandon et al., 2008). Furthermore, a growing body of evidence indicates that schizophrenia has a neurodevelopmental nature (Rapoport et al., 2005; Reichenberg et al., 2010), and that the disease reflects underlying deviations in early brain development (Frangou, 2013; Rapoport et al., 2012; Rund et al., 2015; Seidman et al., 2006). Fetal exposure to obstetric complications (OC) seems to increase vulnerability to schizophrenia (Brown, 2006; Brown et al., 2005; Cannon et al., 2002a). Hence, neurodevelopmental deviations may be caused by OC. However, the way these factors coalesce is still uncertain, yet crucial, for elucidating the pathway underlying psychotic illness (Kotlicka-Antczak et al., 2014; Mittal et al., 2008).

A small group of patients has an illness onset before 18 years of age, also referred to as early-onset schizophrenia spectrum disorders (EOS) (Cannon et al., 1999). These youths often experience increased disease severity compared to those with later onset, with a worse clinical course and outcome (Remschmidt et al., 2007; Schimmelmann et al., 2007) and more profound cognitive deficits (Jepsen et al., 2013; Nieto and Castellanos, 2011; Rajji et al., 2009). Hence, finding reliable prognostic factors that help identify therapeutic targets, is important.

The purpose of this dissertation is to present our research on cognitive development in EOS, with a special focus on the impact of OC and clinical symptoms. The research is based on neuropsychological data from the “Early-onset study”, a longitudinal study carried out at the University of Oslo between 2005 and 2009 (Holmen et al., 2010; Juuhl-Langseth et al., 2014; Thormodsen et al., 2012), and were supplemented with data on OC from the Norwegian Medical Birth Registry (NMBR).

1.1 Schizophrenia spectrum disorders

In the diagnostic systems, schizophrenia is a syndrome rather than a clearly defined disease. A narrow definition of psychotic disorders includes distortion of perception (hallucinations) and thinking (delusions), as well as absence of insight into the symptoms. Wider definitions include insight into the pathological nature of the hallucinations, and other symptoms like disorganized speech and catatonic behavior (Laroi et al., 2012; Laroi and Woodward, 2007; van Os and Kapur, 2009; Waters et al., 2012). The Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) emphasize different aspects of the definitions, and divides *Schizophrenia and other psychotic disorders* into nine subgroups with varying criteria (see Appendix 1 for full text and description of each criterion).

Schizophrenia is considered to be the most prevalent and severe of the psychotic disorders, with a lifetime prevalence of about 1.0% (Mueser and McGurk, 2004), increasing to 4 % when a wider definition of the disorder is included (Perala et al., 2007). It is distinguished from the other psychotic disorders by longer duration, bizarre delusions, negative symptoms, simultaneous social/occupational dysfunction and affective symptoms (van Os and Kapur, 2009). The present thesis concentrates on the diagnoses referred to as the broader schizophrenia spectrum disorders (SSD); schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder and psychotic disorder not otherwise specified (NOS). Common features for SSD, are the characteristic symptoms (A criteria), including delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. However, the definitions vary on the other criteria concerning social or occupational dysfunction, duration, and the presence of affective symptoms. In this thesis, the term schizophrenia will mostly be used, but reflects all diagnoses included in SDD.

1.2 The etiology of schizophrenia in a neurodevelopmental perspective

Before the 18th century, psychotic illnesses were mainly understood to be caused by evil spirits and demons. A dramatic change in the understanding of schizophrenia came with Pinel (1745-1826), who claimed that psychoses were caused by genetic, social and psychological factors. In 1896, Kraepelin was the first to describe psychosis, calling it *dementia praecox*. He considered it to be progressive with severe deterioration in cognitive and social function (Noll, 2007), a stance that became immensely influential. The theory implied

neurodegenerative processes in psychoses. Kraepelin said that behavior peculiarities in children who later manifest dementia praecox are an expression of the “morbid pathology” at the time of life, thereby suggesting that schizophrenia has its origin long before the emergence of psychotic symptoms (Weinberger, 2017b). In 1911, Bleuler was the first to use the word *schizophrenia*. He argued against Kraepelin’s idea of dementia in psychosis, and found that the disorder varied widely, but a common trait was an extensive disintegration of mental processes. He divided symptoms into fundamental and accessory, which correspond with today’s categorization in positive and negative symptoms (Green and Harvey, 2014).

With the introduction of antipsychotic medication in the 1950’s, the treatment of schizophrenia changed dramatically, followed by an increased interest in the etiology, course and outcome of psychotic illnesses. Even though biological models gained immense attention in understanding schizophrenia, research on the association between OC and schizophrenia provided crucial support for developmental and nongenetic etiological models of the disorder.

In 1934, Rosanoff and colleagues published “The Etiology of So-Called Schizophrenic Psychosis” (Cannon et al., 2002a). The study was based on case reports of 142 pairs of twins concordant and discordant for schizophrenia. This is the first study to document an association between birth complications and schizophrenia. The authors suggested that schizophrenia could be regarded as a “decerebration syndrome” caused by birth trauma. About 20 years later, Pasamanick et al. (1956) proposed the dissertation of a “continuum of reproductive casualty”, which had great impact on the field of child psychiatry. The thesis proposed that pregnancy and birth complications can lead to a gradient of injury extending from fetal and neonatal death through epilepsy, cerebral palsy, mental deficiencies, and behavior disorders. In the early 1960s, the thesis gained support from studies showing significant associations between OC and childhood psychosis (Hinton, 1963; Taft and Goldfarb, 1964; Terris et al., 1964). In adult psychosis, a twin study reported associations between low birth weight and schizophrenia (Stabenau and Pollin, 1967), while the Copenhagen High-Risk Study found that the disease could be caused by an interaction between genetic predisposition and OC (Mednick, 1973). Further findings in the 1980’s, especially a meta-analysis showing that a history of OC was twice as frequent among schizophrenia patients compared to healthy controls (Geddes and Lawrie, 1995), as well as brain imaging studies (Andreasen et al., 1986; Murray et al., 1985), lead to the “neurodevelopmental hypothesis” of schizophrenia.

In 1987, Murray, Lewis and Weinberger posited the neurodevelopmental hypothesis of schizophrenia (Murray and Lewis, 1987; Weinberger, 1986; Weinberger, 1987). It suggested that schizophrenia was related to an underlying brain lesion that was caused by a combination of genetic and environmental components, such as insults during gestation. The lesion would interact with the normal maturational process of the brain and would manifest as psychosis in early adulthood when the brain approached its adult anatomical state. The theory led to increased attention on genetics and prenatal insults, like maternal infections and OC (Brown et al., 2000; Cannon et al., 2002a), along with a heightened interest in cognitive assessment and development in schizophrenia. Throughout the late 1980s and the beginning of 1990s, the neurodevelopmental hypothesis gained important support from evidence for an association between OC and schizophrenia (Cannon et al., 2002a). Yet, the measurements of OC were often based solely on maternal recall. In 1989, Lewis and colleagues introduced the “Lewis-Murray” scale for rating retrospective information on obstetric OC based on case notes, birth records, and maternal interviews (Lewis, 1989). However, possibly due to methodological limitations such as biased samples, the absence of comparison groups, and various ways of rating OC, results were inconclusive.

Even though Kraepelin (1919) described neurodegeneration in schizophrenia, it was not until the 1980’s that the cognitive deficits in schizophrenia received increasingly more attention. Considerable progress has been made in understanding the deficiencies, and a main debate has focused on whether schizophrenia follows a neurodevelopmental and/or neurodegenerative course (“the neurodegenerative hypothesis”) (Bora and Murray, 2014). A challenge for research is the large heterogeneity within schizophrenia, both clinically and functionally. Controversies remain concerning the longitudinal cognitive course, and the way cognition coalesces with biological and psychosocial factors in influencing schizophrenia.

1.3 Cognitive deficits – a core feature of schizophrenia

Although cognitive deficits are not included in the diagnostic criteria for schizophrenia, most research today indicates they are a core feature of the disease, independent of symptoms and current treatment (Keefe and Harvey, 2012; Reichenberg, 2010). This is supported by reviews, meta-analyses and research that report cognitive dysfunctions with large effect sizes in schizophrenia samples across cognitive domains (Barder et al., 2013; Dickinson

et al., 2007; Frangou, 2013; Heinrichs and Zakzanis, 1998; Holmen et al., 2012b; Rund, 1998). Cognitive functions cover a range of cognitive domains, including general intellectual abilities, attention, working memory, learning, processing speed and executive function. The term *cognition* describes the function of areas, neural pathways or cortical networks of the brain, and is closely related to *neuropsychology* and *neurocognition*. In this thesis the term cognition will mainly be used.

In schizophrenia, cognitive deficits are present before the onset of illness (Seidman et al., 2010; Woodberry et al., 2008). These premorbid deficits are evident from childhood and manifest at the earliest as deficits in verbal reasoning, and as the child grows older, they lag further behind their peers in working memory, attention and processing speed (Reichenberg et al., 2010). Lower general intellectual abilities are also found among children who later develop schizophrenia, and there is a decline in the same abilities after illness onset (Reichenberg et al., 2005). Moreover, intellectual deterioration from childhood through adolescence is associated with increased risk for schizophrenia (Reichenberg et al., 2005).

A main question with implications both for assessment practice and therapeutic targeting, is whether the cognitive impairments in schizophrenia are generalized or characterized by more independent deficits in separate domains. Findings from domain studies vary on which cognitive domains being most strongly affected in schizophrenia. In a large meta-analysis by Schaefer et al. (2013) that examined schizophrenia studies using contemporary neuropsychological tests, the most impaired domains were processing speed and episodic memory. Results from other studies comparing schizophrenia patients to healthy controls, show more profound impairments in the domains of attention, working memory, executive function and episodic memory (Egeland et al., 2003; Holmen et al., 2010; Reichenberg et al., 2010). The diversity of results led Schaefer et al. (2013) to conclude that the main finding is the indication of a global cognitive impairment in schizophrenia, that are consistent over decades and across cultures. These conclusions have been supported in a meta-analysis by Fioravanti et al. (2012), in a review article by Reichenberg (2010), as well as in several studies (Christensen et al., 2014; Jepsen et al., 2013; Mesholam-Gately et al., 2009; Nieto and Castellanos, 2011; Rajji et al., 2009). The schizophrenia population shows lower scores in a variety of cognitive domains, thus, a natural consequence has been a more frequent use of composite scores in cognitive studies of schizophrenia (Meyer et al., 2014; Rund et al., 2015). In the composite score, the cognitive domains are combined and measured as one generalized ability. Regarding effect

sizes, Holmen et al. (2010) found a generalized cognitive deficit of about 0.8-1.8 SD in EOS compared to healthy controls. The discussion of whether the cognitive deficits are specific or generalized might diffuse the fact that both occur in schizophrenia, some patients have deficits in specific domains, others across all domains. Thus, both should be considered in research.

1.4 Executive dysfunction in schizophrenia

One cognitive domain that is especially important for emotional, behavioral and social functioning, is executive function. Several studies indicate that executive function is the domain most gravely impaired in schizophrenia (Brown et al., 2009; Fioravanti et al., 2012; Reichenberg, 2010). The deficiency affects reasoning and problem-solving, emotional regulation, as well as the ability to use appropriate contextual information to generate and implement adaptive behaviors. Hence, executive function is the complex process that helps us to achieve a particular goal (Elliott, 2003). Whereas good executive functioning is related to treatments success, degree of self-care and occupational functioning, executive dysfunction is related to functional loss and disabilities (Bowie and Harvey, 2006; Bowie et al., 2006; McGurk et al., 2003). Since the impairments strongly adds to poor psychosocial functioning, schizophrenia patients with executive dysfunction require more treatment and rehabilitation resources (Holmen et al., 2012a). Furthermore, the dysfunction is central to the apathy symptoms of the illness (Faerden et al., 2009). Executive function has a central role in cognitive processes by affecting the ability to approach, plan and carry out cognitive tasks, or by defections in performance-monitoring (Burgess et al., 1998). Consequently, the function is closely connected to other cognitive domains (Holmen et al., 2012a). Executive function is especially interesting in schizophrenia because of structural and functional changes in the frontal cortex detected in this group (Kawada et al., 2009; Minzenberg et al., 2009).

Research shows that the development of executive functions starts early in life, and continues, both quantitatively and qualitatively, throughout early adulthood (Davidson et al., 2006; Luna et al., 2010). Moreover, neural networks associated with decision making and cognitive control are located in the dorsolateral prefrontal cortex, an area that matures relatively late (Gogtay et al., 2004). Executive function is not a single dimensional construct but involves multiple facets of cognition (Kerns et al., 2008). Traditionally, it included volition, planning, purposive action (the translation of intention to productive activity) and effective performance

which requires the abilities of self-monitoring and self-correction (Holmen et al., 2012a). Today, the major components included in the executive function domain are inhibition, working memory and shifting, among which shifting matures last (Best and Miller, 2010). During the preschool years, inhibition seems to improve extensively, with less change later. Working memory and shifting show a more gradual improvement throughout development (Best and Miller, 2010). Hence, the ability to perform more complex tasks, is not completed until late adolescence or early adulthood (Romine and Reynolds, 2005). This finding raises questions about how and when children develop individual components of executive function, as well as how and when to evaluate them.

Due to the multiple components of executive function, several tests have been used to examine different aspects of the domain (Brown et al., 2009; Holmen et al., 2012a; Nuechterlein et al., 2004). So far, executive function in schizophrenia is well examined; however, the etiological factors that contribute to the executive dysfunction remain unclear.

1.5 The cognitive course in schizophrenia

A research question that has gained much attention is how cognition develops over time in schizophrenia, or more specifically, whether the disease is neurodevelopmental and/or degenerative. A common hypothesis has been that cognitive decline prior to the onset of symptoms, indicates impairment in neurodevelopment (Rapoport et al., 2012), while further decline after onset indicates degeneration (Rund, 2009; Weinberger, 1987). Originally, a majority in the field of psychiatry considered schizophrenia to be a deteriorating illness. Some longitudinal studies have found a decline in the cognitive development in patients with schizophrenia (Braw et al., 2008; Levander et al., 2001), in elderly, chronic patients (Harvey, 2001) and in samples with early onset of symptoms (Oie et al., 2010). However, an increasing number of longitudinal studies indicates both high levels of stability in the cognitive course, as well as incidents of recovery (Barder et al., 2013; Bora, 2015; Fu et al., 2018; Mesholam-Gately et al., 2009; Rund et al., 2015; Torgalsboen et al., 2018). This research indicates that there is little evidence for a cognitive decline in schizophrenia, at least after symptom onset, supporting the neurodevelopmental hypothesis of schizophrenia.

Research from the last two decades suggests that schizophrenia is the behavioral outcome of deviations in the neurodevelopmental processes starting long before onset of

symptoms (Bilder et al., 2006; David et al., 1997; Davidson et al., 1999; Fuller et al., 2002; Rapoport et al., 2005; Rapoport et al., 2012; Reichenberg et al., 2005; Woodberry et al., 2008). A possible path is an abnormal cognitive lag (Bora, 2015; Gur et al., 2014) that starts pre- or perinatally (Brown, 2006; Khandaker et al., 2011), and continues through childhood (MacCabe et al., 2013; Niemi et al., 2003; Seidman et al., 2006) and adolescence (Brewer et al., 2006; Seidman et al., 2010). More research is needed to understand the origin of the deficits, how it affects some and not others, as well as the interaction between the cognitive deficits and clinical symptoms.

1.6 Early-onset schizophrenia

Among patients with schizophrenia, approximately 4-5% have an onset of symptoms before 18 years of age, which is often referred to as early-onset schizophrenia (EOS) (Cannon et al., 1999; Frangou, 2013; Holmen et al., 2012b; Juuhl-Langseth et al., 2014). The incidence of schizophrenia is extremely rare before the age of 10 but increases steadily throughout adolescence and reaches a peak at early adulthood.

The EOS patients are especially attractive for research, because they are in their adolescence, a period with extensive brain maturation and alterations in cognitive structures and functions (Juuhl-Langseth et al., 2014). The EOS patients offer the opportunity to explore how disease-related mechanisms may affect facets of cognitive development. Such knowledge provide unique neurodevelopmental data that may contribute to a better understanding of schizophrenia at all ages (Rapoport et al., 2012; Remschmidt, 2002). Investigating patients at an early stage of the disease (before or shortly after medication onset) can also elucidate whether cognitive changes are a consequence of long-term pharmacological treatment.

EOS commonly represents a more severe form of schizophrenia. Research indicates that the EOS adolescents have worse prognosis, with poorer function and more severe symptoms, than those with later illness onset (Del Rey-Mejias et al., 2015; Frangou, 2013; Kumra and Charles Schulz, 2008; Oie et al., 2011). The increased severity of EOS may reflect more extensive deviances in developmental trajectories compared to later onset schizophrenia (Frangou, 2013; Kumra and Charles Schulz, 2008; Shaw et al., 2010). Moreover, a long-term follow-up study (40-60 years), found diagnostic stability at 91% for patients who were given a schizophrenia diagnosis in childhood (Remschmidt et al., 2007), though with better prognosis

for those with an acute illness onset and positive symptoms compared to those whose disease begins insidiously (Remschmidt and Theisen, 2012). Also, EOS patients without a family history of schizophrenia and patients from cohesive families, seem to handle the illness better and their condition improved more rapidly during inpatient treatment. More optimistic results were reported in one study by Amminger et al. (2011), in which the authors found fewer positive symptoms and better overall functioning in EOS, compared to patients with onset in adulthood. The findings might be related to early detection and specialized treatment.

Research reveals that the patients with EOS inhibit more pronounced cognitive deficits than those with later onset schizophrenia (Frangou, 2010, 2013). Between 2005 and 2009, the University of Oslo carried out a longitudinal study named “The early-onset study”, to investigate brain function in adolescents with schizophrenia (Holmen et al., 2010; Juuhl-Langseth et al., 2014; Thormodsen et al., 2012). Clinical and cognitive data was collected over three years. Results from the study indicate significant executive dysfunction in schizophrenia compared to both healthy controls and adults with schizophrenia (Holmen et al., 2010; Holmen et al., 2012b). Similar results are reported from research on other cognitive domains, whereas the EOS patients show increased deficiencies in IQ, verbal memory and speed of processing (Jepsen et al., 2013; Rajji et al., 2009).

When investigating the hypothesis of a cognitive decline in EOS, Juuhl-Langseth et al. (2014) from “The early-onset study”, reported a stable and similar longitudinal course in both the EOS and the healthy control group, though with performances at a significant lower level in the EOS group. These findings are supported in other studies that reveal a stable cognitive course that seems to follow the same pattern in EOS compared to controls (Frangou et al., 2008; Jepsen et al., 2010). Hence, as in later onset schizophrenia, there is little evidence for a cognitive decline in EOS after symptom onset.

Due to the increased severity of symptoms, a major objective in EOS is to find reliable prognostic factors that may help identify therapeutic targets, such as specific medication, cognitive training programs or family interventions.

1.7 Obstetric complications as risk-factors for schizophrenia

In the late 1990s, a small study found that a history of OC predicted a poor response to treatment in first-episode schizophrenia (Alvir et al., 1999). The study was based on 59 patients,

of which 12 had early-onset schizophrenia. The findings had important clinical implications for therapeutic understanding and raised questions about the underlying impact of OC; which complications are important, and how do they affect schizophrenia? In the following years, the literature on OC and schizophrenia is increasingly characterized by large sample sizes, with comparison subjects drawn from the same population, and the use of obstetric data from birth registers (Cannon et al., 2002a).

Several studies and meta-analyses support that complications during pregnancy and/or birth are important risk-factors for the later development of schizophrenia (Byrne et al., 2007; Cannon et al., 2002a; Geddes, 1999; Geddes et al., 1999; Kotlicka-Antczak et al., 2014). It has been suggested that fetal hypoxia is a core variable that is involved in a variety of OC associated with schizophrenia (Mittal et al., 2008). However, schizophrenia has also been associated with a low birth weight, especially below 2500 g (Abel et al., 2010; Gunnell et al., 2003; Hultman et al., 1999; Lahti et al., 2015), low and high birth weight (Gunnell et al., 2003; Moilanen et al., 2010) and a low gestational age (Byrne et al., 2007; Geddes et al., 1999; Nosarti et al., 2012).

On the other hand, the association between OC and schizophrenia has been questioned. According to Rosso et al. (2000), most cohort studies have failed to confirm a relationship between fetal insults and schizophrenia. These findings are supported in a Scottish population study by Kendell et al. (2000). They found no relationship between OC and adult onset schizophrenia in one birth cohort, however, in another cohort, caesarean section and long-lasting labor were more common. Similar results were later reported in a Finnish study, with no significant main effect of OC on the risk of adult schizophrenia (Clarke et al., 2011).

Even though the idea of a relationship between OC and the later development of schizophrenia in outcome has become well established (Brown and Patterson, 2011; Cannon et al., 2014; Weinberger, 2017b), the pathophysiological link between OC and schizophrenia remains obscure. An early dichotomy hypothesis suggested that patients with *sporadic schizophrenia* more likely had experienced environmental insults like OC, while patients with *family schizophrenia* had a genetic disposition for the illness (Verdoux et al., 1997). However, research that examined distinct characteristics in patients with a history of OC compared to patients without such a history, had conflicting results (McNeil, 1995; Roy and Crowe, 1994). A complimentary hypothesis, evolving from the neurodevelopmental hypothesis, predicted that among a variety of schizophrenia disorders, *congenital schizophrenia* was a consequence of fetal and neonatal insults, leading to structural brain changes and cognitive impairment, early

illness onset, earlier symptom onset in males than females and poor outcome (Murray et al., 1992). Inconsistent results were obtained by studies exploring these variables, except for the associations with early age at onset, which has been detected by most studies (Preti et al., 2012; Rubio-Abadal et al., 2015; Verdoux et al., 1997), suggesting that schizophrenia associated with OC might be particularly important in EOS. Though results indicate differences due to age of onset, still little is known about the role of prenatal insults in the EOS population (Margari et al., 2011). Among the few studies performed, some find associations between complications and EOS (Matsumoto et al., 1999; Preti et al., 2000). Verdoux et al. (1997) detected that patients with onset before age 22, were approximately three times more likely to have a history of prenatal insults than those with later onset, indicating that earlier onset involves neurodevelopmental impairment. A recent study supported these findings and claimed that birth weight and OC determine age of onset (Rubio-Abadal et al., 2015). As in adult schizophrenia, some small studies also failed to find a relationship between OC and EOS (Margari et al., 2011; Ordonez et al., 2005).

Most research on OC and schizophrenia use obstetric material collected from maternal recall. Maternal recall may be unreliable and should be replaced by information from birth registries (Kotlicka-Antczak et al., 2014; McIntosh et al., 2002). Moreover, many studies investigate EOS in comparison to other schizophrenia patients or other diagnosis groups, without healthy comparison subjects drawn from the same population. In two large studies on early psychosis, both birth registries and healthy control groups were included (Cannon et al., 2000; Rosso et al., 2000). Both studies centered on hypoxia-associated complications and found that these prenatal insults increased the odds of earlier onset of psychosis but not of later onset. These studies used median splits for age of onset, and the mean age in the early psychosis group was above 18 (27.1 and 21.5, respectively). Even so, the results show that complications during pregnancy and birth may have a specific impact on early psychosis and should be subject to further research.

1.8 The relationship between obstetric complications and cognition

An important research question concerns how OC affect schizophrenia. A likely hypothesis suggests deteriorated neurodevelopment. An explanation proposed by Cannon et al. (2002a) is that individual OC interact with unknown genetic or epigenetic factors in the

fetus. Hence, OC might affect the course of the abnormal brain development in schizophrenia (Ellman et al., 2012; Freedman et al., 2013; Ochoa et al., 2013; Torniainen et al., 2013). Even though previous findings indicate that OC may have a specific impact on EOS (Cannon et al., 2000; Rosso et al., 2000), as well as on cognition (Ellman et al., 2012; Freedman et al., 2013; Ochoa et al., 2013; Torniainen et al., 2013), research that examines a relationship between OC and cognition in EOS is absent.

One can assume that different complications could affect different areas of cognition. In adult samples, neurodevelopment has been studied in relation to single OC measures, and findings indicate associations between the complications and various cognitive deficits (Brown et al., 2009; Ellman et al., 2009; Freedman et al., 2013; Torniainen et al., 2013). In one study by Ellman et al. (2012), decreases in hemoglobin levels during pregnancy were found to lead to poorer neuromotor and cognitive function in offspring with schizophrenia. The healthy control group that were exposed to the same low hemoglobin levels in utero, were relatively unaffected on the same measures. When examining executive functioning specifically, Brown et al. (2009) reported that maternal infections predicted executive dysfunction in adults with schizophrenia. The comparison group in the study were other patients unexposed to infections. Previous research has identified strong associations between executive dysfunction and structural and functional deficits in prefrontal cortex (Goldberg et al., 1990; Rusch et al., 2007). These deficits might be affected by gestational infections. In another study by Ellman and colleagues, schizophrenia cases exposed to influenza in utero showed significant impairments in verbal tasks, and moreover, the impairments were present long before onset of symptoms (age 7) (Ellman et al., 2009). Influenza-exposed control children did not show the same verbal impairments, and other cognitive domains were not affected by maternal influenza in either groups. An older but similar study reported opposing results when examining a history of fetal hypoxia among schizophrenia cases (Bearden et al., 2000). The participants had previously been measured on language tasks at 8 months, 4 years and 8 years. The results indicated that hypoxia-associated complications were unrelated to language acquisition deficits in the premorbid period.

In many studies, the cognitive deficits among those exposed to OC were less extensive or absent in the healthy control group with the same labor-conditions (Ellman et al., 2012; Ellman et al., 2009; Freedman et al., 2013). These results indicate a greater effect of OC on neuropsychological development among those who later develop schizophrenia. A likely

suggestion is that a genetic and/or an environmental factor associated with psychosis rendered the fetal brain particularly vulnerable to the effect of the specific complication. However, the findings underscore two important research issues, firstly; the importance of including healthy controls in these studies, and secondly; the necessity to identify the number and severity of specific complications on specific domains of cognition in schizophrenia.

In a study by Ochoa and colleagues a wider range of OC were included and cognitive measurements among schizophrenia patients were conducted (Ochoa et al, 2013). The results showed that first-episode schizophrenia patients with a higher level of what they called “neurodevelopmental contribution” (including OC) had a significantly slower processing speed than patients without the same neurodevelopmental contribution. Even though Ochoa et al. (2013) did not examine complications separately and healthy controls were not evaluated, the findings indicated that a variety of obstetric events may affect aspects of cognition in schizophrenia, and furthermore, that processing speed may be the domain most severely affected by these early developmental insults.

Executive function affects the ability to approach, plan and carry out cognitive tasks, and is suggested to be more influenced by OC than other cognitive domains. In the general population, impairments in executive function have been detected in young children exposed to maternal pregnancy-specific anxiety (Buss et al., 2011). A possible explanation has been that maternal stress contributes to preterm birth, which again causes the impairments (Wadhwa et al., 2011). Research has also indicated an association between executive dysfunction and negative caregiving (Cuevas et al., 2014), prenatal exposure to medication (Meador et al., 2013) and maternal alcohol abuse (Gautam et al., 2014). In the schizophrenia population, the specific relationship between exposure to OC and executive function is examined in some studies, though not in EOS. As mentioned earlier, Brown et al. (2009) found that prenatal infections were associated with impaired executive function in adult schizophrenia patients (Brown et al., 2009). Fetal exposure to influenza has also been linked to executive deviations in children who later developed psychoses (Ellman et al., 2009). Davis et. al. (1991) found that adult schizophrenia patients who have been exposed to a variety of OC commit more perseverative errors than unexposed patients.

One study showed an association between perinatal, but not prenatal OC, and executive dysfunction (Yurgelun-Todd and Kinney, 1993). The prefrontal cortex is the last to mature during pregnancy, and may therefore be more influenced by perinatal OC than prenatal insults

(Abel, 2004). According to Abel et. al., the fetus is especially sensitive to growth abnormalities. Structural images of neonates show extensive brain maturation starting at birth that potentially represents a window of vulnerability for perinatal insults (Gilmore et al., 2006). These perinatal insults may disturb neurodevelopment in newborns predisposed for psychosis and may specifically affect the development of executive dysfunctions. Yet, the relationship between perinatal OC and executive function is uninvestigated in EOS.

1.9 The relationship between symptoms and cognition

Longitudinal cognitive studies of patients soon after onset of psychosis provide useful information about realistic baseline cognitive abilities that are minimally affected by confounding variables associated with chronicity (Bozikas and Andreou, 2011). Furthermore, to find reliable prognosis and provide adequate therapy, studies that highlight the complexity of the interaction between global cognition and clinical symptoms in schizophrenia are needed (Milev et al., 2005; Remschmidt and Theisen, 2012). Among adults with schizophrenia, the relationship between psychotic symptoms and cognition has been investigated with inconsistent results (Harvey et al., 2006; Rund et al., 2004; Ventura et al., 2010). Some studies also indicate that negative symptoms interact with cognition to a greater extent than positive symptoms (Bora et al., 2009; Kravariti et al., 2012; O'Connor et al., 2013). Furthermore, the longitudinal cognitive trajectory and its relation to psychotic symptoms has been reported in some studies (Bagney et al., 2015; Barder et al., 2013; Hoff et al., 1999; Mayer, 2002; Meier et al., 2014; Rund et al., 2015). Meyer et al. (2014) found that negative symptoms mediated the relationship between cognition and functioning, while Hoff et al. (1999) detected associations between reduction in positive symptoms and cognitive improvement. Yet again others report small to no relationship between the two (Rund et al., 2015), which may indicate that the domains are largely separate.

The cognitive course in EOS has received less attention (Thormodsen et al., 2013), as well as the long-term relationship between psychotic symptoms and cognition. In one study, Wozniak et al. (2008) found no relationship between psychotic symptoms and cognition, except for lower IQ predicting more negative symptoms after one year. This study had a short follow-up interval and included few symptoms, raising questions about the relationship between a wider range of symptoms and cognition, and whether the relationship endures.

A clinical characteristic that has gained much research attention, is duration of untreated psychosis (DUP). A hypothesis suggests that longer DUP may accelerate cognitive deterioration and leave some patients with a damaging residual. This “neurotoxicity hypothesis” was introduced by Wyatt (1991), who suggested that neuroleptics may interrupt the toxic process of psychosis and ensure a better long-term course of schizophrenia. In adult samples, some longitudinal studies find a relationship between shorter DUP and better overall cognitive function (Cuesta et al., 2012; Dominguez et al., 2013; Yamazawa et al., 2008), however, a majority of studies report no association between the two (Barder et al., 2015; Goldberg et al., 2009; Melle et al., 2008; Rund et al., 2015; Rund et al., 2007). In EOS, research on the interaction between DUP and cognition is rare. One baseline study by Kravariti et al. (2003a) reported no immediate effect of illness duration on cognitive performance in EOS, while Fraguas et al. (2014) found that a shorter DUP was associated with improvement in executive functions after two years. The findings thereby contradict most results from adult-onset samples and indicate a possible worse impact of DUP on cognition in early psychosis versus adult psychosis. An interesting question is how DUP affects other cognitive domains in EOS, furthermore, if other aspects of the psychotic symptoms, such as remission, influence the cognitive outcome.

Schizophrenia is an illness which often includes a variety of psychological burdens in addition to the psychosis, yet, the relationship between non-psychotic symptoms and cognition has gained less attention in research. About half of all schizophrenia patients attempt suicide, and 9–13% ultimately do commit suicide (Potkin et al., 2003). Important predictors seem to be depression and insight (Hor and Taylor, 2010). Among adolescents with schizophrenia, studies indicate that greater severity of psychotic and depressive symptoms at illness onset increases risk of attempting suicide (Díaz-Caneja et al., 2015; Jarbin and Hansson, 2004; Sanchez-Gistau et al., 2013). So far, the relationship between suicidality and cognition in EOS is unclear. Research from patients with adult illness onset, however, presents inconsistent findings. Some report no correlation between suicidality and cognition (Potkin et al., 2003; Zoghbi et al., 2014), while others suggest that hopelessness, better insight into illness and higher cognitive function is associated with greater suicidality (Delaney et al., 2012; Kim et al., 2003).

1.10 Unanswered questions

Previous research indicates a relationship between OC and schizophrenia, and moreover, some suggest that the incidence increases with earlier age of illness onset. Consequently, one could assume to find a higher frequency of OC among EOS patients. Furthermore, research suggest that OC have an impact on cognitive deficits in adult schizophrenia. The same relationship has not been examined in EOS. Thus, a research question is whether cognitive deficits in EOS may derive from exposure to OC. Moreover, little is known about how the separate complications may affect different areas of cognition in this group.

The longitudinal cognitive trajectories in the present EOS group have previously been examined by Juuhl-Langseth et al. (2014). The study revealed stable deficits in all cognitive domains, with the exception of working memory and processing speed. However, because of dropouts and the use of repeated measures ANOVA, only 65% of the patients were included in the analyses at the last time point. By using linear mixed model analyses, all participants with at least one measure point can be included. Moreover, the longitudinal course of generalized cognition (the composite score) has not been reported.

If clinical characteristics at baseline can predict the cognitive course in EOS, this is essential for prognosis and therapy. It underscores tailoring treatment to individual needs. Hence, an interesting research question is to what extent the cognitive course in EOS is influenced by clinical characteristics during the early illness period, such as symptoms of schizophrenia, DUP, remission, suicide attempts and number and duration of hospitalizations caused by psychosis.

Higher frequencies of OC and more pronounced executive dysfunctions characterize EOS (Holmen et al., 2012b). Research shows extensive brain maturation starting at birth that may lead to a specific vulnerability for perinatal insults. Furthermore, the prefrontal cortex matures lastly during pregnancy (Abel, 2004), and may be more influenced by perinatal OC. A possibility is that exposure to perinatal insults affects neural networks in the prefrontal cortex and disturbs the development of executive function more than other cognitive domains. However, the association between perinatal complications and executive function is unclear in EOS.

2 AIMS

The main aim of this thesis was to investigate the neuropsychological development in EOS, with a special focus on the impact of OC and clinical symptoms.

The aim of Paper I was to investigate a relationship between OC and cognitive deficits in EOS. Our first research hypothesis was that we expected to find a higher frequency of OC among EOS patients than among healthy controls. Secondly, we wanted to examine if pre- or perinatal complications affect the overall cognition in EOS.

In Paper II, we first reported how the cognitive composite score develops over time in EOS, compared to healthy controls. However, the primary aim of the paper was to investigate to what extent the cognitive course in EOS was influenced by clinical characteristics during the early illness period, such as symptoms of schizophrenia, DUP, remission, suicide attempts and number and duration of hospitalizations.

In Paper III, the aim of the study was to examine the association between perinatal OC and executive dysfunction in EOS, compared to healthy controls. Our first hypothesis was that we expected to find a relationship between perinatal conditions, especially lower birth weight and shorter gestational length, and executive dysfunction in EOS. Furthermore, lower Apgar 5-minutes scores have been associated with cognitive deficits in adolescence and early adulthood. Hence, our second hypothesis was to find an association between lower Apgar 5-minutes scores and executive dysfunction in EOS.

3 METHODS

3.1 Design

The Early-onset study is a naturalistic longitudinal case-control study carried out at the University of Oslo between 2005 and 2009, that aimed to investigate brain function of psychotic disorders in adolescents. The study collected clinical and cognitive data, as well as data from functional and structural MRI. The patient group were recruited from different inpatient and outpatient units in Oslo and the region of Eastern Norway and were included if they were between 12 to 18 years of age and met the diagnosis criteria for SSD according to DSM-IV. The healthy controls were randomly selected from the Norwegian population register and contacted by letter, or they were contacted through advertisements at four schools in Eastern Norway. They were all matched to patients on gender, age and length of mother's education. All patients and healthy controls attended regular school classes at normal grade levels.

3.2 Procedure

The clinical and cognitive assessments were carried out by trained clinical psychologists (Holmen et al., 2010; Juuhl-Langseth et al., 2014; Thormodsen et al., 2012). All baseline tests were performed within eight weeks after inclusion in the study. The interviewers participated in regular diagnostic consensus meetings led by well-experienced clinical researchers and completed the training course in SCID assessment arranged by the University of California, Los Angeles (UCLA). The mean overall kappa as assessed in the UCLA training course was .77 (Holmen et al., 2010). IQ tests were administrated within the cognitive test battery.

3.3 Ethical considerations

Approval of the Early-onset study was obtained by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. However, informed consent from adolescents is a complex issue, so the study took care to ensure informed and voluntary participation. All the participants were given a complete description of the study, including both spoken and written information about the study; the aims, procedure, data, security and confidentiality. Everyone was also informed about the possibility to withdraw from the study

at any time. Written informed consent was obtained from all the participating adolescents, both patients and controls, as well as from their parents if the adolescent was younger than 16 years. To avoid participation due to financial interests, the fee for attending was moderate (250 NOK).

The EOS group is rare and vulnerable, with poorer function, more cognitive deficits and more severe symptoms than patients with later onset schizophrenia. Thus, the voluntary participation in the study and the possibility to withdraw at any time were repeated at all measure points. The patients were also recommended to withdraw from the study if participating interfered negatively with ongoing treatment. The testing time was long, and to avoid that the adolescents were overwhelmed, they were given frequent breaks. The interviewers were also flexible in time and place for interviews and assessments.

3.4 Participants

All the participants included in this thesis were participants in the Early-onset Study and were tested three times; at baseline (T1), after one year (T2) and after two years (T3). The exclusion criteria were a history of central nervous system pathology or trauma (loss of consciousness for greater than 30 minutes and/or any neurological sequelae), or an estimated IQ less than 70. In total, 31 patients and 73 controls participated in the study. For information on demographic and clinical characteristics, see Table 1.

Table 1 Demographic and clinical characteristics for early-onset schizophrenia-spectrum disorders and healthy controls

	Paper I (N=19) T1	Paper II (N=31) T1/T2/T3	Paper III (N=19) T1	Healthy controls (N=73)
Gender male/female (%)	9/10 (48/52)	16/15 (52/48)	9/10 (48/52)	35/38 (48/52)
Age in years (SD)	15.3 (1.9)	15.6 (2.0)	15.3 (1.9)	15.8 (2.0)
IQ (SD)	97.1 (13.7)	97.1 (14.6)	97.1 (13.7)	108.5 (14.1)
GAF function (SD)	50.8 (15.5)	47.8 (15.8)/ 58.1 (19.0) /58.2 (12.1)	50.8 (15.5)	
GAF symptom (SD)	51.4 (13.9)	47.5 (14.5) /54.3 (16.1) /58.4 (12.7)	51.4 (13.9)	
Schizophrenia (including paranoid, catatonic, undifferentiated, residual) (%)	9 (48)	17(55)/12(55)/11(55)* ²	9 (48)	
Schizophreniform schizophrenia		1 (3)		
Schizoaffective schizophrenia (%)	3 (16)	3(10)/3(14)/4(20)	3 (16)	
Psychosis not other specified (NOS) (%)	7 (37)	10(32)/4(18)/2(10)	7 (37)	
Antipsychotic medication (second-generation)	74%	74%/41%/50%	74%	
Daily calculated doses (mean at T1/T2/T3)*	1.2	1.2/1.5/1.4	1.2	

* Calculated daily doses (CDD) were based on the international daily dose of medication technical measurement system (WHO, 2010), where the CDD is the outcome of the prescribed daily dose divided by the average recommended daily dose of medication. The results were previously reported by Juuhl-Langseth et al. (2014) who found no significant change in CDD over time, and no relationship between medication and cognitive performance.

*² Three patients had no diagnoses at T3, two of whom had psychosis NOS, and one residual schizophrenia at baseline.

In paper I, 21 patients gave their written informed consent to the collection of data about OC from NMBR. However, two of them were not born in Norway and had to be excluded, resulting in a total of 19 patients used for further analysis. In paper II, all 31 patients were included at baseline and were followed longitudinally. The number of patients who attended

the study at T2/T3 was: 22/20, and the patients who completed all the tests included in the composite score were at T1: 29, T2: 18 and at T3: 18. In paper III, the same patients as previously described in paper I, were included.

The healthy control group was screened for mental problems using the Mini-International Neuropsychiatric Interview (M.I.N.I.) screening module (Sheehan et al., 1998), and a positive response to any of the questions was grounds for exclusion from the study. As in the EOS group, exclusion criteria were any known brain injury or neurological disease, or an IQ<70.

In Paper I, the healthy controls consisted of 67 subjects, of which 53 (tested on included cognitive measures) consented to retrieval of data about them concerning OC from the NMBR. In Paper II, 73 healthy controls were included at baseline and were followed longitudinally. The number of participants who attended the study at T2/T3 was 41/40, and the participants who completed all the tests included in the composite score were at T1: 67, T2: 39 and T3: 40. In Paper III, the healthy control group consisted of 67 subjects, of which 54 (tested on executive measures) consented to retrieval of data about OC from the NMBR.

3.5 Clinical assessments

Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), modules A-D. The age at onset was defined as age at the first SCID-verified psychotic episode.

For the assessment of psychotic symptoms and functioning, the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used. We calculated the PANSS baseline scores for the positive, negative and general component. Age of onset was defined by a PANSS score of 4 or more on the Positive or General Scale, and the mean age of onset in the group was 14 years (range 10-17). In paper II, only baseline scores were used in the analyses. Previous research on the same sample showed stability in symptom levels over the three time points and found no significant changes over time in positive, negative or general symptoms (Juuhl-Langseth et al., 2014). Hence, the baseline group did not differ significantly from those participating at T2 and T3. Global functioning was measured at baseline with the Global Assessment of Functioning-Split version (Split-GAF) (Pedersen et al., 2007), and there were no significant changes in split-GAF (symptoms or function) from T1 to T3.

DUP was measured by the time interval from the first onset of psychotic symptoms [defined as the first week with a PANSS score of 4 or more on one of the Positive Scale items 1 (delusions), 3 (hallucinatory behavior), 5 (grandiosity), 6 (suspiciousness/persecution), or General Scale item 9 (unusual thought content)] to the start of the first adequate treatment of psychosis (defined as the start of adequate antipsychotic medication or admission to the hospital for treatment).

Suicide attempts were assessed in the clinical interviews. The youths were asked if they had ever attempted suicide, and if yes, how many times. The total number of suicide attempts before baseline was recorded as reported by the patients. Out of 31 patients at baseline, 6.7% reported one suicide attempt, 10% had two attempts, 3.3% had three attempts and 3.3% had five attempts.

Hospitalization was measured by the number of times a patient was admitted to psychiatric inpatient treatment due to psychotic symptoms before baseline assessment, and the total length of inpatient treatment was measured in weeks. Mean length of hospitalization in the group was 28.7 weeks (range 0-138).

Remission was defined by the absence of psychotic symptoms for at least seven days, as defined by the same PANSS symptoms as defined in DUP (see above). Of those in remission at baseline, 20% were in remission for seven days, 10% for 14 days, whereas 70% were in remission for 8-17 weeks.

Among the clinical characteristics at baseline, PANSS had three missing values, suicidality had one missing value, and remission had two missing values.

3.6 Cognitive assessments

3.6.1 *The MATRICS Consensus Cognitive Battery (MCCB)*

In paper I and II, all participants were tested with the MCCB (Green and Nuechterlein, 2004; Green et al., 2004; Nuechterlein et al., 2008). The MCCB is often referred to as the gold standard for cognitive assessment in severe psychopathology (Holmen et al., 2010; Mohn et al., 2012). For cognitive assessments of schizophrenia, the MCCB has been widely used in adult schizophrenia samples and is found to have good test-reliability and small practice-effect (Keefe et al., 2011; Rajji et al., 2013). Previous studies indicate that the MCCB is equally

sensitive for cognitive examination in EOS (Holmen et al., 2010; Juuhl-Langseth et al., 2014). However, because there are no norms for the MCCB scores of tests respondents below the age of 20, we calculated our own T scores with a mean of 50 and an SD of 10.

The MCCB covers the following seven domains:

- **Speed of processing** - This domain is assessed using the combined score of three tests. Trail Making Test A (TMT-A) (War Department, 1944) involves connecting numbers arranged in a random order on a sheet of paper, with the score being the total time to completion. Symbol coding (Brief Assessment of Cognition in Schizophrenia, BACS) (Keefe, 1999) requires writing numbers that correspond to different symbols. The score is the number of symbols correctly coded in 90 seconds. Category fluency (CF) (Blair, 1989) involves mentioning as many animals as possible in 60 seconds.
- **Attention/vigilance** - This domain is assessed using the computer-based Continuous Performance Test – Identical Pairs (CPT-IP) (Cornblatt et al., 1988), which requires the participant to monitor two-, three- and four-digit numbers on a computer screen and press a button when two identical digits are presented in a row. The score is the mean value of the signal/noise discrimination across the three conditions.
- **Working memory** - This domain is assessed using the combined score of two tests. The Spatial Span Test from the Wechsler Memory Scale (SS-WMS) (Wechsler, 1997) requires the participant to remember the location of blocks pointed forwards and backwards by the administrator. The University of Maryland Letter Number Span Test (LNS) (Gold et al., 1997) requires the participant to order and repeat random combinations of letters and numbers read aloud by the administrator. The score is the sum of the correct block sequences and letter-number combinations performed.
- **Verbal learning** - The revised Hopkins Verbal Learning Test (HVLT-R) (Brandt, 2001) list of 12 words is presented three times. The score is the sum of words recalled after these three trials.
- **Visual learning** - The revised Brief Visuospatial Memory Test (MBVT-R) (Benedict, 1997) is a test administered in which the participant is asked to draw six geometrical figures after a 10-second exposure. The score is the sum of points awarded for the correct drawings on three trials.

- **Reasoning and problem solving** - This domain is assessed using the Mazes Test (Neuropsychological Assessment Battery, NAB) (White, 2003), in which seven mazes of increasing difficulty are presented on paper and solved with a pencil. The score is the sum of the points awarded for the time needed to solve the mazes.
- **Social cognition** – To measure this domain, the Managing Emotions part of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (Mayer, 2002) is used. The participant is asked to rate the effectiveness of different actions regarding the outcomes of situations involving the regulation of one's emotions or relationships to other people. The score is calculated using a computer-based general consensus scoring.
- **Composite score** – a composite sum score is calculated using the arithmetic average of the seven domains.

3.6.2 *General intellectual function*

General intellectual function (IQ) was assessed according to norms using the four subtests (Vocabulary, Similarities, Block design and Matrix reasoning) of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007).

3.6.3 *Executive function*

In the MCCB, executive function is measured by the Mazes test. However, because of the multiple components of the domain, the Mazes test appears not to be sensitive enough when assessing executive functioning, especially in the EOS population (Holmen et al., 2012a; Holmen et al., 2012b). Thus, in paper III, we added two more test commonly used in the investigation of executive function; the Wisconsin Card Sorting Test (WCST) (Heaton, 1993) and the D-KEFS Color Word Interference Test (CWIT) (Delis, 2001).

The WCST measures the participants capacity for mental flexibility, cognitive inhibition and abstraction. The participants are presented to a series of cards and are required to sort them according to key cards that vary in shape, color, and number of shapes. The sorting principles are deduced from feedback provided by the computer, and new principles are presented arbitrarily throughout the trial. Ten measures from the computerized version of WCST can be obtained. Studies vary in which measures they report. Some include total errors, perseverative errors and non-perseverative errors, while others argue that all measures should be used since

they cover different aspects of executive function. Hence, we included all ten measures for further analyses: total correct; total errors; perseverative responses; perseverative errors; non-perseverative errors; conceptual level responses; categories completed; trials to complete first category; failure to maintain set; and learning to learn.

The CWIT assesses the capacity for verbal inhibition, by measuring the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute. It consists of four conditions; two baseline conditions that measure basic speed abilities, *I*: “*color naming*” of color patches and *II*: “*word reading*” color-words printed in black, followed by two conditions that challenge executive abilities, *III*: “*inhibition*” (inhibiting the impulse of reading the words instead of naming the dissonant ink color of the word), and *IV*: “*inhibition/switching*” (switching back and forth between naming the dissonant ink colors and reading the words). Two measures from condition III and IV were used for further analyses; response time measured in seconds (speed), and total errors.

3.7 Assessments of obstetric complications

Information on OC was collected from the NMBR, a national health registry containing information about all births in Norway, including information about maternal health before and during pregnancy, and any complications arising during pregnancy or birth. The registry includes information about medication during pregnancy, labor interventions, birth complications, maternal complications after birth, whether this was a live birth, any diagnoses in the child or evidence of congenital abnormalities.

A total of 39 variables concerning pregnancy and birth were obtained. The OC were presented in the subgroups used by the NMBR. However, some of the collected variables had no value and did not occur in any of the cases in our sample, and thus, were excluded from the analyses. All the complications were analyzed separately. Moreover, we calculated a sum score, OC Total, by adding the number of occurring OCs in each diagnostic group. In Paper I, all OC measures with value were included. In Paper III, only perinatal measures were included, in addition to Apgar 5-minutes scores.

3.8 Statistical analyses

In all papers included in this thesis, the statistical analyses were carried out using IBM SPSS Statistics version 25 or STATA 14.0 software. The statistical level of significance was set at $p < .05$ in paper I and III, and $p < .001$ in paper III, with a confidence level at 95%.

3.8.1 Paper I and III: Student's t-tests, ANOVA and linear regression analyses

In Paper I, group differences in OC were studied with Student's t-tests and Chi-square tests. Furthermore, group differences in cognition were analyzed with ANOVAs with partial eta squared measurement of effect size.

To analyze the associations between complications and cognition in paper I, linear regression analyses were used, with a cognitive test score as the dependent variable. In each analysis, the independent variable were an OC and an OC x diagnosis interaction variable. Because the control group was considerably larger than the EOS group, all statistical analyses were repeated using pairwise matched samples, based on gender and age. However, this procedure did not alter the results, so we reported the results of the entire samples.

In Paper III, to analyze associations between perinatal complications and executive function, we conducted a series of stepwise linear regression analyses. Each operation included one executive function test score as the dependent variable. The independent variable in each operation was one group variable (EOS versus healthy controls), one perinatal OC, and one between-group-interaction variable (diagnosis x OC). As in Paper I, all statistical analyses were repeated using pairwise matched samples, based on gender and age. The results were stable thus we reported the results of the entire samples.

3.8.2 Paper II: Linear mixed model for repeated cognitive measures

In Paper II, we analyzed the longitudinal cognitive composite scores and used statistical analyses that allowed the inclusion of all participants with at least one cognitive evaluation. For technical reasons a few participants were unable to perform every test of the battery included in the composite score, and there were some randomly missing data points. Hence, to account for missing data and confounding variables, all analyses were achieved with a linear mixed model that has been recommended for repeated measures (Gueorguieva and Krystal, 2004).

Compared to repeated measures ANOVA, the method is assumed to preserve sample size in small longitudinal psychological studies despite missing data, and provide similar measures of significance (Krueger and Tian, 2004; Muth et al., 2016).

To estimate differences between the two groups over the three time points for cognitive composite scores as outcome and control for repeated measurements, we used linear mixed models with an unstructured covariance matrix. The *time*, as measured in years after inclusion, *group* and *time-by-group* interaction were fixed effects in all models. In all models, random intercept and a random effect for time, were included. Based on the linear mixed model, we estimated mean values with 95% confidence intervals (CI) for the three time points (T1, T2 and T3) for each group, and estimated the mean group changes from baseline to two years.

Linear mixed model analyses were also performed to identify risk factors of change in cognitive composite scores over time in the patient group. All models included fixed effects for time as a continuous variable. In these analyses, the following clinical variables at baseline were considered for inclusion: DUP, PANSS (positive, negative and general) baseline scores, suicide attempts, in Split-GAF (symptoms and function), remission and in hospitalizations (number of times and total weeks). As normal in these analyses, any variable with a $p < .15$ from the univariable analysis were included as fixed factors in the multivariable model. Then a manual backward stepwise elimination procedure using a multivariable regression model was performed to identify independent risk factors. In all models a random intercept and random effect for time was included, and an unstructured covariance matrix were performed. Finally, multivariate analyses were preceded by estimation of correlation between risk factors.

4 SUMMARY OF PAPERS I-III

4.1 Paper I: Gestational length affects neurocognition in early-onset schizophrenia

Background: OC are assumed to increase the risk for schizophrenia in offspring, and research suggest a higher incidence of complications among those with an early illness onset. Extensive cognitive deficits occur in adult onset schizophrenia and with more profound deviances in EOS. No study has yet to investigate the relationship between OC and cognition in EOS. Firstly, this study aimed to investigate the frequency of OC in EOS compared to a healthy and age-matched comparison group. The second aim of the study was to examine the relationship between OC and cognitive dysfunction in the two groups.

Methods: Using the MCCB, neuropsychological functioning was examined in nineteen EOS patients and 53 healthy controls. The cognitive measures were combined with obstetric data from the NMBR.

Results: The results gave no indication of group differences in OC in EOS and healthy controls. When examining the relationship between OC and cognition, a shorter gestational length in the EOS group led to significant decreases in the overall cognitive composite score, and in processing speed.

Conclusions: The findings suggested that the poorer neuropsychological performances commonly found in EOS may be partly attributable to the length of gestation. Moreover, the worsened cognitive functioning did not appear among controls, so gestational length had a different impact on the two groups. Hence, a shorter gestational length did not increase the risk for early psychoses but did significantly affect the cognitive difficulties in this group.

4.2 Paper II: Do clinical characteristics predict the cognitive course in early-onset schizophrenia-spectrum disorders?

Background: EOS patients exhibit more severe symptoms and more profound cognitive deviances compared to adult onset schizophrenia, and they have a worse clinical course and outcome. However, there is limited research on both the long-term course of generalized

cognition in EOS and how the cognitive course is influenced by clinical characteristics during the early illness period.

Methods: Thirty-one EOS patients and 73 controls between the age of 12 and 18, were assessed on clinical variables at baseline (PANSS, DUP, hospitalizations, suicide attempts and remission). Neuropsychological assessments were conducted with the MCCB at three time points; at baseline, after one year and after two years, and composite scores of total performances were calculated. All the analyses were performed with a linear mixed model.

Results: Global cognition followed a stable course over the first years of the disease in EOS, though at a significantly lower level in EOS compared to the control group. Our analyses showed that PANSS-general and suicide attempt history at baseline were identified as risk factors of longitudinal cognitive function. We did not detect a relationship between DUP, remission, positive/negative symptoms and hospitalizations and long-term cognition.

Conclusions: Our results showed that the EOS group and the controls had a similar cognitive course over two years, though at different levels. Some baseline clinical characteristics (psychotic symptoms, DUP, remission and hospitalization) had no influence on cognition within the first two years of illness. In contrast, higher levels of general symptoms and a history of suicide attempts at baseline were more potent risk factors of a deteriorating cognitive course than the psychotic-specific symptoms. General symptoms and suicidality should therefore be subject to specific attention in the evaluation and treatment of patients with early onset psychosis.

4.3 Paper III: Perinatal complications and executive dysfunction in early-onset schizophrenia

Background: The study examined the association between perinatal OC and executive dysfunction in EOS, compared to healthy controls. Higher incidences of OC and more extensive executive dysfunctions characterize EOS. Research shows considerable brain maturation in newborns, suggesting them to be particularly vulnerable for perinatal insults. Executive function is mediated by the prefrontal cortex, an area that matures last during pregnancy. Thus, exposure to perinatal OC may influence executive dysfunction in EOS.

Methods: The participants were 19 EOS patients and 54 healthy controls. Executive function was assessed with the D-KEFS battery and the Wisconsin Card Sorting Test.

Information on perinatal OC and Apgar 5-minutes scores were obtained from the NMBR. Associations between perinatal conditions and executive function were studied using stepwise regression analyses.

Results: Perinatal OC, and especially shorter gestational length, were associated with significant executive dysfunctions in EOS, but did not influence executive function among healthy controls. Lower Apgar 5-minutes scores were related to executive dysfunction in both groups.

Conclusions: Exposure to perinatal OC and particularly shorter gestational lengths, was associated with increased executive difficulties in EOS. Exposed healthy controls did not exhibit similar executive dysfunctions, indicating that the EOS patients are especially vulnerable for executive deficits due to perinatal insults. The findings indicate that exposed EOS youths learn more slowly and experience more difficulty with problem-solving, which carry important implications for clinical practice. Lower Apgar 5-minutes scores were associated with executive dysfunction in both groups, thus, may be an indicator of executive difficulties among adolescents, independent of diagnosis.

5 DISCUSSION

After a brief summary of the main findings, this section will discuss our results in relation to current research in the field of schizophrenia.

5.1 Summary of results

- The poorer neuropsychological performances commonly found in EOS may be partly attributable to the length of gestation. There were no significant differences in frequency of exposure to complications in EOS compared to healthy controls. A shorter gestational length did not increase the risk for early psychosis but significantly affected the cognitive difficulties found in this group.
- Exposure to perinatal complications, and especially shorter gestational length, were associated with significant impairments in executive function in EOS. The exposed EOS youths seem to learn more slowly and experience more difficulty with problem-solving, which carry important implications for clinical practice.
- Healthy controls exposed to the same OC as EOS cases did not exhibit the same cognitive deficiencies, indicating that EOS patients seem particularly vulnerable to cognitive deficits due to obstetric insults.
- Patients with EOS show a stable long-term course of global cognition, with no indication of neurodegeneration within the first years after illness onset.
- High levels of general symptoms at baseline were associated with significantly worsen cognitive course in EOS. Cognitive deterioration seems influenced by a strong affective response to the illness, rather than a result of psychotic symptoms alone, and should be subject to specific attention in the evaluation and treatment of patients with early onset psychosis.
- A history of suicide attempts was associated with a deteriorated cognitive course in EOS. Other clinical variables, such as psychotic symptoms, DUP, remission and hospitalization did not affect the long-term cognitive course in EOS.

5.2 Discussion of findings

5.2.1 *Obstetric complications as a risk-factor for early-onset schizophrenia*

Our first hypothesis in paper I was that we would find a higher frequency of OC among EOS than among healthy controls. Contrary to our hypothesis, we found no significant associations between such complications, neither separately nor combined, among EOS compared to healthy controls. These results were stable when we excluded the participants in the EOS group who had the diagnosis of Psychosis NOS, and when we pair-matched the samples on age and gender.

A possible explanation for the nonsignificant results may be the sample size, which was small with the total frequency of complications higher in the EOS group than in the control group (48% versus 31%, respectively), though this was not statistically significant. A larger sample might have altered our results. In a meta-analysis by Cannon et al. (2002a), a majority of research on OC and schizophrenia is weakened by small sample sizes, thereby failing to detect small and interactive effects that might be revealed in studies with larger samples. Because the effect sizes in these studies generally are small, with odds ratio of less than 2, we are far from strong causalities, i.e. the power in the largest population-based studies to detect odd ratio of 1.5 was less than 70% (Cannon et al., 2002a). Nevertheless, previous research report associations between OC and EOS (Matsumoto et al., 1999; Preti et al., 2000). Verdoux et al. (1997) found that patients with onset before age 22 were almost three times more likely to have a history of OC compared to those with later onset. Verdoux and colleagues' findings were based on data from 854 schizophrenia patients (Lewis and Murray scale) that was categorized in four age-groups; ≤ 18 (N=123), 19-21 (N=130), 22-25 (N=137), ≥ 25 (N=117) (Verdoux et al., 1997). Their findings indicated that the earlier the age of onset, the more likely the history of OC. The study involved a considerably larger patient group than ours. Even so, our EOS group showed a higher (but not significant) frequency of complications than controls, which indicates that more significant results may be found with a larger sample size, underlining the need to interpret our null-result with caution.

A further explanation for the nonsignificant result concerns the selection and grouping of OC. According to Cannon and colleagues, the individual OC might be proxy effects for other factors, such as lifestyle or socioeconomic status, or interactive effects with unknown genetic or epigenetic factors. The study of individual obstetric risk factors for schizophrenia can be

understood as “the search for rare risk factors for a rare disease and is therefore truly suitable neither for the classic cohort study nor for case-control designs” (Cannon et al., 2002a) (page 1087). Cannon et. al. criticize measurements of OC for being unspecific, and suggest, rather of a broad definition of OC, more careful definitions of exposures, such as prenatal assessments of maternal antibodies, as well as more quantitative measures, such as birth weight and head circumference, to show larger and more consistent effects. They also introduce three categories of OC; complications of pregnancy, abnormal fetal growth and development, and complications of delivery, and suggest dividing schizophrenia into subgroups, such as EOS patients, to detect subgroup effects (Cannon et al., 2002a). In our study, due to the material available at NMBR, we examined the complications separately. Some of the OC in the categories suggested by Cannon were not included in our material. On the other hand, we collected information on OC not included in their categories. Information on fetal hypoxia was not available to us, so we decided to analyze the collected complications separately and combined in one total score, to see if we could find a subgroup effect in our EOS sample. This may have weakened our results. Cannon et. al. also suggest that more careful definitions of exposures (i.e. prenatal measurements of antibodies) and more extensive use of quantitative measures of OC (i.e. birth weight and head circumference) may show larger effects. In a study by Rubio-Abadal et al. (2015), including 90 patients of all ages, birth weight seemed to contribute to age of onset. In other studies, low birth weight and low gestational age have been found to be likely risk-factors for adult onset schizophrenia (Abel et al., 2010; Geddes, 1999; Gunnell et al., 2003; Hultman et al., 1999; Lahti et al., 2015; Nosarti et al., 2012). In our EOS sample though, the same complications were not significantly more frequent among EOS patients than healthy controls.

Finally, when examining the relationship between obstetric events and EOS, we compared EOS to healthy controls. Verdoux et al. (1997) and Rubio-Abadal et al. (2015) grouped schizophrenia patients after age of onset, and compared the groups. In our study, if we grouped our patient sample after age of onset, the groups would be far too small to detect any significant associations, but we could have used an adult schizophrenia comparison group. This might have altered our results or provided new hypotheses for further research. Nevertheless, our findings raise questions about the strength of the association between OC and EOS, but due to our small sample, the relationship should be investigated in larger samples.

5.2.2 *The relationship between gestational length and cognition*

When we examined a variety of OC in relation to cognitive functioning in EOS in Paper I, we found that shorter gestational length in the EOS group was associated with significant decreases in the overall composite score and in processing speed.

The importance of full-term pregnancies has been underlined in research on the general population, and prematurity is related to cognitive deficits (Lawrence et al., 2010), which may be a likely explanation for our findings. An association has been detected between preterm births, neuroanatomical alterations in the brain network and impaired neurodevelopment, and furthermore, the same alterations have been found to be disruptive in groups that have mental health problems (Lawrence et al., 2010; Nosarti et al., 2012; Nosarti et al., 2009). However, these studies consider very preterm births, while our sample gestational age was not particularly short. Still, the length of gestation had a significant impact on cognition in the EOS group. Interestingly, the relationship between gestational length and cognitive deficits did not appear among healthy controls. Hence, gestational length may have a greater impact on neuropsychological disruption among those who are especially vulnerable to psychosis.

How can we explain how a shorter gestational length affects the fetus to cause or contribute to cognitive deficits and EOS? It is assumed that a variety of pre- or perinatal exposures may potentially disturb the fetus' neural development and cause malformations in the brain (Brown and Derkits, 2010; Preti and Wilson, 2011). Research shows that OC may result in hypoxic-ischemic damage, and reductions in overall grey matter and hippocampal volume in schizophrenia patients (Cannon et al., 2002b; Haukvik et al., 2010; Nicodemus et al., 2008), as well as reduced cortical folding (Haukvik et al., 2012; Nesvag et al., 2014). Moreover, structural brain alterations are found in individuals with fetal exposure to inflammation who later develop schizophrenia (Ellman et al., 2010), and exposure to stress hormones during pregnancy is found to affect emotional and cognitive regulation in the childhood, and a reduced brain volume (Sandman and Davis, 2012). Findings also indicate a link between structural and functional deficits in prefrontal cortex and cognitive dysfunctions in schizophrenia patients (Brown et al., 2009; Goldberg et al., 1990; Rusch et al., 2007). From this one might postulate that the obstetric exposures would affect all fetuses in the same way, whether or not they develop psychosis. According to Cannon et al. (2002a), the individual OC might interact with unknown genetic or epigenetic factors. Some fetuses may have a specific biological vulnerability to develop schizophrenia that interact with certain complications (Cannon et al.,

2002a; Cannon et al., 2008). Preti and Wilson (2011) claim that a wide range of genes can influence, positively or negatively, the effect of different OC, and the same genes are involved in neurodevelopment. They infer a causal line of mechanisms; from pre and perinatal brain insults, to neuronal reorganization and synaptic plasticity in adolescence, to onset of psychosis (Preti and Wilson, 2011). Another theory that emphasizes the interplay between epigenetic and genetic risk factors suggests that schizophrenia in parts stems from abnormal fetal growth, caused by environmental influences on imprinted genes and placental and cerebral development (Abel, 2004). In continuation of this theory, different cognitive deficits occurring in schizophrenia may derive from abnormalities of genomic imprinting and placentation, resulting in defects specific to the neocortical development of the fetus (Abel, 2004). This theory may explain how OC affect fetuses in different ways, as well as why the risk for schizophrenia increases with i.e. paternal age, season of birth, urbanicity and migration, and is more likely to be inherited from an affected mother than father (Abel, 2004; Byrne et al., 2002; Malaspina et al., 2001; Mortensen et al., 1999). The theory further suggests a bridge between in utero conditions and different cognitive deficits in schizophrenia. It implies that abnormal fetal growth may affect a variety of cognitive difficulties in schizophrenia. Newborn can be born preterm, but still be normal birth weight, however, shorter gestational length often also includes lower birth weight.

A connection between genes, schizophrenia, neurodevelopment and neurodegeneration is also reported in other studies (Allan and Rothwell, 2001; Nawa et al., 2000). According to Weinberger (2017b), new evidence from Ursini et al. (2017) supports a neurodevelopmental origin of schizophrenia in which a sizable fraction of genes in the schizophrenia GWAS, directly influence placental biology and placental health and can cause complicated pregnancies. With respect to our findings, shorter gestational lengths may affect those vulnerable to psychosis, but the opposite may also be true, that a specific genetic vulnerability in the fetus affects the length of gestation.

Earlier accounts of the neurodevelopmental theory regarded schizophrenia as the outcome of lesions often occurring in the second trimester of intrauterine life, causing cognitive deficits in the fetus (Weinberger, 1986). But as Bora and colleagues object, neurodevelopment is an extended process, in which some aspects of normal cortical development occur during the prenatal life (proliferation and migration), while other aspects (arborization and myelination) continue through the first post-natal decades (Bora, 2015). This may explain the neurobiological

heterogeneity seen among schizophrenia patients. Those with severe cognitive abnormalities apparent from childhood are more likely to experience problems in migration, gyrification and activity-independent, hard-wired connectivity problems, while those with less cognitive deficits have abnormalities in activity-dependent fine-tuning of synaptic connectivity (myelination, synaptic remodeling/dendritic arborization) in high-level association cortices (Bora, 2015). Furthermore, in some patients, the interaction of neurodevelopmental abnormalities and low cognitive reserve, may lead to further loss of functioning over years (Bora, 2015). In recent publications, Weinberger highlights genetic and epigenetic research indicating that the prenatal period is critical of schizophrenia risk, and have a particular molecular impact on early development (Weinberger, 2017a). Nevertheless, how OC may contribute to the causations of schizophrenia, as well as how complications affect cognitive difficulties, is still uncertain. Research investigating the association between developmental trajectories of cognitive skills, its brain imaging correlates, and psychosis-risk genes, are essential to fully understand the cognitive impairments in schizophrenia (Bora, 2015).

Maternal hemoglobin levels have been found to influence neuromotor tasks and general IQ in adult schizophrenia (Ellman et al., 2012). In our EOS sample, we found no significant association between hemoglobin levels and cognition. The lack of association may be caused by a small sample size, but Ellman and colleagues had 24 cases in their study, and a smaller control group compared to our study, so another possibility is that the fetal insults affect the two groups of patients (EOS vs. adult schizophrenia) differently. As mentioned earlier, the individual OC might interact with unknown genetic or epigenetic factors. There may be unknown genetic and epigenetic factors that have influence on the effect of environmental exposures, leading some exposures to have a large effect in those with a specific genetic make-up, but less effect in others (Cannon et al., 2002a). This could imply differences not only between groups, but also variations within groups, which means that same OC may affect some fetuses within the same group, but not others. Thus, the different results in our studies may be caused by maternal hemoglobin levels being less important as a risk factor in our EOS group than in the specific adult schizophrenia group examined by Ellman et al. (2012).

There may have been prenatal factors not included in our analyses. In the general population, maternal psychosocial stress and depression, as measured by levels of maternal cortisol early in pregnancy, affect gestational length (Sandman et al., 2006), and are found to increase children's risk for later cognitive and language difficulties (Sohr-Preston and

Scaramella, 2006; Wadhwa et al., 1993), as well as impaired physical and mental development (Davis and Sandman, 2010). Information on maternal cortisol was not available to us, but it is possible that mothers in our EOS group had higher levels of cortisol during pregnancy than mothers in the healthy control group. Neither did we have information about maternal infections during pregnancy, that have been found to affect verbal tasks and executive functions in offspring with adult schizophrenia (Brown et al., 2009; Ellman et al., 2009).

Our findings suggest that a reduced processing speed among EOS patients may be partially attributable to gestational length. Processing speed is found to be important for other higher cognitive operations such as executive function and memory (Dickinson et al., 2007; Kelleher et al., 2013; Knowles et al., 2010), and our results indicate a specific connection between processing speed and OC, and support the idea that this cognitive domain is especially sensitive to underlying brain dysfunction and damage (Perianez et al., 2007).

5.2.3 Associations between perinatal complications and executive dysfunction

The analyses in Paper I included seven cognitive domains. Some of the domains involve problem-solving and working memory, but the study did not examine common measures of executive function. The previous results suggested that perinatal complications and especially gestational length, could have a special impact on EOS patients. As noted in the introduction, extensive brain maturation starting at birth may represent a vulnerability for especially perinatal insults (Gilmore et al., 2006). It is suggested that perinatal OC influence the prefrontal cortex in particular, because the area is the last to mature during pregnancy (Abel, 2004). A likely hypothesis is that exposure to perinatal insults affects neural networks in the prefrontal cortex and disturbs the development of executive function more than other cognitive domains. Thus, in Paper III we analyzed only perinatal conditions and included executive function tests found to be especially sensitive to frontal lobe deficits (Asarnow et al., 1994); the WCST and the CWIT (Liu et al., 2011; Yatham et al., 2010).

Our findings suggest that EOS patients exposed to perinatal OC show significant executive dysfunction, compared to unexposed patients and healthy controls. Some perinatal OC (birth weight, dystocia and bleeding) had no significant impact on executive function in either groups. However, in the EOS group, a variety of perinatal exposures, including a shorter gestational length, were significantly associated with more trials to complete the first category of the WCST. A reduced ability to complete the first category can be explained by a lower

capacity to generate or apply cognitive inhibition. This often manifests as cognitive control deficits and frequent distraction by non-pertinent inhibition (Everett et al., 2001). The difficulty seem closely related to several clinical symptoms frequently encountered by this illness, such as incoherent thought and speech (Gray et al., 1991).

The results suggest that length of gestation is especially critical to development of executive function in EOS. According to Abel (2004) neocortical areas such as prefrontal cortex, are the last to mature during pregnancy, and may be more vulnerable to growth abnormalities. It seems likely that not only growth abnormalities, but also other perinatal OC would influence the prefrontal cortex. These insults may affect neural networks in the prefrontal cortex causing executive deviations. It follows that other cognitive domains, less associated with prefrontal cortex, may be less influenced by perinatal insults. A possible explanation is that shorter gestation halts a natural in utero maturation of the prefrontal cortex, and thereby affects the development of neural networks associated with executive function. This theory is in line with research suggesting that perinatal complications disturb the extensive brain maturation in newborns, starting at birth (Gilmore et al., 2006). Thus, full term pregnancies may be critical for this group to prevent executive deterioration. We found no association between executive dysfunction and lower birth weight which is a measure often linked to growth abnormalities and poorer neurodevelopment (Abel, 2004; Freedman et al., 2013). Though prematurity is often found with growth abnormalities and low birth weight, there is not necessarily a link between the two, because the newborn can be premature and still have an average birth weight, or vice versa. Our results suggest that full term delivery affects the development of executive function more than birth weight.

EOS cases exposed to emergency caesarean section and the use of vacuum needed more trials to succeed at the first category in the WCST than unaffected cases and controls. Those exposed to forceps also committed more inhibition and switching errors on the CWIT. The results are based on few participants and should be interpreted with caution. Yet, similar findings were reported by Yurgelun-Todd and Kinney (1993), who found executive dysfunctions in adults with schizophrenia exposed to perinatal OC. These exposures may disturb the extensive brain maturation starting at birth causing executive deviances in EOS. The perinatal OC, as well as gestational length, were mainly connected to the use of more trials to succeed at the WCST. This indicate that EOS patients with a history of perinatal OC learn more slowly and need considerably more practice trials to complete tasks than healthy controls and

those with no history of perinatal OC. The finding that these patients seem to have a poorer learning curve and larger difficulties with problem-solving carry important implications for clinical practice.

Healthy controls exposed to the same perinatal conditions as the EOS patients, did not exhibit similar executive deficits. One study found executive dysfunctions in all participants exposed to pre- and perinatal OC (schizophrenia patients, their siblings and healthy controls) (Yurgelun-Todd and Kinney, 1993). Most studies report deficits among OC exposed schizophrenia patients, but not among controls with the same OC history (Cannon et al., 2002a; Cannon et al., 2008; Ellman et al., 2012; Preti and Wilson, 2011). Our findings support this.

Apgar score is an early assessment of the potential consequence of OC. The score is an index used worldwide to evaluate the overall status of the newborn in the first, fifth, and tenth minutes after life, and measures breathing effort, heart rate, muscle tone, reflexes and skin color (Apgar, 1953). The score was introduced more than 60 years ago, but still has value in contemporary practice (Iliodromiti et al., 2014). The score seems influenced by a variety of pre- and perinatal events, such as hypoxia, prematurity, head injury and infection (AAP, 2015) and reflects the severity and/or accumulation of OC, but without specifying the causes and outcomes (Ehrenstein et al., 2009; Gardener et al., 2011; Odd et al., 2008). In our study, we found that a lower Apgar score at 5-minute was significantly associated with more total errors and more perseverative errors in the WCST in the EOS group. However, lower Apgar scores at 5 minutes were also linked with one measure of executive dysfunctions (perseverative responses) in the healthy control group. Previous research in the general population has found a relationship between lower 5-minute Apgar scores and increased risk of severe neurological outcome (Moster et al., 2001; Nelson and Ellenberg, 1984; Sun et al., 2006; Thorngren-Jerneck and Herbst, 2001). A Danish study that included almost 20 000 young men (median 19 years), showed that lower 5-minutes Apgar scores were associated with neurological disabilities and lower cognitive function (Ehrenstein et al., 2009). Similar results from Sweden found a relationship between a low Apgar score at 5 minutes and poorer cognitive functioning in adolescents (15-16 years) (Odd et al., 2008). The findings contradict previous results from Seidman et. al. (1991) that show few associations between Apgar scores and cognitive function in Israeli adolescents (mean 17 years). Though not including cognition, a recent study by Kotlicka-Antczak et al. (2017) found that a combination of OC and low Apgar scores increased the probability of conversion to schizophrenia in teenagers (mean 18 years) at high risk for

psychosis. Previous results from the same research group showed that both exposure to OC and lower Apgar score were significantly more frequent in teenagers at risk for psychosis than healthy controls (Kotlicka-Antczak et al., 2014). Our findings support most previous research suggesting a relationship between Apgar 5-minutes scores and cognitive deficits in the general population, and suggest that lower Apgar 5-minutes scores are also associated with executive dysfunction in youths, independently of diagnosis. However, the result does not specify the cause for the condition but suggests that low 5 minutes score may be an early indicator of executive dysfunctions.

It is important to note that a variety of conditions may contribute to perinatal complications. Research indicate that individual maternal characteristics, i.e. BMI (Nieman et al., 1999), stress (Coussons-Read et al., 2007; Sandman and Davis, 2012) and exercise (Pedersen and Hoffman-Goetz, 2000) are associated with alterations in immune functioning, susceptibility to infection, and schizophrenia (Fineberg and Ellman, 2013). These conditions might affect the pregnancy and may influence prematurity or vulnerability to perinatal insult. Such individual characteristics were not available to us but could have affected our findings. Research that includes a variety of potential interactions is important for future investigations.

It has been suggested that prenatal exposure to infections is associated with increased risk for schizophrenia, and that the association is mediated by the maternal immune response (proinflammatory cytokines), that may disrupt fetal brain development (Zuckerman et al., 2003). In an animal study, Zuckerman and colleagues found that prenatal immune activation in pregnant rats, did not affect inhibition deficits in the juvenile offspring, but led to inhibition disruptions in adulthood. Information on prenatal exposure to infections was not available to us, and conclusions based on animals should be interpreted with caution, but the study indicates that some obstetric events may influence executive dysfunction over time, and that the executive difficulties may not be apparent before adulthood. Brown et al. (2009) examined this hypothesis in adults with schizophrenia and found that prenatal exposure to infections were associated with executive dysfunction. A possibility is that these executive deficiencies would not emerge among adolescents but appear at adulthood and would not be detected in EOS samples. Our results, however, showed inhibition deficits among youths with schizophrenia that were exposed to perinatal OC. We found stronger associations between perinatal conditions and executive dysfunction, than between other obstetric exposures and cognitive deficits in the EOS group reported in our first paper. Perinatal insults could therefore affect executive

dysfunction more extensively than other cognitive domains in this group. It may be that executive deficits indirectly affect other cognitive functions as a result of inadequate strategies to approach, plan or accomplish cognitive tasks (Burgess et al., 1998). Hence, the deficits in the other cognitive domains are diffuse and appear less prominent.

Our results indicated that the WCST seems particularly sensitive to executive dysfunctions, which is consistent with earlier reports (Liu et al., 2011; Yatham et al., 2010), especially in the EOS group (Holmen et al., 2012a). As noted earlier, inhibition is the first executive function to mature, while other executive components show a more gradual improvement throughout development (Best and Miller, 2010). The WCST mainly assesses inhibition deficits and could give a better assessment of executive dysfunctions in the adolescent group than other executive tests.

5.2.4 The generalized cognitive course in early-onset schizophrenia

In paper II, we examined the long-term course of global cognition in EOS and how this is influenced by clinical characteristics during the early illness period. Our results support previous findings reported in the Early-onset Study (Juuhl-Langseth et al., 2014), as well as other longitudinal studies (Frangou et al., 2008; Jepsen et al., 2010), namely that there is a deficit in the cognitive function in EOS compared to controls, and that this course is relatively stable.

The control group had above average IQ, which might have affected the results. When we adjusted for IQ in the analyses, the controls did experience a larger cognitive change compared to patients, but the difference was not significant. Moreover, dropouts from the EOS group had larger cognitive deficits at baseline than the ones that stayed in the study, which could indicate a different cognitive course for these patients. Nevertheless, a stable global cognitive course indicates that degeneration, defined as a progressive neurodegenerative process after illness onset, does not occur in EOS within the few first years of diagnosis. The finding is consistent with most previous studies (Frangou et al., 2008; Jepsen et al., 2010), but not all (Oie et al., 2010).

5.2.5 Do clinical characteristics predict the cognitive course in early-onset schizophrenia?

When we investigated how the cognitive course was influenced by clinical characteristics, we found that a higher number of general symptoms (PANSS-general) at baseline significantly predicted a deteriorated longitudinal composite score in EOS. In the separate univariate analyses, both positive symptoms (PANSS-positive) and negative symptoms (PANSS-negative) predicted the cognitive course, but they both lost their predictive value in the multiple regression analyses. Our findings are in line with previous research from adult schizophrenia that reports no longitudinal relationship between positive/negative symptoms and cognition (Harvey et al., 2006; Rund et al., 2015; Rund et al., 2004), indicating similarities between EOS and schizophrenia with later onset. Like us, Wozniak et al. (2008) found no significant relationship between psychotic symptoms and cognition in EOS, but their study did not include general symptoms.

While the positive and negative scales of the PANSS measure the amount of typical psychotic symptoms, the general psychopathology scale measures the severity of the schizophrenic illness (Kay et al., 1987). The general scale includes 16 non-specific psychiatric symptoms, i.e. depression, anxiety, guilt feeling and social avoidance. In our study, we examined the total general score and not the symptoms separately, so we have no information of the relative effect of specific symptoms included in the scale. Our findings suggest that general symptoms, relative to the psychotic symptoms, better predict the cognitive course in EOS. This may imply that cognitive deterioration is influenced by a strong affective response to the illness, rather than being a result of irrational or psychotic symptoms in and of themselves.

5.2.6 A deteriorating course among patients with a history of suicide attempts

As is the case with adults with schizophrenia, those with EOS have an increased risk of suicide within a year after the onset of psychosis (Sanchez-Gistau et al., 2013), particularly if they have a history of depression and previous suicide attempts (Melle, 2013). Our results indicate that a history of suicide attempts is related to cognitive deterioration. An association between suicidality and cognitive functioning has also been reported in some adult onset studies, suggesting a relationship between hopelessness, a greater insight into one's own illness and a higher cognitive functioning on the one side, and a higher risk of suicidality on the other

(Delaney et al., 2012; Kim et al., 2003). However, other studies fail to find such associations (Potkin et al., 2003; Zoghbi et al., 2014).

As far as we know, our study is the first to suggest that a history of suicide attempts at baseline affect a worsened cognitive course in EOS. This relationship should be understood in the context of general symptoms, because both suicidal ideation and suicide attempts most likely interact with several symptoms on the general scale, i.e. depression and social avoidance. According to Fialko et al. (2006), suicide attempts in psychosis appear to be caused by an entire range of general symptoms, rather than by the psychotic symptoms alone. People with psychosis are often met with stigma, pessimism and exclusion in society (van Os and Kapur, 2009), adding an extra burden to the illness that may affect both general symptoms and suicidality. Moreover, suicide attempts among patients with schizophrenia have been associated with impulsivity as measured by cognitive tests (Wang et al., 2014; Wu et al., 2009). Impulsivity is also associated with cognitive deterioration (Arce and Santisteban, 2006), and both suicide attempts and impulsivity may indicate a higher level of general symptoms. Even so, the high rate of suicidality in schizophrenia strongly suggests that suicidal ideation and history need to be determined, and protective measures must be taken while planning the inpatient and outpatient treatment of these patients.

There are some controversies in our findings. On one hand, we detected a stable longitudinal cognitive course in EOS, and on the other hand that higher levels of general symptoms and suicide attempts at baseline was associated with cognitive deterioration. This may indicate heterogeneity within EOS. There may be a subgroup of patients who deteriorates over time due to higher levels of general symptoms and suicidality. However, our sample size is too small to isolate such a subgroup, but the hypothesis should be subject to investigation in future research with larger sample sizes.

5.2.7 The cognitive course is not influenced by longer duration of untreated psychosis and remission

The null-results from our study are possibly as interesting as the statistically significant findings. In adolescence the brain matures extensively, and one could assume that a longer DUP would have a more severe impact on cognition in this time period than later in life. However, we found no significant influence of DUP on long-term cognition in EOS. There were no signs of neurotoxicity in the timeframe measured, and no indication of DUP being

more critical in adolescent psychosis than in adult psychosis. In line with our findings, though only measured at baseline, Kravariti et al. (2003a) did not detect an effect of illness duration on cognitive performance in EOS. Another study by Fraguas et al. (2014) indicated, on the other hand, that DUP predicts reduced long-term executive functioning in EOS. A possibility is that DUP affects executive functions more severely than other cognitive domains, and by evaluating composite scores in our study the impact was diffused.

Our analyses did not reveal a connection between remission before baseline and the longitudinal composite score in EOS. In an adult sample, stable remission without relapse in the first year predicted a better cognitive course, implying that patients with a stable remission respond better to treatment, and have good prognosis and cognitive trajectories (Rund et al., 2015). The divergent results may be explained by a more unstable remission in adolescents, so remission may not be a good predictor of the cognitive course in EOS. We also defined remission by the disappearance of psychotic symptoms for at least seven days, which may be short. Previous research has suggested that six months is an indication of clinical remission assessed with the PANSS (Andreasen et al., 2005; Opler et al., 2007). Among our patients, 70% were in remission over a period of 8-17 weeks, but none of the patients was symptom-free for more than five months before baseline. Thus, remission in our group seemed quite unstable, and would have been nonexistent with a stricter definition.

5.2.8 *Other clinical variables and longitudinal cognition*

Our results showed no significant relationship between Split-GAF and the number of hospitalizations or length of stay in institutions on the one hand, and longitudinal cognition on the other. Long-term institutional stays have decreased markedly, but hospitalizations occur, often caused by severe psychosis. Our findings support a review concluding with minimal indications of cognitive changes due to institutionalizations, whether long or short (Harvey et al., 2013).

5.3 Implications

The findings of this thesis add to the research field of cognitive deficits in EOS, as well as to the etiology of this illness. Our results suggest that there is no cognitive degeneration in EOS within the first two years after symptom onset. Since the EOS group shows profound

overall cognitive deficits compared to controls, these deficits seem to exist prior to illness onset. Even though we have limited knowledge of the origin of the deficits, our findings lend greater validity to the neurodevelopmental theory than the neurodegenerative hypothesis. Our results also suggest that exposure to OC may not influence the development of EOS but seems to be associated with the cognitive deficits occurring in this group.

Some of these findings have consequences for clinical practice, described below.

5.3.1 *Clinical implications*

Our results suggest that more profound cognitive deficits in EOS may be caused by exposure to OC, indicating heterogeneity in cognitive achievements due to obstetric exposure. Depending on conditions during pregnancy and at birth, our results imply that some groups of patients with EOS might be closer to healthy controls in cognitive performance, which coincides with the results of MacCabe et al. (2013) and Ochoa et al. (2013). OC should be considered in future research on cognition in EOS, but heterogeneity within the EOS group should be addressed.

Even though the health care system in Norway is already is comprehensive, our findings emphasized a need for a special focus on gestational length, both in maternal care and to ensure the necessary treatment to avoid preterm births. The results also draw attention to children born prematurely. Understanding the adolescent outcome of OC could aid the development of cognitive and neuroprotective remediation strategies. The association between OC and cognition in EOS provide an opportunity to identify at-risk subjects before symptom onset, and furthermore, to offer intervention programs aiming to preserve or improve the youths cognitive functioning. Such interventions, i.e. cognitive remediation programs, could affect daily functioning and prognosis.

Perinatal OC, as well as gestational length, were connected to inhibition difficulties in EOS. These patients seem to learn more slowly and need considerably more practice trials to complete tasks than healthy controls and unexposed patients. They have a lower learning curve and larger difficulties with problem-solving, findings that carry important implications for clinical practice.

Even though our sample size is small, processing speed seems to be highly affected by a shorter gestational age. A clinical implication of our results is the necessity to investigate tempo difficulties among EOS patients with a history of OC. Along with processing speed, our

findings indicate that executive function is the cognitive domain most affected by OC in EOS. Executive function should be examined in this group of patients, and intervention programs (as mentioned above) aiming at improving or preserving processing speed and executive function, should be administrated. Intervention programs that target cognitive dysfunction, such as cognitive remediation, has shown promising results in recent years (Deste et al., 2019; Lystad et al., 2017; Nuechterlein et al., 2011; Ventura et al., 2019; Wykes, 2008). Moreover, cognitive remediation in combination with rehabilitation, such as school and work training, enabled many patients to attain and maintain daily occupation (Lystad et al., 2017). For this vulnerable group of adolescents, it is especially important to provide cognitive remediation that may counteract a negative neurodevelopment and improve their prospects of achieving academic and professional success.

A final, but important clinical implication is that our findings indicate that higher scores of general symptoms, as well as suicide attempt history, predict a deteriorated cognitive course. In addition to individualized cognitive treatment programs aimed to stabilize or improve cognition, the results suggest therapeutic interventions designed to treat general symptoms, such as depression and anxiety.

5.3.2 Implications for future research

In general, all our findings should be replicated in larger samples with longer follow-up periods. A history of suicide attempts and higher general symptoms at baseline was associated with a deteriorated cognitive course in EOS over two years. Future research may investigate which general symptoms that affect the deterioration, and whether the cognitive worsening endures. On the one hand, we detected a stable longitudinal cognitive course in EOS, while on the other that higher levels of general symptoms and suicide attempts at baseline predicted cognitive deterioration, indicating heterogeneity within the group. Subgroups of patients who deteriorate over time due to higher levels of general symptoms and suicidality should be investigated in future research. Larger samples may also provide an opportunity to investigate other potential subgroups, classified by i.e. cognitive achievements, diagnostic subgroups, symptom severity, gender and medication.

Finally, OC not evaluated in this thesis, such as maternal cortisol levels, infections and influenza, should be subject to further research of cognitive function in schizophrenia.

5.4 Strengths and limitations

The in-depth structured clinical interviews and the comprehensive neuropsychological assessments conducted in the study, are among its most important strength. Two papers in this thesis present the first effort to examine a variety of OC in relation to neuropsychological functioning in EOS. The access to a medical registry with objective measures of OC gives the study considerable strength. However, the choice and analyses of complications also present a limitation. We wanted to collect a wider range of OC than most studies in the field and have concentrated on the material available in the NMBR. The collected OC were analyzed separately, which means that the complications that may be involved in, e.g. hypoxia, are not examined together. Furthermore, some complications, such as maternal cortisol, influenza and infections during pregnancy, were not available in the NMBR and not included in this study. A strength, however, is the use of an age and gender matched healthy control group, often requested in other studies.

A major limitation in all our papers is the modest sample size, especially compared to most adult schizophrenia studies. The sample size limits the interpretation of our findings in a wider context of neurodevelopment in schizophrenia and should be interpreted with caution until they are replicated in larger samples. While the sample is small, there might be potential covariates not considered, and moreover, some of the null results may be explained by a Type II error. Paper I and III included many obstetric measurements, in which multiple tests were conducted without adjusting for multiple comparisons, which increases the risk of a Type I error. However, even with such a small sample, our results exhibited clear, significant associations between OC and cognition, strengthening our findings. Moreover, our sample size is not particularly smaller than those of other studies in this field (Ellman et al., 2012; Freedman et al., 2013; Ochoa et al., 2013). Even so, future studies with larger samples are necessary.

In Paper II, a larger sample might have revealed more significant associations between clinical variables and long-term cognition, although our sample was about the same size as other EOS studies with a similar attrition rate (Fraguas et al., 2014; Kravariti et al., 2003a, b; Wozniak et al., 2008). A further limitation stems from the dropouts of patients and missing data. The ideal in longitudinal studies is to have a complete set of data and no dropouts, but this has been difficult to achieve. To meet this limitation, the mixed model has been recommended over repeated measures ANOVA in longitudinal psychological studies with small sample sizes, because of its ability to accommodate missing data points (Krueger and Tian, 2004; Muth et

al., 2016). It is as always important to stress that results based on missing data should be interpreted with caution. Furthermore, the dropouts in the EOS group had more profound cognitive deficits than the ones who continued, which raises questions about the generalizability of the results. When comparing the participants throughout the study, the EOS patients at baseline were clinically very similar to those who participated at T2 and T3, both in diagnoses, symptoms and global functioning. Moreover, only one of the patients who had attempted to commit suicide before baseline left the study, thereby indicating that our findings were minimally influenced by dropouts.

A limitation in Paper II is in the measurement of clinical variables, especially the assessment of suicide attempts that was based solely on the patient's self-reports. It is difficult to obtain reliable measures of suicide attempts. However, our clinical psychologists involved in the assessments attended regular diagnostic consensus meetings led by well-experienced clinical researchers throughout the entire assessment process, to help ensure inter-rater reliability.

A limitation in all papers concerns medication effect. Approximately 70% of the patients received second-generation anti-psychotics, and we had limited control over medication effects in relation to the cognitive measures. In one study, Kravariti et al. (2003a) found that longer exposure to medication predicted a lower level of performance in aspects of attention, psychomotor processing speed and spatial working memory. In our material however, previous analyses did not detect a relationship between medication and cognitive performance (Juuhl-Langseth et al., 2014).

6 CONCLUSION

Paper I present the first study to suggest a relationship between gestational length and cognitive deficits in EOS, suggesting that some of the poorer neuropsychological performances commonly found in EOS may be partly attributable to OC. The worsened cognitive functioning did not appear among healthy controls, indicating that gestational length may have a greater impact on neuropsychological disruption in EOS. We detected no group differences in the frequency of OC. Hence, our results suggest that gestational length does not increase the risk for early psychosis, but significantly affects the cognitive difficulties seen among cases. Our findings indicate that gestational length should be included in future studies on cognition and schizophrenia, and the results emphasizes the importance of maternal care and cognitive remediation programs for adolescents with cognitive dysfunction due to OC.

In Paper II, we found that the EOS patients follow the same stable cognitive course as schizophrenia patients with later illness onset, thus confirming continuity between EOS and adult-onset schizophrenia. Clinical characteristics in the early illness period, such as DUP, remission and hospitalization, did not seem to influence the cognitive course in EOS. Our results indicated that higher scores of general symptoms, as well as a suicide attempt history, predicted a deteriorated cognitive course within the first years of diagnosis, and should be subject to specific attention in the evaluation and treatment of patients with EOS.

In Paper III, our data suggested that perinatal complications are associated with considerably impaired executive function in EOS. A shorter gestational age was linked to significant executive dysfunctions, but also emergency caesarean section, the use of forceps and the use of vacuum were associated with executive deficits. Healthy controls exposed to the same perinatal OC did not exhibit the same executive dysfunctions, indicating EOS patients to be particularly vulnerable to executive deviations due to obstetric events. These patients seem to learn more slowly and experience more difficulty with problem-solving, which carry important implications for clinical practice. Finally, our data revealed that lower Apgar 5-minutes scores are associated with executive dysfunction, both among EOS patients and among healthy controls. The findings suggest that low 5 minutes score may be an early indicator of executive dysfunctions, independent of diagnosis.

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Appendix

Appendix 1 DSM-IV Diagnostic criteria for schizophrenia

<p>A. Characteristic Symptoms: Two or more of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):</p> <ol style="list-style-type: none">1. Delusions2. Hallucinations3. Disorganized speech4. Grossly disorganized or catatonic behavior5. Negative symptoms <p>Note: Only 1 criterion is required if delusions are bizarre or hallucinations consist of a single voice keeping a running commentary on the person's behavior or thoughts, or if multiple voices are conversing with each other.</p>
<p>B. Social/Occupational Dysfunction: For a significant portion of the time since the onset of the disturbance, 1 or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.</p>
<p>C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms that meet Criterion A and may include periods of prodromal or residual symptoms.</p>
<p>D. Schizoaffective and Mood Disorder Exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief, relative to the duration of the active and residual periods.</p>
<p>E. Substance/General Medical Condition Exclusion: The disturbance is not due to the direct physiologic effects of a substance or a general medical condition.</p>
<p>F. Relationship to a Pervasive Developmental Disorder: If a history exists of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month.</p>
<p><i>DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.</i> Adapted from reference 13.</p>

Gestational length affects neurocognition in early-onset schizophrenia

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ABSTRACT

Obstetric complications (OC) have been linked to an increased risk for schizophrenia in offspring, especially in early-onset schizophrenia (EOS). Extensive cognitive deficits occur in EOS, although no study has yet to investigate the relationship between OC and cognition in EOS. This study aims to examine the frequency of OC in EOS compared to controls, and also investigates the relationship between OC and neurocognitive dysfunction in the two groups. Nineteen EOS patients and 53 healthy controls were tested with the MATRICS Consensus Cognitive Battery (MCCB), and the cognitive measures were combined with OC data from the Norwegian Birth Registry. The results indicated no group differences in OC in EOS and healthy controls, but a shorter gestational length in the EOS group led to significant decreases in the overall neurocognitive composite score, and in processing speed. This suggests that the poorer neuropsychological performances commonly found in EOS may be partly attributable to the length of gestation. The worsened neurocognitive functioning did not appear among controls, so gestational length had a different impact on the two groups. Our findings indicated that a shorter gestational length did not increase the risk for developing EOS, but did significantly affect the cognitive difficulties in this group.

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1. Introduction

According to neurodevelopmental models, schizophrenia is the behavioral outcome of deviations in early neurodevelopment, including prenatal insults such as obstetric complications (OC) (Brown, 2006; Brown et al., 2005; Cannon et al., 2002). Several studies and meta-analyses indicate an association between OC and the later development of schizophrenia, and suggest three groups of complications; complications of pregnancy, abnormal fetal growth and development, and complications of delivery (Brown et al., 2011; Byrne et al., 2007; Cannon et al., 2002; Clarke et al., 2012).

While fetal hypoxia has strong support as a risk factor for schizophrenia (Clarke et al., 2012; Rosso et al., 2000), it has also been proposed to mediate the effects of other OC (Cannon et al., 2000; Clarke et al., 2012). Research also indicate an association between schizophrenia and prenatal exposure to infection (Brown, 2006; Brown et al., 2000, 2009; Mittal et al., 2008b), to inflammation (Cannon et al., 2014; Chaves et al., 2015), to stress (Holloway et al., 2013; Khashan et al., 2008; Malaspina et al., 2008; van Os and Selten, 1998) and to diabetes (Cannon et al., 2002; Van

Lieshout and Voruganti, 2008). Though the results diverge, a few studies find a relationship between risk of schizophrenia and a low birth weight, especially below 2500 g (Abel et al., 2010; Gunnell et al., 2003; Hultman et al., 1999; Lahti et al., 2015), a low and high birth weight (Gunnell et al., 2003; Moilanen et al., 2010) and a low gestational age (Byrne et al., 2007; Geddes et al., 1999; Nosarti et al., 2012). However, the direct association between OC and schizophrenia has been debated, and cohort studies have mostly failed to confirm this effect (Rosso et al., 2000). In a Scottish population study by Kendell et al. (2000), there were no significant associations between OC and schizophrenia in one birth-cohort, while a caesarean section and long-lasting labor were more common in a later birth-cohort. Similar results were found in a Finnish study with no significant primary effect of OC on the risk of schizophrenia (Clarke et al., 2011).

A meta-analysis suggests that risk of schizophrenia associated with OC might be particularly important for those with a young age at symptom onset, indicating that it involves neurodevelopmental impairment (Verdoux et al., 1997). Recent studies support these findings; Preti et al. (2012) detect an associations between OC and earlier age of onset, while Rubio-Abadal et al. (2015) claim that lower birth weight and more OC determine an earlier onset-age. Because research indicates different results due to age of onset, several studies have examined young people with psychosis. A common cut-off point in early-onset schizophrenia (EOS) has been on symptom onset before 18 years of age, which includes

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about 5% of the schizophrenia population (Cannon et al., 1999; Frangou, 2013; Holmen et al., 2012; Juuhl-Langseth et al., 2014). EOS patients are especially interesting for research because they are in their adolescence, a period with extensive brain maturation and alterations in cognitive structures and functions (Juuhl-Langseth et al., 2014). Consequently, they provide unique neurodevelopmental data that may contribute to a better understanding of schizophrenia at all ages (Rapoport et al., 2012; Remschmidt, 2002). Nonetheless, most studies of OC and schizophrenia include all patients, thus; a majority with onset after 18 years of age (adult-onset schizophrenia (AOS) (Juuhl-Langseth et al., 2014; Oie et al., 2011)), implying that the findings from AOS studies could potentially be influenced by the small number of participants in the sample with EOS.

So far, little is known about the role of prenatal insults on EOS (Margari et al., 2011). One study reports no relationship between OC and EOS (Margari et al., 2011). In a populations with onset before 13 years of age, Matsumoto et al. (1999) detect an association between OC and psychosis, while Ordonez et al. (2005) find no such relationship. A number of studies use obstetric material collected from maternal recall, which may be unreliable (Kotlicka-Antczak et al., 2014; McIntosh et al., 2002). We have found only two studies on OC and early psychosis that have used information from birth registries in comparison to healthy controls (Cannon et al., 2000; Rosso et al., 2000). Both centered on hypoxia-associated OC, and found that these complications increased the odds of earlier onset of psychosis but not of later onset. The studies used median splits for age of onset, hence implying that the mean age in the early psychosis group was above 18 (27.1/21.5, respectively). Even so, the findings indicate that complications during pregnancy and birth may have a specific impact on early psychosis. Consequently, studies of the relationship between OC and EOS are of particular interest.

It has been suggested that cognitive dysfunction is a central feature of schizophrenia that often exists prior to symptoms, which reflects underlying abnormalities in brain neurodevelopment (Frangou, 2013; Rund, 2009; Rund et al., 2015; Seidman et al., 2006). Patients with EOS and AOS seem to have a similar cognitive profile (Holmen et al., 2010; Oie et al., 2011), but EOS is reckoned to be more severe with worse premorbid abnormalities, as well as worse long term symptomatic and functional outcomes (Frangou, 2013; Kumra and Charles Schulz, 2008). In understanding the course of the abnormal brain development in schizophrenia, some suggest an association between OC and cognitive impairment (Ellman et al., 2012; Freedman et al., 2013; Ochoa et al., 2013; Torniainen et al., 2013). Comprehending the manner in which OC and cognition coalesce may help clarify the pathway that underlies psychotic illness, which is essential for developing primary prevention strategies (Mittal et al., 2008a).

Earlier findings indicate that OC may have a specific impact on EOS (Cannon et al., 2000; Rosso et al., 2000), as well as on neurocognition (Ellman et al., 2012; Freedman et al., 2013; Ochoa et al., 2013; Torniainen et al., 2013). Still, we find no previous study that has examined the relationship between OC and cognition in EOS. So far, most research on OC and neurodevelopment have investigated AOS and single OC measures, such as hemoglobin levels during pregnancy (Ellman et al., 2012), maternal infections (Brown et al., 2009), maternal influenza (Ellman et al., 2009) or birth weight (Freedman et al., 2013; Torniainen et al., 2013).

There are reasons to believe that different OC would likely affect different areas of cognition. In one study, Brown et al. (2009) found that prenatal infections were associated with impaired executive function in schizophrenia. While previous research has identified strong associations between executive dysfunction and structural and functional deficits in the prefrontal cortex (Goldberg et al., 1990; Rusch et al., 2007), both deficits might be affected

by gestational exposure to infections. Other research suggests that schizophrenia cases that have been exposed to influenza during gestation have a higher risk of impairments in verbal tasks (Ellman et al., 2009), whereas hypoxia-associated OC were found to be unrelated to language acquisition deficits in the premorbid period (Bearden et al., 2000). Interestingly, reductions in neurocognitive performance among those exposed to OC was less extensive in the healthy control group with the same labor-conditions (Ellman et al., 2012; Ellman et al., 2009; Freedman et al., 2013), which may indicate a greater effect of OC on neuropsychological development in schizophrenia. This underscores the importance of studies in which an assessment of healthy controls is included, as well as studies that aim to identify the magnitude of specific OC on specific domains of cognition in schizophrenia.

Ochoa et al. (2013) examined a wider range of OC in relation to cognitive functioning, and found that first episode schizophrenia (FES) patients with a higher level of “neurodevelopmental contribution” (including OC) had a significantly slower processing speed than that of other FES patients. Healthy controls were not evaluated. Even though Ochoa et al. (2013) did not consider OC separately, the findings supported an association between fetal development and cognition in schizophrenia.

The present study is the first to investigate a relationship between OC and cognitive deficits in EOS. Earlier results from our research group have found significant neurocognitive deterioration in EOS patients (Holmen et al., 2010; Juuhl-Langseth et al., 2014; Thormodsen et al., 2012), and an interesting question is whether there may be associations between OC and cognition in the same sample.

Due to previous research that indicates an association between OC and earlier age of symptom onset in schizophrenia; our first research hypothesis is that we expect to find a higher frequency of OC among EOS patients than among healthy controls. Furthermore, findings suggest an association between OC and cognitive dysfunction in schizophrenia. There are reasons to assume that different OC may affect different areas of cognition, such as executive functions and processing speed. Our second hypothesis is therefore that OC affect the overall cognition in EOS, but have a more profound impact on executive functions and processing speed.

2. Materials and methods

2.1. Subjects

The patients were participants in the Early-onset Study (starting in 2005), a broader research project at the University of Oslo on early-onset psychotic disorders (Holmen et al., 2010; Juuhl-Langseth et al., 2014; Thormodsen et al., 2012). The patients were recruited from different inpatient and outpatient units in Oslo and the region of Eastern Norway, and were included if they were between 12 and 18 years of age and met the diagnosis criteria for a broad schizophrenia-spectrum disorder according to DSM-IV (Paranoid schizophrenia: $n=2$ (11%), Undifferentiated schizophrenia: $n=6$ (32%), Schizoaffective disorders: $n=3$ (16%), Residual schizophrenia: $n=1$ (5%) and Psychosis not otherwise specified (NOS): $n=7$ (7%)). The exclusion criteria were a history of central nervous system pathology or trauma (loss of consciousness for greater than 30 min and/or any neurological sequelae), or with an estimated IQ less than 70. Out of a total of 29 patients, 21 gave their written informed consent to the collection of data about obstetric complications from The Norwegian Medical Birth Registry (NMBR). Two of the participants were not born in Norway and had to be excluded, resulting in a total of 19 patients used for further analysis.

The healthy control group consisted of 67 subjects, of which 53 consented to retrieval of data about them concerning obstetric complications from the NMBR. They were recruited through personal letters to a group of randomly selected individuals from the Norwegian population registry and through advertisements in four schools in Oslo and the region of Eastern Norway, and were matched to patients on gender, age and length of mother's education. Moreover, all attended regular school classes at normal grade levels. The healthy controls were screened for mental problems using the Mini-International Neuropsychiatric Interview (M.I.N.I.) screening module (Sheehan et al., 1998), and a positive response to any of the questions was grounds for exclusion from the study. As in the EOS group, exclusion criteria were any known brain injury or neurological disease, or an IQ < 70.

The participants were given a complete description of the study, and written informed consent was obtained from patients and controls, as well as their parents if the participant was younger than 16. Approval of the study was obtained by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Demographic and clinical characteristics are presented in Table 1.

2.2. Procedure

All assessments were carried out by the same two trained psychologists, within a period of 0–8 weeks between the clinical assessments and the two hour neurocognitive testing (Holmen et al., 2010; Juuhl-Langseth et al., 2014; Thormodsen et al., 2012). IQ tests were administered within the neurocognitive test battery.

2.3. Clinical assessments

Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), modules A–D, and the age at onset was defined as age at the first SCID-verified psychotic episode. For assessing psychiatric symptoms, the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used. The interviewers were trained in use of the SCID, participated in regular diagnostic consensus meetings led by well-experienced clinical researchers and finished the training course in SCID assessment based within the training program at the University of California, Los Angeles (UCLA). The mean overall kappa as assessed in the UCLA training course was 0.77 (Holmen et al., 2010). Global functioning was assessed with the Global Assessment of Functioning (GAF) Scale (split DSM-IV version) (Pedersen et al., 2007).

2.4. Assessment of obstetric complications

Information on OC was collected from the NMBR, a national

health registry containing information about all births in Norway, including information about maternal health before and during pregnancy, and any complications arising during pregnancy or birth. The registry includes information about medication during pregnancy, labor interventions, birth complications, maternal complications after birth, whether this was a live birth, any diagnoses in the child or evidence of congenital abnormalities.

All subjects were born between 1986 and 1996. A total of 35 variables concerning pregnancy and birth were obtained and are presented in the subgroups used by the NMBR (Table 2).

Some of the collected variables had no value, and did not occur in any of the cases in our sample. Therefore, we excluded them from the analyses. All the complications were analyzed separately. Moreover, we calculated a sum score, OC Total, by adding the number of actually occurring OCs in each diagnostic group (see Table 3).

2.5. Neurocognitive assessments

All participants were tested with the MATRICS Cognitive Consensus Battery (MCCB) covering the following seven domains (Green and Nuechterlein, 2004; Green et al., 2004; Nuechterlein et al., 2008): 1) *Speed of Processing* [Trail Making Test A (TMT-A; War Department, 1944), Symbol Coding (Brief Assessment of Cognition in Schizophrenia, BACS; Keefe, 1999), and Fluency (Category Fluency; Blair and Spreen, 1989)], 2) *Attention* [The Continuous Performance Test-Identical Pairs (CPT-IP; Cornblatt et al., 1988)], 3) *Working Memory* [Spatial Span (The Wechsler Memory Scale, SS-WMS; Wechsler, 1997) and Letter Number Span (The University of Maryland Letter Number Span test, LNS; Gold et al., 1997)], 4) *Verbal Learning* [The revised Hopkins Verbal Learning Test (HVLT-R, immediate recall; Brandt and Benedict, 2001)], 5) *Visual Learning* [The revised Brief Visuospatial Memory Test (BVM-T-R; Benedict, 1997)], 6) *Reasoning/Problem Solving* [The Mazes test (Neuropsychological Assessment Battery, NAB; White and Stern, 2003)], and 7) *Social Cognition* [The Managing Emotions part of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT; Mayer et al., 2002)]. In addition, a Composite Sum Score was calculated using the arithmetic average of the seven domains.

For neurocognitive assessments, the MCCB has been widely used in AOS samples and is found to have good test-reliability and small practice-effect (Keefe et al., 2011; Rajji et al., 2013). Our previous studies indicate that the MCCB is equally sensitive for cognitive examination in EOS (Holmen et al., 2010; Juuhl-Langseth et al., 2014).

Because there are no norms for the MCCB scores of tests respondents below the age of 20, we calculated our own T scores with a mean of 50 and an SD of 10. General intellectual function (IQ) was assessed according to norms using the four sub-tests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007).

2.6. Statistical analyses

All analyses were carried out using IBM SPSS Statistics version 20. Group differences in OC were studied with Student's *t*-tests and Chi-square tests. Group differences in neurocognition were analyzed with ANOVAs with partial eta squared measurement of effect size. The associations between OC and neurocognition were studied using linear regression analyses with a cognitive test score as the dependent variable. The independent variables in each analysis were an OC and an OC x diagnosis interaction variable. The control group was considerably larger than the EOS group. Hence, all statistical analyses were repeated using pairwise matched samples, based on gender and age. This procedure did not alter the results, so we reported the results of the entire samples.

Table 1
Demographic and clinical characteristics.

	EOS (n=19)	HC (n=53)	Group statistics
Gender female/male (%)	47.8/52.4	50.9/49.1	χ^2 0.03, p 0.85
Age in years (SD)	15.3 (1.9)	15.5 (2.0)	T 0.15, p 0.88
IQ (SD)	97.1 (13.7)	111.0 (12.8)	T 4.01, p 0.001
Mother's age at delivery (SD)	28.2 (5.7)	30.7 (4.8)	T 1.73, p 0.10
Father's age at delivery (SD)	31.7 (5.9)	33.0 (9.9)	T 0.79, p 0.43
DUP, weeks (SD)	28.0 (43.8)	–	
General PANSS (SD)	56.5 (12.8)	–	
GAF function (SD)	50.8 (15.5)	–	
GAF symptom (SD)	51.4 (13.9)	–	

EOS: Early-onset schizophrenia, HC: Healthy controls. DUP: Duration of untreated illness. T and χ^2 : Group tests of significances.

Table 2

Obstetric complications collected from the Norwegian Medical Birth Registry.

Baby's health	Complications of pregnancy	Interventions during labor	Complications of delivery
Gestational length	Drugs in pregnancy	Forceps	Placenta previa
Birth weight in grams	Folate in pregnancy	Vacuum	Rupture, grade3–4
Apgar score 1 min	Bleeding (< week 13)	Episiotomy	Bleeding (> 500 ml)
Apgar score 5 min	Bleeding (week 13–28)	Caesarian section, acute	Dystocia
Abstinence	Bleeding (> week 28)	Caesarian section, planned	Premature rupture of membranes (PROM)
Folate before pregnancy	Hypertension		Abruptio placentae
CPAP	Eclampsia		No complications
ICH (Intra-Cranial Hemorrhage)	Pre-eclampsia		
Ventilator	Pre-eclampsia (early)		
Respiratory distress	Eclampsia/Pre- eclampsia		
	Anemia (HB < 9)		
	Rubella		
	Sexually transmitted infections		

Table 3

Baby's health at birth and frequency of actually occurring obstetric complications.

	EOS (n=19)	HC (n=53)	Group statistics
Birth weight in grams (SD)	3304.2 (855.5)	3591.1 (562.9)	T 1.36, p 0.19
Birth weight < 2500 g	15.8%	3.8%	χ^2 3.22, p 0.07
Gestational length, weeks (SD)	38.8 (3.1)	39.8 (1.8)	T 1.30, p 0.21
Length in cm (SD)	49.4 (2.9)	50.6 (2.2)	T 1.50, p 0.15
Apgar 1/5 min (SD)	8.4/9.1 (8.4/9.2)	8.8/9.2 (0.7/0.5)	T 1.46, p 0.16/ T 0.36, p 0.72
Hypertension	21.1%	11.3%	χ^2 1.18, p 0.28
Preeclampsia	15.8%	7.5%	χ^2 1.14, p 0.29
Use of forceps	5.3%	5.7%	χ^2 0.10, p 0.75
Use of vacuum	5.3%	5.7%	χ^2 0.10, p 0.75
Emergency caesarean section	10.5%	7.5%	χ^2 0.18, p 0.67
Rupture grade 3–4	5.3%	1.9%	χ^2 0.09, p 0.77
Bleeding > 500 ml	10.5%	5.7%	χ^2 0.54, p 0.46
Dystocia	15.8%	9.4%	χ^2 0.61, p 0.43
Total mean OC	47.4%	30.2%	T –1.25, p 0.22

EOS: Early-onset schizophrenia, HC: Healthy controls. T and χ^2 : Group tests of significances.

3. Results

There were no statistically significant differences in frequency of OC between the EOS group and the healthy controls (Table 3). Some of the participants in the EOS group have the diagnosis of psychosis NOS. When the group of NOS (N=7) was excluded from the analyses, the results were unchanged.

As expected and previously reported (Holmen et al., 2010; Juuhl-Langseth et al., 2014; Thormodsen et al., 2012), the EOS group performed significantly worse than the HC in all cognitive domains, except in measures of attention and social cognition. The results are presented in Table 4.

Our regression analyses with diagnostic group as an interaction variable revealed a significant relationship between gestational length and cognition (Fig. 1). However, we found no relationship between other OC and cognitive functioning.

The significant relationships are illustrated in Table 5. In the EOS group, gestational length was significantly correlated with Speed of Processing and the overall Composite Score. There were no statistically significant correlations between gestational length and cognition in the control group.

4. Discussion

The present study is the first to examine a large number of obstetric complications in relation to neuropsychological

Table 4

Neuropsychological data for the EOS and the HC group.

	EOS (N=19) Mean (SD)	HC (N=45-53) Mean (SD)	F	η^2
Composite Score	44.8 (6.3)	51.9 (4.8)	24.39, p 0.0001	0.28
Speed of Processing	44.4 (7.9)	52.1 (6.4)	18.23, p 0.0001	0.22
Attention/Vigilance	46.9 (9.6)	51.1 (10.0)	2.58, p 0.11	0.04
Working Memory	42.2 (6.3)	53.1 (8.3)	29.43, p 0.0001	0.29
Verbal Learning	42.3 (11.4)	53.1 (7.4)	23.55, p 0.0001	0.25
Visual Learning	43.9 (14.8)	52.3 (5.9)	12.35, p 0.001	0.15
Reasoning/Problem Solving	44.4 (11.5)	52.3 (8.4)	10.75, p 0.002	0.13
Social Cognition	48.9 (13.1)	50.3 (8.4)	0.25, p 0.62	0.01

EOS: Early-onset schizophrenia, HC: Healthy controls. F: Group test of significances. η^2 : Effect size. **Fig. 1.** The association between gestational length and the Composite score in EOS patients and healthy controls.

functioning in early-onset schizophrenia. Contrary to our first hypothesis, we found no significant associations between OC and EOS in comparison to healthy controls. These results were

Table 5

The associations between gestational length and cognitive domains (MATRICS Cognitive Consensus Battery) in EOS patients and healthy controls.

	Gestational length	
	EOS (n = 19)	HC (n = 45–53)
Composite Score	B 1.15 β 0.60, p 0.01 CI 0.31–2.00	B –0.55 β –0.20, p 0.19 CI –1.37–0.27
Speed of Processing	B 1.34 β 0.50, p 0.03 CI –1.47–2.52	B –0.38 β –0.11, p 0.49 CI –1.47–0.71
Attention/Vigilance	B 0.81 β 0.25, p 0.31 CI –0.81–2.43	B –0.08 β –0.01, p 0.93 CI –1.80–1.65
Working Memory	B 0.65 β 0.30, p 0.21 CI –0.40–1.70	B 0.79 β 0.17, p 0.25 CI –0.57–2.15
Verbal Learning	B 1.54 β 0.44, p 0.06 CI –0.07–3.15	B –0.98 β –0.23, p 0.10 CI –2.15–0.20
Visual Learning	B 1.05 β 0.23, p 0.35 CI –1.25–3.35	B –0.46 β –0.13, p 0.35 CI –1.42–0.51
Reasoning/Problem Solving	B 0.88 β 0.25, p 0.30 CI –0.87–2.64	B –0.58 β –0.12, p 0.40 CI –1.97–0.81
Social Cognition	B 0.96 β 0.25, p 0.34 CI –1.13–3.05	B –1.14 β –0.24, p 0.12 CI –2.58–0.30

EOS: Early-onset schizophrenia, HC: Healthy controls, B: Unstandardized regression coefficient, β : Standardized regression coefficient, CI: 95% confidence interval.

sustained when we excluded the participants in the EOS group who had the diagnosis of Psychosis NOS, and when we pair-matched the samples on age and gender. Earlier research suggested an association between preterm birth and AOS (Byrne et al., 2007; Geddes et al., 1999; Nosarti et al., 2012). Although our sample size was small, our study found no relationship between gestational age and EOS. Previous research has raised questions about the strength of the association between OC and schizophrenia (Clarke et al., 2006), as well as the way in which OC is conceptualized (Zornberg et al., 2000).

Our results supported the hypothesis of a relationship between OC and neurocognitive deficits in EOS. Previous studies on the same group of patients found that the EOS patients performed worse on all the neuropsychological measures compared to healthy controls (Holmen et al., 2012; Juuhl-Langseth et al., 2014; Thormodsen et al., 2012). The present study found no significant impact of OC on executive functions in EOS. However, we found that gestational age in the EOS group was associated with statistically significant decreases in the overall composite score and in processing speed in particular. Considering the different response in neurocognitive measures among EOS patients versus control subjects, our findings suggested that a shorter gestational length did not increase the risk for developing EOS, but significantly affected the cognitive difficulties seen among cases. Previous studies have found associations between increased maternal hemoglobin levels and deficits on the neuromotor tasks and general IQ (Ellman et al., 2012), between influenza and verbal tasks (Ellman et al., 2009), and between infections and executive functions (Brown et al., 2009) in offspring with schizophrenia. In line with these findings, our results suggested that poorer overall cognition, as well as reduced processing speed in the EOS population, may be partially attributable to gestational length.

Processing speed is considered a core cognitive deficit in psychosis, being important for other higher cognitive operations such as executive function and memory (Dickinson et al., 2007; Kelleher et al., 2013; Knowles et al., 2010). Our results suggested a specific connection between processing speed and prenatal insults. Furthermore, they supported the theory that processing speed is especially sensitive to underlying brain dysfunction and damage (Perianez et al., 2007).

In the general population, studies have led to theories about an association between preterm births, neuroanatomical alterations

in the brain network and impaired neurodevelopment, and furthermore, the same alterations have been found to be disrupted in populations with mental health problems (Lawrence et al., 2010; Nosarti et al., 2012; Nosarti et al., 2009). Many studies consider very preterm births. Nonetheless, in our material, the durations of the pregnancies were not particularly short; still, the length of gestation had a significant impact on neurocognition in the EOS group. In previous research, decreases in gestational length have been associated with maternal psychosocial stress and depression, as measured by higher levels of maternal cortisol early in pregnancy (Sandman et al., 2006). Though the maternal cortisol level is not available in the NMBR and was not evaluated in our study; higher levels of maternal cortisol are found in other studies to increase children's risk for later cognitive and language difficulties (Sohr-Preston and Scaramella, 2006), in addition to impaired physical and mental development in outcome (Davis and Sandman, 2010).

Of particular note was that our results demonstrated a relationship between gestational age and cognition in the EOS group, although the same relationship did not appear among healthy controls. Our findings implied that gestational length may have a greater impact on neuropsychological disruption in early-onset schizophrenia than in healthy controls. As suggested by Cannon et al. (2008), this might be caused by a specific biological vulnerability for developing the disease.

4.1. Clinical implications

Depending on conditions during pregnancy, the findings from the present study implied that some groups of patients with EOS might be closer to healthy controls in cognitive performance, which coincides with the results of MacCabe et al. (2013) and Ochoa et al. (2013). Consequently, OC should be considered in future research on neurocognition in EOS. Furthermore, our results emphasized a need for a special focus on gestational length, both in maternal care to ensure the necessary treatment to avoid preterm births, and also by drawing attention to children already born premature. Finally, our study found that processing speed seemed to be highly affected by a shorter gestational age, thus supporting the necessity of measuring processing speed when studying patients with psychosis, as suggested by Leeson et al. (2010).

4.2. Strengths and limitations

The present study is the first to examine a variety of obstetric complications in relation to neuropsychological functioning in early-onset schizophrenia. The study has several strengths, including the use of a comprehensive neurocognitive test battery. Other pronounced strengths are the collection of data from medical records with a large number of objective measures of obstetric complications, and the use of a well defined healthy control group matched on relevant demographic variables.

A major limitation of the study is the modest sample size, especially compared to most AOS studies, which limits the interpretation of our findings in a wider context of neurodevelopment in schizophrenia. While the sample size is small, there might be potential covariates not considered in the study. Additionally, some of the null results may be explained by a Type II error, and it is possible that a larger sample might have revealed more significant associations between OC and EOS, as well as between neurocognition and OC in both groups. The findings are therefore preliminary, and should be replicated in larger samples. The study also included a large number of OC, in which multiple tests were conducted without adjusting for multiple comparisons, which increases the risk of a Type I error. However, even with such a small sample size, our results exhibited clear, significant

associations between gestational length and neurocognition, which further strengthens our findings. Also, our sample size is not particularly smaller than those of other studies in this field (Ellman et al., 2012; Freedman et al., 2013; Ochoa et al., 2013). Even so, future studies with larger sample sizes are necessary to test whether our results are resilient under more conservative *p*-values.

A further limitation is the choice and analyses of OC. We wanted to collect a wider range of OC than most studies in the field, and have concentrated on the material available in the NMBR. The collected OC were analyzed separately. Consequently, OC that are likely involved in, e.g. hypoxia, are not examined together. Furthermore, some complications, such as maternal cortisol, influenza and infections during pregnancy, were not available in the MBRN and were not included in this study.

4.3. Conclusion

The present study is the first to suggest a relationship between gestational length and cognitive deficits in EOS. The findings support the notion that some of the poorer neuropsychological performances commonly found in EOS may be partly attributable to OC. Moreover, the worsened neurocognitive functioning did not appear among healthy controls, thereby indicating that gestational length may have a greater impact on neuropsychological disruption in EOS. Finding no group differences in the frequency of OC, our results suggest that gestational length does not increase the risk for developing EOS, but significantly affects the cognitive difficulties seen among cases. Lastly, our findings indicate that gestational length should be considered in future studies on neurocognition and schizophrenia, which emphasizes the importance of maternal care and on the prevention and intervention for pregnant women, aiming at avoiding preterm births.

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