Migration and Vitamin D in psychotic disorders
– A cross sectional study of clinical and cognitive correlates

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SUMMARY

Migration is a major environmental risk factor associated with schizophrenia and other psychotic disorders. Furthermore, people with migration background may have specific challenges due to their migration background or ethnic background influencing clinical correlates in established disease. An observed high prevalence of vitamin D deficiency in ethnic minorities in Northern European countries has generated hypotheses around the role of vitamin D in psychotic disorders.

In this thesis we investigated the influence of migration, ethnicity and vitamin D levels in early phases of psychotic disorders and later in the course of illness. As vitamin D is found to have receptors widespread in the human brain and has been linked to the pathogenesis of core features in psychotic disorders, we wanted to explore the potential clinical relevance of vitamin D. Thus, investigating how vitamin D levels relate to specific symptom profiles and cognitive functioning.

We conducted four cross-sectional studies in large clinical samples of patients with a DSM-IV diagnosis of a psychotic disorder from the public health care system in Norway. In two of the studies we also included healthy controls from the same catchment area as the patients. In the first study we investigated the associations between having migration background or ethnic minority status and duration of untreated psychosis. In the second, we explored the vitamin D levels in a first episode sample compared to a sample with longer duration of illness and a matched control group. In the third and fourth study we investigated the associations between vitamin D levels and symptom profiles in patients, and the associations between vitamin D deficiency and cognitive function in patients and in controls.

Our main results are that migration after the age of six was significantly associated with prolonged duration of untreated psychosis while ethnic minority status only had a trend level significance for the same. Furthermore being an ethnic minority with ancestry from Asia, Africa or Latin-America, had a significant impact on vitamin D levels. Ethnic minorities had lower vitamin D levels than the majority population across groups; we found significantly lower levels both in first episode psychosis, in a sample of patients with a longer duration of illness, as well as in controls. However, we did not find any significant differences in vitamin D levels between patients and healthy controls, after controlling for ethnic minority status, as opposed to previous studies.

Secondly we found that low vitamin D levels were associated with more severe negative and depressive symptomatology when controlling for a variety of potential confounding variables. Furthermore, a vitamin D level below a critical threshold, defined as vitamin D deficiency, was associated with cognitive functioning in terms of impaired processing speed and impaired verbal fluency, also after adjusting for patient versus control status and other potential confounders. In patients the associations between vitamin D deficiency and cognition were partly mediated by negative symptoms. The severity of the problems related to negative and depressive symptoms and cognitive impairments for patients with psychotic disorders indicate that these aspects are of clinical relevance. Negative symptoms and cognitive impairments have large impact on function and outcome both in the early phases of the disease and in a long term perspective and depressive symptoms are associated with reduced quality of life and impaired long term prognosis.

Our studies demonstrated that migration and ethnic minority status provide specific challenges related to duration of untreated psychosis and vitamin D levels. The current findings in a health care based sample may suggest that further emphasis on the specific challenges of this population is needed. People experiencing migration and/or are ethnic minorities represent a vulnerable population both related to severity of severe mental illness related to prolonged duration of untreated psychosis, as well as vitamin D- derived somatic health problems.

Our studies are cross-sectional and do not allow us to conclude about the directions of the associations. Our findings however provide support for initiating a randomized controlled trial to evaluate whether vitamin D substitution in individuals with low vitamin D levels has beneficial effect on either negative symptoms, cognitive impairments or depressive symptoms, as an adjuvant treatment strategy.

ABBREVIATIONS

BD	Bipolar spectrum disorders
CDSS	Calgary Depression Scale for Schizophrenia
CNS	Central Nervous System
D-KEFS	The Delis-Kaplan Executive Function System
DSM	Diagnostic and Statistical Manual for Mental Disorders
DUP	Duration of untreated psychosis
FEP	First episode psychosis
HUBRO	The Oslo Health Study
MCCB	MATRICS Cognitive Consensus Battery
MEP	Multi episode psychosis
NORMENT	Norwegian Centre for Mental Disorders Research
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
S-25(OH)D	Serum- 25 hydroxy vitamin D, referred to as vitamin D in the thesis
SCID-1	Structured Clinical Interview for DSM-IV Axis 1 disorders
TOP	Thematically Organized Psychosis Study

DEFINITIONS

Immigrant: A foreign born person or a person with one or two foreign born parents. The term *first generation immigrant* is applied for foreign born people while the term *second generation immigrant* is applied for people born in the residence country with at least one foreign born parent. *First generation immigrants* and *second generation immigrants* are collectively referred to as *immigrants* (https://www.ssb.no/en, 2016).

Ethnic group: people with common cultural background understood as a national, racial or tribal group (Soanes, 2005)

Ethnic minority group: a group within the community which have different national or cultural traditions from the main population

Ethnic minority: a person belonging to an ethnic minority group. In some studies referred to as *visible ethnic minority* if their appearance differ from the main population

Note; people referred to as ethnic minorities may or may not be *immigrants*. In this thesis we have used the term *ethnic minority* to describe people with African, Asian and Latin-American ancestry

Majority: a people with cultural background from the main population also referred to as the *reference population*.

Note; people referred to as majorities may or may not be *immigrants*. In this thesis we have used the term *migrant majority* to describe immigrants from European or North-American countries

Native: people from the majority, born in the residence country with parents from the residence country

In this thesis we have also used the term *non-immigrant* to describe native people

Psychotic episode: Psychotic symptoms at a level 4 or above on the PANSS item P1 (delusions), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution) or G9 (unusual thought) with a duration for at least one week

First episode psychosis: A participant in his/her first year of treatment for a psychotic episode.

1.   GENERAL INTRODUCTION

1.1   Psychotic disorders

Psychosis is the main symptom of severe mental disorders collectively referred to as psychotic disorders (van Os and Kapur, 2009). Psychosis is a state characterized by grossly impaired reality orientation often involving symptoms of delusions and prominent hallucinations (First, 2002). The German psychiatrist Emil Kreapelin (1856-1926) has been influential to modern psychiatry. He aimed to develop diagnostic tools and recorded thoroughly patients' symptoms and behavior over long term course to be able to recognize specific disease entities (Engstrom et al., 2006). He described psychiatric illness based on pattern recognition and introduced the diagnostic syndromes of "Demetia praecox" and "Manic depression" in late 19th century. The description of diagnostic syndromes consisting of a set of characteristics is still the basis for psychiatric diagnoses, now over hundred years later. Schizophrenia is the corresponding diagnosis of Kreapelin's "Dementia praecox" and is considered the most severe disease among the psychotic disorders. Psychosis is a central symptom criterion for the DSM-IV diagnoses of schizophrenia, schizophreniform-, schizoaffective-, delusional-, and brief psychotic disorder, and in psychosis not otherwise specified. Psychosis may however also be present as a symptom in unipolar and bipolar affective disorders, but is not a central part of these diagnoses (First, 2002).

Schizophrenia and other psychotic disorders typically emerge during late adolescence, a critical phase of neuronal, psychological and social development. The peak age-of-onset is between 15-25 years. The course of illness is typically relapsing-remitting between psychotic or affective episodes and more stable phases in the absence of active phase symptoms. The clinical course shows large heterogeneity both in terms of number of episodes and the degree of severity of episodes, and there is also considerable heterogeneity on the course of illness between episodes; some have grossly impaired function between active phases while others regain premorbid function. However, people suffering from a psychotic disorder have a large risk of dropping out from education and work life. The Global Burden of Disease project affiliated the World's Health Organization (WHO) estimates disease burden as a sum of years lost due to premature death and years lost due to disability. According to these data mental disorders, including the psychotic disorders are major contributors to the global burden of disease and are in particular accounting for a for a large percentage of medical disability load

already at young age (Whiteford et al., 2013). Mental disorders are a leading cause of death in a global perspective (Walker et al., 2015). In addition to the direct impact of the symptoms of the psychotic disorders there are also high frequencies of co-morbid conditions. This includes increased risk of suicide (Mork et al., 2012), increased drug abuse (Ringen et al., 2008) and high rates of cardiovascular co-morbidity (Iacovides and Siamouli, 2008). Life expectancy is as much as 20 years shorter than in the general population (Laursen et al., 2014),

The incidence per year for a schizophrenia diagnosis is estimated to be 1.5 ‰ in men and 1‰ in women (McGrath et al., 2008). The lifetime prevalence of schizophrenia is estimated 0.8 %, and when including a broader spectrum of psychotic disorders, lifetime prevalence increases to 3 % (Perala et al., 2007). However, there are large variations across studies reporting prevalence and incidence, where increased incidence and prevalence have been noted especially in some immigrant groups in epidemiological studies (Saha et al., 2005).

Schizophrenia and other psychotic disorders are viewed as a multi- factorial brain disorder with largely unknown etiology (Brietzke et al., 2012; Saugstad, 2008; van Os and Kapur, 2009). Epidemiological and twin studies have estimated heritability to be 60-80 % (Cardno et al., 1999; Lichtenstein et al., 2009). However , the etiology is polygenic and genetic findings so far only explain a small proportion of the heritability (Owen et al., 2016). There are different approaches to discover the genetic etiology, such as candidate gene studies (Gatt et al., 2015); finding rare copy number variants (Stefansson et al., 2008); and searching for common genetic variants with pleiotropic effect (i.e. genes affecting multiple traits) (Tesli et al., 2014). There have been breakthroughs in large sample Genome Wide Association Studies (GWAS) over the last years and over 100 susceptibility genes for schizophrenia have been identified (PGConsortium, 2014). We will need refined methodology to explore the underlying genetic pathology (Schork et al., 2016).

In addition to genetic risk, environmental risks also have an important role in the etiology. Family and twin studies have concluded that schizophrenia and other psychotic disorders are complex traits resulting from both genetic and environmental etiology (Lichtenstein et al., 2009; Sullivan et al., 2003). Furthermore, the large observed variation in incidence and prevalence studies have over the last decades formed the basis for more focused research into environmental risks factors (Owen et al., 2016; Selten et al., 2013). The current hypotheses on causes and pathogenesis thus involve complex gene-environment interactions and these

factors are working together dynamically throughout the life span (Davis et al., 2016; Owen et al., 2016). Environmental factors found to be especially important involve cannabis abuse, childhood trauma and migration (Cantor-Graae and Selten, 2005; van Os et al., 2005). There are also findings supporting investigation of winter birth, urban upbringing and infectious diseases as environmental risk factors, for schizophrenia in particular (Brown, 2011; Davies et al., 2003; Suvisaari et al., 2000).

Schizophrenia is basically viewed as neurodevelopmental disorder where the brain is especially vulnerable to abnormal development caused by genes and environmental factors in two critical periods; in the very early fetal development in first trimester and in late adolescence where pruning of synaptic activity and maturation of the brain take place (Selemon and Zecevic, 2015). There is less evidence for these processes in other psychotic disorders, however abnormal neurodevelopment is found to be present also in bipolar and affective disorders (Bortolato et al., 2015; Schmitt et al., 2014). Recent findings also report neurodegenerative mechanisms as part of the pathogenesis across psychiatric diagnoses (Falkai et al., 2015; Hong et al., 2016; Lindqvist et al., 2015).

In this setting where etiology is found to be based in interactions between genes and environment related to both neurodevelopment and neurodegeneration, both large scale genetic studies and clinical studies with thorough characterization of the study participants and their personal and environmental risk exposures are essential for the discovery of underlying mechanisms. Clinical studies can discover specific symptoms or impairments and thereby contribute to better understanding of the pathogenesis and to better treatment and/or prevention of the psychotic disorders (Owen et al., 2016; Shanmugan et al., 2016).

1.2   Clinical characteristics

The various symptoms seen in psychotic disorders are commonly grouped together and described as symptom dimensions of the disorders (van Os and Kapur, 2009). Below is a clinical description of the core symptom dimensions followed by some theories about underlying mechanisms.

Positive symptoms include hallucinations and delusions and represent the reality distortion of psychotic disorders. These symptoms are often the most noticeable aspects of the disease. People having positive symptoms are unable to distinguish personal subjective experiences from the reality of the external world and may behave or communicate in an inappropriate or incoherent way, and have impaired functioning in relation to other people and activities of daily living. They may talk to themselves and express beliefs and ideas that are implausible or incomprehensible.

More recently however, it has been revealed that psychotic symptoms like hallucinations and delusions also occur in the general population and it is proposed that psychotic symptoms are present as a continuum not only including the psychotic disorders, but also the general population (Johns and van Os, 2001). Thus, a positive psychotic symptom is not necessarily an expression of a disorder; yet positive symptoms are what defines the disorders in the section "schizophrenia and other psychotic disorders" in the DSM-IV disease classification (DSM-IV, 1994).

The predominant biological hypothesis for a neurochemical defect causing positive symptoms is the dopamine hypothesis. This hypothesis states that schizophrenia may be related to a relative excess of dopamine-dependent neuronal activity and was derived from pharmacologic evidence; drugs that decrease dopamine activity may be antipsychotic and drugs that promote dopamine activity may have psychotic effects (Meltzer and Stahl, 1976). Neurochemical imaging studies to test the dopamine hypothesis are consistent in showing that schizophrenia, in its acute psychotic state, is associated with an increase in dopamine synthesis, dopamine release, and increased resting state synaptic dopamine concentrations (van Os and Kapur, 2009).

Dopamine-antagonists are the major antipsychotic drugs (Howes and Kapur, 2009). Since the discovery that some drugs exerted antipsychotic effect through blockade on postsynaptic dopamine D2 receptors in the brain, a range of antipsychotic agents were developed acting on the same receptors (typical antipsychotics). Later, in the 1990s, a second generation of antipsychotic medication was developed, exerting more unspecific monoamine receptor effects, including the dopamine, serotonin and noradrenaline receptors (atypical antipsychotics).

Negative symptoms refer to avolition, asociality, anhedonia, alogia and flat affect. Patients with such symptoms show decreased initiative, poor self-care, social withdrawal, and/or diminished expression. Negative symptoms are often more persistent than positive symptoms and have high impact on functioning (Faerden et al., 2013; Mucci et al., 2016). Negative symptoms are difficult to treat and antipsychotic medication has little effect (Woodward et al., 2005). However, some improvement in negative symptoms has been reported for clinical approaches such as social skills training, cognitive behavior therapy for psychosis, cognitive remediation, and family intervention (Aleman et al., 2016).

Negative symptoms are thought to have a neurobiological background, but the etiology is largely unknown (Galderisi et al., 2015). Researchers focusing especially on negative symptoms have suggested a two factor model of negative symptoms with apathy/avolition as one dimension and diminished expression as another dimension, and propose that these two have different neuronal correlates (Galderisi et al., 2016; Kirschner et al., 2016).

There is some support of a hypothesis suggesting that hypo-function of N-methyl-D-aspartate receptors (NMDA receptor) contributes to the negative and cognitive symptoms of schizophrenia (Coyle, 2006). NMDA receptors are receptors for glutamate, an important excitatory neurotransmitter. Dysregulation of glutamatergic activity is increasingly perceived to be involved in the pathophysiology of schizophrenia (Kinon et al., 2015). The main neurotransmitter for inhibitory responses is GABA. One hypothesis is that the hypo-function of NMDA receptors is secondary to a hyperstimulation of glutamate due to reduced activity in GABA, and that this imbalance between inhibitory and excitatory responses has neurotoxic effect (Aleman et al., 2016).

Disorganized/concrete symptoms refer to the clinical deterioration and impaired goal-directed behavior, and has been linked to motor behavior disturbances (Rinaldi and Lefebvre, 2016; Walther et al., 2014). The effect from antipsychotics is smaller in the treatment of disorganized symptoms than of positive symptoms (Corves et al., 2014), and high levels of disorganization are found to be associated with less beneficial effect from cognitive remediation programs compared to patients with lower levels (Vita et al., 2013).

Excited symptoms include agitation, hostility, and impulsivity. These features are found to be associated with aggression, suicidality, and involuntary treatment in first episode psychosis (Huber et al., 2012). Increased impulsivity, impaired attention, and impaired executive

function are proposed as underlying features for aggression and suicidality (Iancu et al., 2010; Serper et al., 2008); however, patients with excited symptoms is a heterogeneous group and findings on underlying mechanisms are inconsistent (Huber et al., 2012).

Depressive symptoms are common in psychotic disorders especially in the early phases and depressive symptoms are associated with impaired function (Birchwood et al., 2005; Romm et al., 2010). Also, in long-term follow up depression in early phases of the disorder is found to predict poorer outcome (Sonmez et al., 2014). Emotional dysfunction is considered to be a part of the psychotic disorders and depressive symptoms, or episodes, can be understood both as intrinsic to the psychosis, as a psychological reaction to psychosis or as a product of development influenced by childhood trauma and the antecedents of psychosis (Birchwood et al., 2005). Depression is also associated with impaired quality of life for the patients suffering from psychotic disorders (Gardsjord et al., 2016). It is thus important to assess depressive symptoms and treat clinical depressions as this may improve function, quality of life and outcome.

The etiology of depression is a complex variety of biological, social, and psychological factors, including genetic vulnerability, childhood adverse effects and emotional dysfunction. Affect can be divided into two separate dimensions; positive affect and negative affect (Watson and Tellegen, 1985), and depression is considered to be characterized by high and dysregulated negative affect in addition to diminished positive affect (Boumparis et al., 2016).

The neurotransmitter serotonin has an important role in depression and selective serotonin reuptake inhibitors (SSRIs) have been the medical treatment of choice over the last 20 years. The serotonin (5-hydroxytryptamin/ 5-HT) transporter may be understood to be a link between genetic risk, pathophysiology and depressive symptoms (Spies et al., 2015). Reduced serotonin transporter binding potential is found in major depressive disorder and genetic variation with one short allele in the gene coding for serotonin transporter has been linked to increased risk for depression.

1.3   Diagnostic criteria

We have used the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) 4th edition in our research.

The diagnosis of *schizophrenia* is in DSM-IV defined as having two (or more) of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior or negative symptoms (criterion A). Having only one of the symptoms is sufficient to fulfill the criterion A if delusions are bizarre, or if hallucinations consist of a voice keeping up a running commentary on the individual's behavior or thoughts, or two or more voices conversing with each other. In addition, the individual's functioning in one or more areas such as work, interpersonal relations or self-care are markedly below the level achieved prior to the onset (criterion B). Signs of the disturbance persist over at least 6 months and may include prodromal or residual symptoms. This period must include at least one month of active phase symptoms meeting criterion A (or shorter if treated adequately). Finally, schizoaffective- or mood disorders are excluded (criterion D) and the disturbance is not due to substance abuse or a general medical condition (criterion E). If there is a history of autistic disorder or another pervasive developmental disorder, the schizophrenia diagnosis is made only if prominent delusions or hallucinations are also present (criterion F).

A diagnosis of *schizophreniform disorder* is assigned if the patient meets criteria A, D and E for schizophrenia with duration of at least one month, but less than six months.

Schizoaffective disorder is described as an uninterrupted period of illness during which, at some time, there is a major depressive episode, a manic episode or a mixed episode concurrent with symptoms that meet criterion A for schizophrenia. Additionally, delusions and hallucinations have been present for at least two weeks in the absence of prominent mood symptoms. However mood symptoms must be present for a substantial portion of the total duration of the active and residual periods of the illness.

Delusional disorder is characterized by non-bizarre delusions for at least one month. Criterion A for schizophrenia has never been met and function is not markedly impaired. If mood episodes have occurred within the same period, they are brief relative to the duration of the delusional periods.

Psychosis Not Otherwise Specified (Psychosis NOS) includes, in our sample, situations where the clinician has concluded that a psychotic disorder is present, but is unable to determine whether it is primary or substance induced, or where there are persistent non-bizarre delusions with periods of overlapping mood episodes that have been present for a substantial portion of the delusional disturbance.

Bipolar disorder is characterized by recurrent abnormal mood variations ranging from mania, euthymic state and depression. In addition to elevated mood, a manic episode is typically accompanied by psychosis and often leads to severe impairment in social function and hospitalization. A *bipolar disorder I* diagnosis may be given on the basis of manic episodes only, while in *bipolar disorder II* at least one hypomanic and one major depressive episode are required to fulfill diagnostic criteria. The diagnosis *Bipolar Not Otherwise Specified (Bipolar NOS)* refers to bipolar symptoms that do not fulfill criteria for a specific bipolar disorder due to shorter duration, or symptoms that are not possible to determine to be primary or secondary to substance abused or somatic state. A *manic episode* is characterized by a distinct period with duration at least one week with either abnormally and persistently elevated, expansive, or irritable mood accompanied by three or four of the following; inflated self-esteem, decreased need for sleep, pressure of speech, flight of ideas, distractibility, increased involvement in goal-directed activities or psychomotor agitation and/or excessive involvement in pleasurable activities with a high potential for painful consequences. A *hypomanic episode* has shorter duration than a manic episode and the disturbance is not sufficiently severe to cause marked functional impairment.

Major depressive disorder with mood incongruent psychotic symptoms is defined by depressed mood most of the day, nearly every day, and/or markedly diminished interest or pleasure in almost all activities most of the day. This is followed by at least three/four of following; significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feeling of worthlessness or excessive or inappropriate guilt, recurrent thoughts of death, suicidal ideation , suicide attempt or a specific suicide plan. The symptoms cause clinically significant distress or impairment in functioning and are accompanied by mood incongruent psychotic symptoms like hallucinations or delusions.

1.4   Cognition

Cognitive decline in schizophrenia was first described by Kraepelin and his
diagnosis "Dementia Praecox", however first defied by the Swiss psychiatrist Eugen Bleuler
(1857-1939) when he noticed that impairments in cognition and change in behavior were also
present between psychotic episodes. Bleuler proposed that cognitive symptoms were
subordinate of other symptoms. Later, general intellectual deficits in chronic schizophrenia
have been demonstrated, and it has been suggested that the cognitive dysfunction is primary
and not secondary to institutionalization or symptoms of the disease (Johnstone et al., 1978).
Since then, a growing interest in the field and acknowledgment of its importance has emerged.
However cognitive impairments are not included in the diagnostic criteria for the psychotic
disorders.

Cognition is a broad term that may be defined as the mental action or process of acquiring
knowledge and understanding through thought, experience, and the senses. However, in the
literature cognition is often specified as neurocognition; including brain specific tasks like
perception, attention, memory, problem solving and some aspects of language or social
cognition, including social and interpersonal interactions (Green, 2006a; Vaskinn et al., 2015).

Patients with psychotic disorders, schizophrenia in particular, have impairments in both
neurocognitive and social cognitive domains (Green, 2016). We have focused on the major
areas of neurocognition in this thesis. The use of terms may be somewhat confusing in
previous literature where both neurocognition and cognition are used to describe the same
phenomena. We chose to use the term "cognition" in our studies.

Cognitive functioning is assessed by neuropsychological tests measuring performance on
tasks in specific domains or on tasks demanding interaction between different domains.
Cognitive impairments are reported across all cognitive domains in psychotic disorders
including problems in processing speed, attention/vigilance, working memory, verbal learning,
visual learning, reasoning and problem solving, (Green, 2006a). These impairments are found
to be present already at the start of first treatment (Demmo et al., 2016; Haatveit et al., 2015;
Mesholam-Gately et al., 2009) and across diagnostic categories within the psychosis
continuum (Bora et al., 2009). This is also found to be relatively stable after the onset of
disease despite fluctuations in symptom severity and use of medication (Barder et al., 2013;
Bergh et al., 2016). Cognitive impairments have also been noted in the prodromal phases and

in siblings of patients suffering from psychotic disorders (Nuechterlein et al., 2012). Taken together, these findings imply that cognitive impairments have a neurodevelopmental cause and represent a primary core deficit in psychotic disorder, not a secondary effect of symptoms or medication (Bortolato et al., 2015; Green, 2016).

Most importantly, impairments in cognitive performance have substantial impact on daily functioning (Green, 2016; Mohamed et al., 2008). The effect of medication on cognition in schizophrenia and bipolar disorder is considered to be small to moderate (Balanza-Martinez et al., 2010; Mishara and Goldberg, 2004), and finding clinical or biological correlates to cognitive function is thus a major goal. Cognitive remediation programs however have been developed for treatment of these impairments and have promising effects (McGurk et al., 2007).

Theories affiliated with negative symptoms hypothesizing the involvement of a disturbances in the excitatory glutamate signaling pathway and reduced activity in GABA inhibitory responses, have also been linked to the pathophysiology of cognitive impairments (Coyle, 2006). Furthermore oxidative stress during critical neuronal development has been proposed as a possible mechanism for the excitation- inhibition disturbances (Sullivan and O'Donnell, 2012).

1.5   First episode psychosis

The first episode of psychosis marks the transition from the prodromal phase to overt psychosis, and usually refers to the first period where the patient meet the symptom criteria for a psychotic disorder (Keshavan and Schooler, 1992). There are however several definitions of "First episode psychosis" in use across studies. First episode psychosis in our research is defined as patients coming to treatment for their first psychotic episode within the last year before inclusion to the study. Other research groups have defined first episode as first admission or inclusion within the first two or five year from the first psychotic episode (Breitborde et al., 2009).

The focus on the early phases of psychotic disorders is based on notions of a "critical period" and includes the duration of untreated psychosis of the first episode psychosis and the first

two – three years of treatment of this episode (Birchwood et al., 1998). These early phases are perceived as "critical" as it is found that deterioration for the patient occurs during this period, and that critical psychosocial influences, including family and psychological reactions to psychosis and psychiatric services, develop during this period (Birchwood et al., 1998). Furthermore the psychotic disorders are perceived as dynamic processes that can be delayed, modified or reversed with pharmaceutical, psychological, family-oriented and social interventions during this "critical period" (Birchwood et al., 1998; Melle et al., 2008; Millan et al., 2016; Rossberg et al., 2010). Adequate treatment of first episode psychosis is found beneficial for long term outcome (Friis et al., 2016; Karson et al., 2016).

For research purposes these early phases or "critical period" provides a window for assessing risk factors, symptoms and disease burden less influenced by medication, treatment and chronicity than later in the course of illness. Long term follow up of these patients can provide valuable information about course of illness, and help uncover predictors for prognosis (Schubert et al., 2015).

1.6   The psychosis continuum model

Kraepelin's dichotomy from late 19th century has, as mentioned, been influential to the modern diagnostic structure of the psychiatric diseases, and the categorical diagnoses in the diagnostic manuals. Schizophrenia represents the classical psychotic disorder (Kraepelin's Dementia Praecox) and Bipolar Disorder represents the classical affective disorder (Kraepelin's Manic Depression).

However, schizophrenia and bipolar disorder are increasingly perceived as dimensions of a psychosis continuum rather than separate disorders (van Os and Kapur, 2009). We have in our research used the psychosis continuum model as framework. In addition to the understanding of symptom syndromes as a continuum, the reason for including diverse diagnoses is especially important in the early phases of disease, because the diagnoses in the early phases are less stable than later on (Fusar-Poli et al., 2016). As an example a first episode patient meeting the criteria for a major depressive disorder with mood incongruent psychotic features may develop symptoms fulfilling the criteria for schizophrenia later in the course of illness (Haahr et al., 2008).

There are findings on several levels supporting the psychosis continuum model. On a clinical level there are symptom overlap where more than half of patients with bipolar disorder experience psychotic symptoms (Toh et al., 2015), and more than half of patients with schizophrenia experience affective syndromes (i.e. major depression) (Millier et al., 2014; Romm et al., 2010). Both disorders share important environmental risk factors like migration (Kirkbride et al., 2012); childhood trauma (Aas et al., 2016); and drug abuse (Lagerberg et al., 2011). Similar findings in both disorders are found in cognitive functioning (Bortolato et al., 2015; Green, 2006a) and in neuroimaging (Rimol et al., 2010a). Overlapping genetic vulnerability and immunological disturbances across the psychosis continuum have been found, supporting the continuum model (Morch et al., 2016; Tesli et al., 2014). There are also overlapping biological and social risk factors for developing depression with psychotic symptoms and schizophrenia (Heslin et al., 2016).

2. SPECIFIC INTRODUCTION TO THE THESIS

2.1 Migration

The diversity in incidence and prevalence of psychotic disorder found in epidemiological studies has uncovered that having migration background is an important environmental risk factor (Owen et al., 2016; Saha et al., 2005). Migration was first identified as a possible risk factor for schizophrenia in Norwegian immigrants in US in the 1930s (Ødegaard, 1932). Ødegaard concluded that the high prevalence of schizophrenia in the Norwegian population in the US was due to selective migration of people with increased risk. This hypothesis has later been tested in Surinamese immigrants in the Netherland. The authors did not find that selective migration explained the heightened risk, and launched the ideas that the migration experience or environmental factors in the new residence country were also involved (Selten et al., 2002). Another study found that children of parents with schizophrenia were less likely to immigrate to another country than children of healthy parents (Rosenthal et al., 1974), also weakening the hypothesis of selective migration.

The knowledge of migration as a risk factor has been revived over the last two decades. Recent research indicates that the post-migration factors account for most of the heightened risk of developing a psychotic disorder (Veling, 2013; Veling and Susser, 2011), as opposed to the hypothesis of selective migration. The "social defeat hypothesis" for schizophrenia focuses especially on environmental risk factors, where social disadvantages and social exclusion in the new country of residence are thought to increase vulnerability for psychotic disorders. This theory implies that being or feeling excluded from the majority group is pathogenic (Selten and Cantor-Graae, 2005; Selten et al., 2013). The social defeat hypothesis includes the environmental factors urban upbringing, migration, childhood trauma, low intelligence, and drug abuse. The hypothesis is that long-term exposure to the experience of social defeat or social exclusion may lead to sensitization of the mesolimbic dopamine system and thereby increase the risk for schizophrenia (Selten et al., 2013). Immigrant groups are more often subject to social disadvantages, such as poor socioeconomic position relative to the majority population and minority discrimination (Cooper et al., 2008). Ethnic discrimination is found to be associated with increased psychological stress (Hansen and Sorlie, 2012). Additionally early traumatic events is an important environmental risk factor for psychotic disorders (van Os et al., 2005), and there are indications that patients from some

immigrant groups are more exposed to early separation than other (Morgan et al., 2007). The observation of higher risk of psychotic disorder in immigrants is found to persist or increase for second generation immigrants (Bourque et al., 2011; Cantor-Graae and Selten, 2005). A possible explanation for this is that second generation immigrants may have been exposed for social exclusion and disadvantages already from childhood (Veling, 2013). Studies also report that the risk of psychosis increases with decreasing proportion of immigrants in a geographical area, a phenomenon described as low "ethnic density" (Bosqui et al., 2014; Kirkbride et al., 2007). On the other hand there is a possible protective influence of integration and social support in countries with longstanding immigration or where immigrants are perceived as belonging to the majority population (Dealberto, 2010; Selten et al., 2013). Thus "being the exception" is considered to be a very stressful state (Veling, 2013) while being included and part of the majority is considered to be protective (Selten et al., 2013).

A large meta-analysis from the UK found an increased risk for all psychotic disorders in immigrants, ethnic minorities in particular, compared to native British, with a relative risk for schizophrenia: in black Caribbean 5.6 (95% CI 3.4, 9.2), in black African 4.7 (95% CI 3.3, 6.8) and in South Asian groups 2.4 (95% CI 1.3, 4.5) (Kirkbride et al., 2012). These findings are in line with a former meta-analysis also indicating increased risk of schizophrenia for immigrants (relative risk of 2.7 (95% CI 2.3, 3.2), with an additional finding of higher increased risk for second generation immigrants (relative risk of 4.5 (95% CI 1.5, 13.1) and in ethnic minorities (defined based on skin type "black") (relative risk of 4.8 (95% CI 3.7, 6.2) (Cantor-Graae and Selten, 2005). In Sweden, a country with many similarities to Norway regarding health care systems and demographic variables, there is also found an increased risk for psychotic disorder in immigrants from all areas compared to natives and the risk was particularly high in ethnic minorities with African ancestry (Gilliver et al., 2014). Another Swedish study had similar findings and concluded that immigrants with refugee background had higher risk than non-refugees (Hollander et al., 2016). In ethnic minorities from sub-Saharan continent however, the risk was as increased in non-refugees as in refugees (Hollander et al., 2016). Increased risk of being diagnosed with a psychotic disorder is particularly found in ethnic minorities from developing countries (Cantor-Graae and Selten, 2005; Hollander et al., 2016; Kirkbride et al., 2012), and involves groups described as visible ethnic minorities with a non-white skin type (Veling, 2013). Migration as a risk factor for bipolar disorder is less established,; however, recent literature indicate that migration is a risk

factor for the full spectrum of psychiatric disorders (Cantor-Graae and Pedersen, 2013; Kirkbride et al., 2012), affective psychosis in particular (Coid et al., 2008; Kirkbride et al., 2008). Investigations in adolescents also imply a higher incidence of attenuated psychotic symptoms and mania in minority groups (Paksarian et al., 2016).

Findings from the large European studies mentioned above support the "social defeat hypothesis" where people perceived as visible ethnic minorities and with recent immigration are at particular risk of developing a psychotic disorder. In addition, a person's cultural background may also influence several aspects of established psychotic disorders. Compared to the reference population psychiatric patients with migration background are more often diagnosed with schizophrenia than with bipolar disorder (Anglin and Malaspina, 2008; Schaffer et al., 2009; Schrier et al., 2001). Some studies have shown more severe positive symptoms in ethnic minorities (Dealberto, 2013; Kennedy et al., 2004) and higher rates of affective symptoms, depressive symptoms in particular (Haasen et al., 2001; Veling et al., 2007). Other studies indicate higher rates of negative symptoms (van der Ven et al., 2012) and cognitive impairments (Dassori et al., 1998). A study from our research group showed that being a visible ethnic minority may have impact on some context-dependent aspects like delusions and ability to abstract thinking (Berg et al., 2014). Furthermore, being a visible ethnic minority and subject to discrimination was associated with more severe psychotic and depressive symptoms (Berg et al., 2011). These studies have however been conducted in a variety of immigrant and ethnic minority populations and findings may be cofounded by the diversity between the groups of interest. Contributing to the need for a closer look into this, similarities in symptom profiles between ethnic minorities and in the reference population have also been found (Douzenis et al., 2011).

2.2   Duration of untreated psychosis

Duration of untreated psychosis (DUP) is defined as the number of weeks from the first psychotic symptoms until the start of adequate treatment, in terms of hospitalization or in outpatient clinics with antipsychotic medications in adequate doses (Polari et al., 2011).

A long DUP is strongly associated with poorer outcome, especially in the early course of illness (Chang et al., 2012; Melle et al., 2005), but also in long-term follow up, studies indicate a more severe course of illness with more time spent in psychosis (Barder et al.,

2013). Finding predictors for DUP is therefore a highly prioritized research area and on a clinical level the establishment of early intervention programs is very much based on the focus on shortening DUP.

Insidious mode of onset (Compton et al., 2008), early age at onset, poor premorbid adjustment, diagnosis within the schizophrenia spectrum (Bechard-Evans et al., 2007) and residence in highly urbanized areas (Boonstra et al., 2012) are all factors correlated with long DUP. In contrast, close family relations and frequent family and social contacts are identified as factors that might reduce DUP (Goulding et al., 2008; Melle et al., 2005; Morgan et al., 2006).

Ethnic minority status and/or a migrant background may have implications for help-seeking behavior and access to pathways into the health care system (Lindert et al., 2008) and thereby possible associations with DUP (Boonstra et al., 2012; Morgan et al., 2006; Sterk et al., 2010). Findings regarding DUP's relation to ethnic minority status and migrant background however, have been ambiguous. A Dutch study focusing on ethnic minority status found significantly longer DUP in ethnic minorities than in the majority population (Sterk et al., 2010). In the UK based AESOP cohort (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) however, ethnic minorities with African ancestry actually had shorter DUP than the majority population (Morgan et al., 2006); while no ethnicity-based differences in DUP was found in a Canadian study (van der Ven et al., 2012). A predominantly African–American group with economic disadvantages from the US had significantly longer DUP than other patients (Compton et al., 2009). A second Dutch study, focusing on migration background, found longer DUP in first generation immigrants (Boonstra et al., 2012).

The effects on DUP from ethnic minority status versus migration can be difficult to evaluate since ethnic minorities often have a migration background. However, some groups have migrated from countries that resemble the majority and may not be perceived as ethnic minorities. Beliefs about psychiatric illness and whether or not symptoms are considered as a medical condition that will benefit from treatment in psychiatric clinics are probably rooted in the culture of origin (Sterk et al., 2010). It is thus of importance to differentiate between migrants perceived as ethnic minorities in the country of residence, and migrants having cultural backgrounds from similar countries as the country of residence, when evaluating the influence of ethnic minority status on DUP. On the other hand having migration background from all parts of the world could influence knowledge about the health care system and abilities to benefit from the available treatment options. In this regard, differentiating between

first or second generation immigrants (Boonstra et al., 2012), or assessing age at migration are important factors.

In Norway health service access is for practical purposes, without costs for the patients. This makes it possible, to a large degree to disentangle effects of migration and ethnic minority status from the effects of economic disadvantage.

2.3   Vitamin Ds role in psychotic disorders

In addition to the social and cultural challenges for visible ethnic minority groups, as described above (chapter 2.1 Migration), there are also great diversities in basic environmental characteristics between some countries of origin and the countries of current residence. The most obvious differences are the colder climate and less sunlight between countries near the equator, and the countries in the Northern Hemisphere (Wacker and Holick, 2013). The main source of vitamin D is sun exposure; more specifically, the exposure of the skin's epidermis to ultra violet B radiation (UVB). UVB radiation causes photolysis of a cholesterol metabolite in the skin to precholecalciferol (previtamin D3) and represents the first step of the endogenous vitamin D metabolism. Other vitamin D sources are in the diet; fatty fish, fortified dairy products and supplements in particular. Vitamin D deficiency is common among visible ethnic minorities in the Northern Hemisphere (Holvik et al., 2005), as dark-skinned individuals must be exposed for more UVB radiation than light-skinned to obtain adequate levels of vitamin D (Holick, 2007). Melanin, responsible for the skin's pigmentation, inhibits this first step of the endogenous vitamin D metabolism (Harms et al., 2011). Body covering clothing inhibits the UVB radiation on the skin and thus the vitamin D synthesis (Alagol et al., 2000; Allali et al., 2006). Based on the concurrent risk of both psychotic disorders and vitamin D deficiency in ethnic minorities in the Northern hemisphere, vitamin D has been proposed as a possible biological correlate for the increased risk of psychotic disorders in ethnic minorities (Dealberto, 2007; McGrath, 1999; Veling, 2013). There are indications of vitamin D is having an important role in neurodevelopment and brain function (Eyles et al., 2012) (see chapter 2.2.2).

The observed associations between winter birth and increased risk of schizophrenia (Davies et al., 2003), and the lower vitamin D levels found during winter seasons, also implies a potential role for vitamin D (Kinney et al., 2009). Another environmental factor associated

with both psychotic disorders and ethnic minority status is urban living (March et al., 2008; Suvisaari et al., 2000), and it is plausible that urban living involves more indoor life and work, and thus less sun exposure compared with a traditional country-life. Increased risk of schizophrenia is also found to be associated with famine and infections during neurodevelopment and vitamin D may be linked to these associations, possibly through the immune system (Brown, 2011; McGrath et al., 2011).

2.3.1 Vitamin D -the metabolism

Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in the liver, and converts vitamin D to 25-hydroxyvitamin D (S-25(OH)D). The second occurs primarily in the kidneys, and forms the physiologically active 1,25-dihydroxyvitamin D (1,25(OH)$_2$D). Serum concentration of 25(OH)D reflects both vitamin D produced from the skin and that obtained from food and supplements. The half-life of S-25(OH)D is several weeks and S-25(OH)D is perceived as a satisfactory indicator of the vitamin D level in the body (Annweiler et al., 2011). The half-life of 1,25(OH)$_2$D is only about 4-8 hours which make this metabolite less useful in a clinical practice. The active form binds to cells through a specific receptor; 1,25(OH)$_2$ D-receptor (VDR).

2.3.2 Vitamin D and the brain

A breakthrough study from 2005 showed that the VDR and the 1α-hydroxylase, the enzyme that transforms 25(OH)D into 1,25(OH)$_2$D, are widely distributed in the human brain (Eyles et al., 2005). Both the circulation form S-25(OH)D and to a lesser degree 1,25(OH)$_2$D pass the blood-brain barrier (Pardridge et al., 1985), and the different vitamin D metabolites including both 25(OH)D and 1,25(OH)$_2$D are shown to be presented in human cerebrospinal fluid (Balabanova et al., 1984). These findings indicate that vitamin D is a neuroactive component. The binding between vitamin D and its receptor activates vitamin D as a transcription factor with the ability to turn genes on and/or off. This makes vitamin D involved in the proliferation, differentiation and growth of neurons (Eyles et al., 2011), with an important role in neuroplasticity (Deluca et al., 2013). The strongest staining for both the VDR and the 1α-hydroxylase enzyme in the human brain is found in the hypothalamus and in

neurons within the substantia nigra (Eyles et al., 2005). Other studies have used receptor microscopic autoradiography on rat brains and found target areas in stria terminalis and central amygdala (Stumpf, 2012).

The influence from vitamin D on cell proliferation, differentiation and growth may be specifically important in the developing fetal brain. Animal studies of offspring exposed to vitamin D deficiency in fetal life have shown less differentiated brains (Eyles et al., 2011), structurally alterations with larger ventricles, and thinner cortex (Eyles et al., 2003). Epidemiologic studies in humans have shown that vitamin D levels below a critical limit at birth is associated with increased risk of developing schizophrenia (McGrath et al., 2010b), and that intervention in terms of vitamin D supplementation during the first year of life, is associated with a reduced risk (McGrath et al., 2004).

In the adult brain, low vitamin D levels could both have direct and indirect effect through loss of neuroprotection (Annweiler et al., 2015). Vitamin D is considered to inhabit neuroprotective properties through its prevention of oxidative stress in the CNS (Wrzosek et al., 2013). In line with that, findings indicate that low vitamin D is associated with increased oxidative stress (Zhang et al., 2014), and that vitamin D supplementation can reduce this (Nikooyeh et al., 2014). Vitamin D has the ability to buffer toxic effects from unbound calsium by stimulation calciumbinding proteins (Eyles et al., 2011).

In animal models it is found that vitamin D also acts as a mediator on neurotransmitters, both in the developing and the adult brain (Groves et al., 2014; Stumpf, 2012). Dopamine is, as mentioned, a central neurotransmitter in psychotic disorder, affecting positive symptoms. Vitamin D is found to be important for normal function of the dopamine circuits in animal models (Eyles et al., 2009; Schoenrock and Tarantino, 2016). Vitamin D has recently also been discovered as a regulator of the serotonin synthesis (Patrick and Ames, 2014), and serotonin has an important role in the pathogenesis of depression, as mentioned (Spies et al., 2015). Furthermore, insufficient vitamin D is proposed to disrupt serotonin activation (Patrick and Ames, 2015).

2.3.3   Vitamin D and the immune system

Vitamin D is described as a modulator of the immune system (Deluca et al., 2013; Fernandes de Abreu et al., 2009), and the vitamin D receptor (VDR) is expressed in almost all immune

cells (Kreutz et al., 1993). This is of relevance, as the immune system is perceived to have an important role in the pathogenesis of psychotic disorders (Goldstein et al., 2009; Potvin et al., 2008). Vitamin D has anti-inflammatory effects and modulates both the innate and the adaptive immune system (Baeke et al., 2010).

A recent review proposed that vitamin D's modifying actions on inflammatory and immunological processes were related to the co-morbid metabolic conditions found in schizophrenia such as obesity, insulin resistance, hyperlipidemia and cardiovascular diseases (Chiang et al., 2016). Vitamin D could also affect clinical symptoms through this regulation of the immune system (Chiang et al., 2016). High C-reactive protein (CRP), as a marker of general inflammation, has been found to be associated with lower vitamin D in patients with schizophrenia compared to controls (Zhu et al., 2015).

In the brain, vitamin D is considered to have neuroprotective properties through the immune system when present in sufficient amounts. Animal models show both recruitment of microglia (Garcion et al., 1998) and immune-regulation through dendritic cells (Bscheider and Butcher, 2016) from vitamin D.

2.4 Vitamin D levels in psychotic disorder and in healthy controls

Recent meta-analyses including cross-sectional studies have shown significantly lower vitamin D levels in patients with psychiatric disorders compared to healthy controls (Belvederi Murri et al., 2013; Valipour et al., 2014). There was however no significant differences in vitamin D levels between psychotic disorder samples compared to other psychiatric samples in the first meta-analysis, and the authors concluded that the low vitamin D levels were probably due to secondary factors to the disease rather than involved in the disease mechanisms (Belvederi Murri et al., 2013). Another meta-analysis did however find indications that being diagnosed with schizophrenia was associated with lower vitamin D levels than being diagnosed with other psychiatric disorders (Valipour et al., 2014). Two prospective studies in non-clinical samples found higher levels of vitamin D to be related to lower rates of definite psychotic experiences (Tolppanen et al., 2012) and psychotic-like experiences (Hedelin et al., 2010). There are thus relatively consistent indications of lower vitamin D levels in patients with a psychotic disorder, specifically schizophrenia.

Most of the case- control studies have been conducted in chronic patient groups and the results may be influenced by treatment, hospitalization status or disease behavior. Only two studies on vitamin D levels in psychotic disorder samples are conducted on first episode samples. One of these found significantly lower vitamin D levels in both patients from the majority population and with African ancestry, but not in patients with Asian ancestry, compared to healthy control (Crews et al., 2013). The other smaller study did not find any patient/ control differences (Graham et al., 2014). In the lack of longitudinal studies, assessments of vitamin D levels in first episode compared to a more chronic sample from the same catchment area and the same health care system could contribute to disentangle whether vitamin D levels are low already at first episode, or if they decrease along the course of illness.

As skin color is closely attached to the ability to produce vitamin D from the skin when exposed to the sun (Holick, 2007), there should also be a specific focus on how skin color/ visible ethnic minority status influences vitamin D levels in psychotic disorder samples. Unfortunately this has not been sufficiently taken into account in all studies. Ethnic minorities are often overrepresented in clinical samples due to their heightened risk for psychosis (Kirkbride et al., 2012); however, in many cases the clinical samples are compared with control groups that tend to include only the majority population. This may bias the results and mislead our understanding.

2.5 Vitamin D and symptomatology

Vitamin D levels may have impact on symptom profiles in established disorders (Dealberto, 2013). There are several findings indicating a potential role for vitamin D on different symptoms. Lower serum- levels of circulating vitamin D has been found in patients with acute psychotic episodes compared to patients in remission (Yuksel et al., 2014) and in acute psychosis with excitement or stupor, bizarre, and disorganized behaviour (Dealberto, 2013). There has been proposed sex differenses where low vitamin D has been found associated with negative symptoms in males, and increased anti-social aggression in females (Cieslak et al., 2014a). In mentally ill adolescents with primarily affective disorders, low vitamin D has been found to be associated with increased disease severity in terms of positive psychotic symptoms (Gracious et al., 2012). In animal models vitamin D has been found to modulate the dopamine circuits (Howes and Kapur, 2009) and one may speculate if this may represent a

possible biological mechanism for low vitamin D levels being associated with positive psychotic symptomatology.

Low vitamin D levels have also been found associated with higher degree of negative symptoms, like social anhedonia and poverty of speech in males (Cieslak et al., 2014a) and the total negative symptom factor in a first episode (Graham et al., 2014). Negative symptoms are hypothesized to be expressions of neurodevelpmental disturbances (Limosin, 2014), however there might also be an association between current vitamin D levels and the degree of negative symptoms. One possible mechanism contributing to the influence of vitamin D on negative symptoms is through vitamin D's neuroprotective properties against oxidativ stress (Wrzosek et al., 2013), as negative symptoms are hypothesized to have oxidative stress as part of the etiology (Albayrak et al., 2013; Sullivan and O'Donnell, 2012).

The strongest link between low vitamin D and psychiatric symptomatology has nevertheless been found in depression (Anglin et al., 2013; Milaneschi et al., 2014). In line with this, suicide attempters have shown significantly lower vitamin D levels compared to non-suicidal patients in a sample consisting of patients with depression (Grudet et al., 2014). Many patients with psychotic disorders experience depressive episodes (Romm et al., 2010), and previous findings indicate that low vitamin D is associated with depression also in psychotic disorders (Berg et al., 2010). It is important to investigate the relations between vitamin D and symptomatology in psychotic disorders as vitamin D supplements are easily accessiable, and may represent a possible beneficial adjuvant therapy for some patients.

Since vitamin D is closely related to the immune system, possible interactions between vitamin D and inflammation should also be explored in relation to symptomatology. Previous publications from our research group have shown associations between psychotic symptoms and increased levels of pro- inflammatory markers (Hope et al., 2013). Pro-inflammatory markers such as soluble tumor necrosis factor receptor 1 (sTNF-R1) and interleukin- 1 receptor antagonist (IL-1Ra) have been found to be increased in relation to psychotic symptoms and severity both in schizophrenia and bipolar disorder (Hope et al., 2013). Furthermore depressed mood has been associated with low levels of the same markers, sTNF-R1 and IL-1Ra, along with a low level of osteoprotegerin (OPG) in bipolar disorder. Due to the possible anti-inflammatory effects from vitamin D in the brain (Baeke et al., 2010), there might be interactions between vitamin D and the immune system in the etiology of clinical symptoms. In the study showing a negative association between suicidality and vitamin D, a

second finding was an association between low vitamin D and increased interleukin 1 β (IL-1β) in the suicidal depressive patients (Grudet et al., 2014). IL-1Ra is a marker for IL-1β activity.

2.6   Vitamin D and cognition

There are findings indicating a potential role for vitamin D in cognitive functioning. Especially in the elderly population, low vitamin D has been associated with general cognitive impairments (Llewellyn et al., 2009), and it has been found to be a predictor for cognitive decline in the older population (age> 70 years) in longitudinal studies (Miller et al., 2015; Perna et al., 2014). Another longitudinal study found mid-life vitamin D levels to be predictive of later fluency and working memory performance in a low education group. However, no such association was found for people with higher education (Assmann et al., 2015); making the authors suggest that vitamin D may modify cognitive reserves. There are also findings indicating an association between vitamin D deficiency and reduced processing speed (Darwish et al., 2015). This association appear as stable in a longitudinal study of the elderly (van Schoor et al., 2015).

In young and healthy individuals no significant associations between vitamin D levels and cognitive performance have been found (Jorde et al., 2015; McGrath et al., 2007; Tolppanen et al., 2011). The number of studies in young populations is however few and in addition the majority of these studies have participants with normal cognitive abilities and vitamin D levels within the normal range (Anastasiou et al., 2014).

From clinical studies of disorders affecting cognition, notably in Alzheimer's disease, there are indications that vitamin D deficiency is associated with cognitive impairments (Annweiler et al., 2013; Brouwer-Brolsma and de Groot, 2015; Wood and Gupta, 2015). These impairments are mainly found in executive functions in terms of switching and updating information, and in processing speed. In Parkinson's disease, vitamin D has also been associated with cognition, where higher vitamin D levels are associated with better performance on category fluency and verbal memory tests (Peterson et al., 2013). In line with this, a study of patients with Multiple Sclerosis, with a mean age 45 years, found that higher vitamin D levels were associated with better long term memory (Koven et al., 2013). In a

sample of elderly, described as frail, vitamin D levels were associated with executive functions and, on a trend level, with processing speed (Brouwer-Brolsma et al., 2013).

Despite the importance of cognitive impairments in psychotic disorders, and the link between vitamin D deficiency and impaired cognition in other disorders with compromised CNS functioning, surprisingly few studies have investigated vitamin D deficiency and cognition in psychotic disorders. A small study of patients with first episode psychosis found an association between a cognitive summary score and low serum levels of vitamin D (Graham et al., 2014). More studies targeting the associations between vitamin D and cognitive functioning in psychotic disorders are required.

3   AIMS OF THE THESIS

The main aim of this thesis was to disentangle the relations between migration background, ethnic ancestry, and vitamin D levels in reference to important clinical and cognitive aspects of schizophrenia and other psychotic disorders, as to increase knowledge about the complex interactions.

Subaim I was to determine if patients with migration background or ethnic minority status have longer duration of untreated psychosis (DUP) than the patients from the majority population, and to explore if this was best explained by ethnic minority status or migration background, including age at migration (before or after start of compulsory schooling in Norway).

Subaim II was to identify possible differences in vitamin D levels between first episode psychosis patients, multi-episode patients and healthy controls matched for age, gender and ethnic background. We hypothesized that first episode patients and multi-episode patients had lower vitamin D than the healthy controls, and that participants from ethnic minorities across the two patient groups and in the healthy control group had lower vitamin D than participants from the majority population of Norway.

Subaim III was to investigate the relations between low vitamin D and symptom profiles in a large sample of psychotic disorders. We specifically tested the hypothesis that low vitamin D was associated with positive and negative symptoms, depression, and suicidality. A second aim was to explore if associations between vitamin D and symptom profiles were influenced by selected inflammatory markers.

Subaim IV was to determine the association between vitamin D deficiency (vitamin D levels ≤ 25 nmol/L) and cognition in a large sample of patients with psychotic disorders and healthy controls using a neuropsychological test battery focusing on cognitive domains previously found to be associated with psychotic disorders and vitamin D levels, i.e. processing speed, verbal learning and - memory and executive functions. The hypothesis was that vitamin D deficiency would be associated with impaired cognitive function in these domains.

4   METHODS

4.1   Design

All studies in this thesis are cross-sectional. Participants were recruited consecutively between May 2003 and September 2014 from in- and out-patient psychiatric units in the catchment areas of the four major hospitals within the South-Eastern health region in Norway and from an early intervention unit at Stavanger University Hospital, in the Thematically Organized Psychosis (TOP) Study as part of the NORMENT research center.

Psychiatric assessments were conducted by trained research fellows who were all clinicians (medical doctors or psychologists), and the physical examination was conducted by medical doctors.

4.2   Ethics

The Regional Committee for Medical Research Ethics approved the study and our research methodology followed The Code of Ethics of the World Medical Association, Helsinki Declaration. REK approval reference number 2009/2485. The collecttion and handling of data was approved by the Norwegian Data Protection Agency, certificate number 03/02051.

Psychotic disorder patients are considered to be among especially vulnerable groups and this requires extra cautions regarding research methods. The researchers must be certain that the participants understand what participation entail, what the purposes of the study is, and how data are handled and used. Participation was based on written informed consent. In the first meeting with a potential participant, thorough information about the study was given and the participants' ability to give informed consent was evaluated. In cases where there was doubt about a participants' ability to give informed consent, the inclusion was postponed until the participant was in a more stable phase of the disease and given a new evaluation. The participants were also thoroughly informed that participation was voluntary and that they could withdraw at any point, and if necessary, request all their collected data to be deleted.

4.3 Material

4.3.1 Clinical sample

Lifetime diagnosis was determined based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID I module A-E), and information from medical records and the contact clinician. The recruitment team responsible for diagnostic and clinical assessments completed a three month education program including specific education, training and reliability testing using of the SCID-I and the structured interview for the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) based on the same program as the University of California, Los Angeles, UCLA. A satisfactory inter-reliability on the UCLA training procedure was achieved with an overall agreement of 82%, $\kappa = 0.77$ (95% Cl: 0.60-0.94) for diagnoses.

General inclusion criteria: Age between 18 – 65 years, with a DSM-IV diagnosis of schizophrenia spectrum disorder (schizophrenia, schizoaffective- or schizophreniform disorder), delusional disorder, psychosis NOS, depressive disorder with mood incongruent psychotic symptoms or bipolar spectrum disorder (bipolar I, bipolar II, bipolar disorder NOS)

General exclusion criteria: Presence of a pronounced cognitive deficit (IQ below 70), severe brain damage, inability to speak a Scandinavian language or inability to give informed consent.

4.3.2 Controls from the TOP sample

An age and sex matched sample of healthy controls from the same catchment area were randomly selected from national statistical records. The participants were contacted by a letter of invitation. All controls were evaluated with clinical interviews for severe mental disease symptoms and the Primary Care Evaluation of Mental Disorders (Spitzer et al., 1994), and were excluded if they or any of their first degree relatives had a history of severe psychiatric disorder (major depression, bipolar disorder or schizophrenia). Other exclusion criteria were substance or alcohol abuse and dependency, medical conditions involving the central nervous system and severe head injury. In our study II, the data from 102 of these control participants were used. In study IV, an additional number of 57 healthy controls were included, in total 159 in the thesis.

4.3.3 Controls from the HUBRO sample

The HUBRO study (Norwegian Institute of Public Health) is a population based study conducted in the years 2000-2001 in the Oslo region equal to the catchment area for the clinical sample. A total number of 996 individuals with background from Asia, including Turkey were included in the HUBRO study. For the study II, we randomly selected 40 individuals from this HUBRO file that matched our clinical sample with ethnic minority background on age and gender.

4.3.4 Total sample

Total clinical sample for all four studies consisted of N= 705 patients and 199 controls. There was some overlap between the participants in all four studies; however the study samples differed in each study as shown in this figure:

Figure 1. Overview of study participants in the four studies
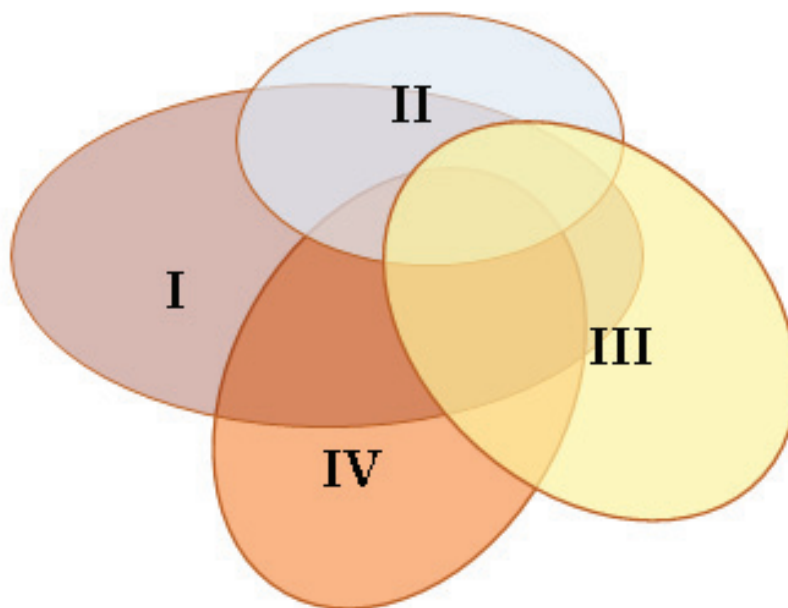
In *study I* we included all first episode psychosis patients with reported duration of untreated psychosis. The diagnostic distribution was the following: schizophrenia group i.e. schizophrenia, schizophreniform and schizoaffective disorder (N= 250) and non-schizophrenia group i.e. bipolar I, major depressive disorder with mood incongruent psychotic

features psychotic depression, delusional disorder and psychosis NOS (N=212). We did not have available vitamin D measurements for this sample.

In *study II* we included all first episode psychosis patients with available vitamin D measures, and we matched a multi-episode sample with the first episode sample 1:1 based on age, gender and ethnic background, i.e. being ethnic minority or belonging to the majority population. The first and multi episode sample was also matched on diagnosis (schizophrenia spectrum or other psychoses). The first episode sample was then matched on gender, age and ethnic background with a control sample (1:2). All patients, both from first- and multi-episode samples had a history of psychosis with following diagnostic distribution; schizophrenia group i.e. Schizophrenia, schizophreniform and schizoaffective (N=46) and non-schizophrenia group i.e. delusional disorder, brief psychotic episode, major depressive disorder with mood incongruent psychotic features and psychosis NOS (N= 25).

In *study III* we included all patients with a history of one or more psychotic episodes with available symptom measures and vitamin D assessments within the same season. The diagnostic distribution was the following: schizophrenia group i.e. Schizophrenia, schizophreniform-, and schizoaffective disorder (N=232) and non-schizophrenia group i.e. delusional disorder, brief psychotic episode, major depressive disorder with mood incongruent psychotic features, psychosis NOS, psychotic bipolar disorder I, bipolar disorder II with a history of psychosis and bipolar disorder NOS with a history of psychosis (N= 126).

In *study IV* we included all patients and healthy controls who had been assessed with a neuropsychological test battery within the same season as the vitamin D assessments. As an additional inclusion criteria all participants had to have all education in Norway, to ensure language skills did not bias the results on cognitive tests. The patient subsample had the following diagnostic distribution: Schizophrenia group i.e. schizophrenia, schizophreniform, and schizoaffective disorder (N=122) and non-schizophrenia group i.e. major depressive disorder with mood incongruent psychotic features, bipolar disorder I, bipolar disorder II and bipolar disorder NOS, delusional disorder, and psychosis NOS (N= 103). From the non-schizophrenia group, 11 patients diagnosed with bipolar II disorder did not have a history of psychosis.

Table I. Overview of the study samples

	STUDY I	STUDY II	STUDY III	STUDY IV
Patients/Healthy controls	462 / 0	142 / 142	358 / 0	225 / 159
Age (mean ± SD	27 ± 8	28 ± 8	30 ± 9	30 ± 9
Males (N / %)	277 / 60.0	184 / 64.8	217 / 60.6	218 / 56.8
Ethnic minority (N / %)	100 / 21.6	80 / 28.2	123 / 34.4	46 / 12.0
Schizophrenia spectrum (N%)	250 / 54.1	100 / 70.4	232 / 64.8	122 / 31.8

A specification of how the patients overlapped between the four studies is presented in this table 2.

Table 2. Overview of how participants in the clinical samples (patients) overlapped between the four studies

	Study I	Study II	Study III	Study IV
Patients (N)	462	142	358	225
N= 25	x	x	x	x
N= 43	x	x	x	
N= 68		x	x	x
N= 68	x		x	x
N= 26	x	x		x
N= 46	x	x		
N= 134		x	x	
N= 208			x	x
N= 115	x		x	
N= 70	x			x
N= 70		x		x
No overlap	343	4	55	14

See also figure I above

4.4 Measures

4.4.1 Clinical assessments

Demographic and clinical variables, as well as current medications, were obtained by clinical interviews and from conferring with medical records.

Having a migration background; being an immigrant, was defined by being foreign born or having one or two parents that were foreign born. This is in accordance with the statistical records used in Norway (https://www.ssb.no/en, 2016). The immigrants where further categorized as being an ethnic minority or not. Ethnicity was assessed by registry of participants' country of birth and the country of birth for his/her parents. This subdivision was selected firstly because being visible ethnic minority is considered more distressing than to be perceived as belonging to the majority population (Veling and Susser, 2011). Secondly, we used ethnic background from countries where the majority has darker skin color than the typically Scandinavian/ European skin type as a proxy for skin pigmentation, as skin type pigmentation has influence on the vitamin D metabolism originating from the skin's exposure to the sun. In our studies, ethnic minorities are thus represented by participants born in, or having at least one parent born in, African, Asian (including Arabic countries), or Latin-American countries.

We used the SCID-I A-D module to diagnose psychotic and/or affective disorders and the E module to diagnose any substance use disorder.

Current symptomatology was assessed by The Structured Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) (Kay et al., 1987). This interview asses the patient's symptom burden over the last week. The patient's responses, behavior under the interview, and available information from relatives and care-givers over the same period are used to score out 30 different items on a scale ranging from 1-7. The score 1 indicates no such symptom and the score 7 indicates extreme symptoms. As an example "delusions" is one item and a score 1-3 represent differences within normal range, while a score 4 or more represent delusions as a psychotic symptom. The original PANSS scale is divided into three sections, positive symptoms (7 items), negative symptoms (7 items), and general pathology (16 items). However, a variety of factor analyses have revealed that a modified division of the items may

have better clinical validity, and we have used a five-factor model proposed by Wallwork and colleagues (Wallwork et al., 2012). This five-factor model is found to be valid in clinical samples of different cultural background (Wallwork et al., 2012) and in early psychosis (Langeveld et al., 2012).

The *positive* symptom factor includes item P1 (delusions), P3 (hallucinations), P5 (grandiosity), and G9 (unusual thought). The *negative* symptom factor includes item N1 (blunted affect), N2 (emotional withdrawal), N3 (poor rapport), N4 (passive/apathetic social withdrawal), and G7 (motor retardation). The *disorganized/Concrete* factor includes the score from item P2 (conceptual disorganization), N5 (difficulty in abstraction), and G11 (poor attention) in the five factor model. The *excited* factor includes P4 (excitement), P7 (hostility), and G8 (uncooperativeness). The *depressed* symptom factor from the five factor model factor is the mean score from G2 (anxiety), G3 (guilt feelings), and G6 (depression). However, depressive symptoms are better assessed by dedicated depression scales, where a given cut off score is thought to mark the limit for a clinical depression.

The Calgary Depression Scale for Schizophrenia (CDSS) was developed to identify depression in patients with psychosis by excluding symptoms that overlap with negative symptoms of schizophrenia (Addington et al., 1992; Addington et al., 1990). Thus it differentiates better between depression and negative symptoms than other depression scales (Addington et al., 1994). This scale consists of 9 items with scores from 0-3, where 0 represent not present and 3 is the most severe score. A total score of 5 or above is considered depressive symptoms of clinical importance. A sub-group in our sample was assessed by another depression scale; the Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) (Rush et al., 1996). This scale covers 30 items and has the same scores ranging from 0-3 as the CDSS. To avoid decreasing sample size we made a regression equation to transform the IDS-C score to a corresponding CDSS score for the individuals with missing CDSS scores. The equation was calculated based on the relation between the CDSS- and IDS-C-scores in a subsample assessed by both depression scales at the same point of time. The formula CDSS = (-0,314) + (IDS-C x 0,282) was derived and gave adjusted $R^2 = 67.1$ for the total scores from the two scales.

In item 8 in the CDSS and in item 18 in the IDS-C, suicidal thoughts, plans or attempts are evaluated. We dichotomized this item into *non-suicidal* with a score 0 (no) or having *suicidal ideations* with a score 1 (mild), 2 (moderate) or 3 (severe) on these items.

Premorbid adjustment was assessed with the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982) The premorbid phase is defined as the time from birth until 6 months before onset of psychosis. It measures both social and academic functioning during four age ranges. To make ratings on items regarding sociability and withdrawal, peer relationships, academic performance, and adaptation to school, information was collected within each age range based on information from the patient, medical journal, and significant family members, when appropriate. High scores indicate poor functioning.

Duration of untreated psychosis (DUP) was measured following the criteria; time from the first onset of positive psychotic symptoms (the first week with a PANSS score of 4 or above on at least one of the Positive Scale items 1, 3, 5, 6 or General scale item 9) to the start of first adequate treatment of psychosis (Larsen et al., 1998).

The participants went through a physical examination conducted by physicians. Blood pressure and pulse were assessed by standardized procedures. Heart, lungs and the abdomen were evaluated by clinical examination and brief neurological status was conducted. Any findings was noted and reported in the files. The patients were also asked for comorbid somatic diseases. Height and weight were measured and Body Mass Index (BMI) calculated as kg/m^2.

Detailed records of the patient's current medication were obtained through medical records and self-reported use from the patients. In cases of discrepancy between the records and the information given by the patient, the contact clinician was consulted.

4.4.2 Biochemical assessments

Blood samples were withdrawn the same day as the physical examination. Blood was analyzed for a diversity of tests. The following paragraphs explain the biochemical tests used in this thesis.

Vitamin D: Total serum levels of 25(OH)D was used in the analyses. From September 2012; total S- 25(OH)D (a sum of 25(OH)D2 and 25(OH)D3) was determined using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method developed at the Hormone laboratory (Oslo University Hospital, Aker. Prior to September 2012, S-25(OH)D was

measured by radioimmunoassay (RIA kit from Diasorin) (Holvik et al., 2005) in the same laboratory. The difference between the two methods are that LC-MS/MS are more specific and determine different metabolites separately; 25-(OH)D3, 25-(OH)D2, 3-epi-25(OH)D3 and 24,25-(OH)D3. In the RIA method however only the total 25(OH)D is measured and this is a sum of 25(OH)D3, 25-(OH)D2 and 3-epi-25(OH)D3. We have used the total 25(OH)D and from the LC-MS/MS this is the sum of 25(OH)D3 and 25(OH)D2. In RIA total 25(OH)D is the sum of 25(OH)D3 and 25(OH)D2 and 3-epi-25(OH)D. The regression equation LC-MS/MS = 1.16 x (RIA) -9 was obtained at the laboratory during method comparison and was used to convert all S-25(OH)D concentrations obtained by RIA to equivalent concentrations obtained by LC-MS, which are used in the analyses.

In study II and III S-25(OH)D was used as a continuous variable suggesting a linear relationship. The residual plots showed god model fit supporting our assumptions. However in study IV we hypothesized based on previous literature that vitamin D would have to be under a critical level to have influence on cognitive functioning. We defined this levels as S-25(OH)D ≤ 25 nmol/L in accordance with definitions used in other studies (McGrath et al., 2010a) and in accordance to the limit for vitamin D deficiency in Norwegian treatment tutorials where S-25(OH)D below 50 nmol/L is defined insufficient and levels below 25 nmol/L are defined as deficient. One might argue that finding the critical level in our study sample would have been a more appropriate approach; however we chose to use a predefined threshold.

The plasma levels of sTNF-R1, OPG and IL1-Ra were measured at the laboratory at Research Institute of Internal Medicine (Oslo University Hospital, Rikshospitalet) using enzyme immunoassays (EIA) obtained from R&D systems (Minneapolis, MN, USA). (Hope et al., 2011). sTNF-R1 and IL-1Ra are both markers of the activity of the proinflammatory TNF and IL-1 cytokine systems (Aukrust et al., 2011; Michael et al., 2015). sTNF-R1 is a receptor for Tumor necrosis factor (TNF) which is a major mediator for inflammation (Chen and Goeddel, 2002). Plasma levels of IL-1Ra reflect a recent activity in IL-1α and IL-1β and are thus used as an indicator of inflammatory response (Perrier et al., 2006). OPG is a cytokine receptor and belongs to the TNF family (Khosla, 2001) and a is a marker of calcium related vascular inflammation (Corallini et al., 2008).

CRP in plasma, serum –thyroxin (T4) and thyroid stimulating hormone (TSH) were analyzed at Department of clinical Biochemistry (Oslo University Hospital, Ullevaal).

4.4.3 Cognitive assessments

The participants were assessed with two different neuropsychological test batteries over the study period. Battery I is a comprehensive test battery found to be sensitive for cognitive impairments both in schizophrenia and in bipolar disorders (Simonsen et al., 2011; Simonsen et al., 2008) where the executive part of the battery I is based on the Delis-Kaplan executive function system (D-KEFS) (Delis 2005). Battery II is based on the MATRICS Consensus Cognitive battery (MCCB) (Nuechterlein et al., 2008). The tests used in the current study are described below.

Some tests were overlapping between Battery I and Battery II and could be merged directly into the same outcome variables. Others differed in the assessments however were measuring the same functions. "Inhibition" and "Set-shifting" were assessed with the same tests in both batteries and the raw scores could be merged directly. For the cognitive outcome variables "Processing speed", "Verbal learning", "Verbal memory", "Verbal fluency", and "Working memory" we were able to compute Z- scores based on a healthy control group for each of the corresponding subtests from the two different batteries in order to merge the scores. Details are given in table 1 in study IV.

Below is the list of which cognitive domains were included and the tests assigned for these domains:

"Processing speed" was measured with the Digit-symbol test from WAIS-III or Brief assessment of Cognition in Schizophrenia (BACS). In these tests the participant is given a printed sheet with a key, linking a number (one to nine) to a nonsense symbol. In the same sheet a row with randomly assigned numbers appears. The participant is then asked to fill out the right corresponding symbol to each number based on the given key, as many as possible in given time. In the Digit-Symbol coding test from the WAIS-III, the participant is given 120 seconds for this task, while in the BACS the participant has 90 seconds for the same task.

"Verbal learning" and "Verbal memory" were measured with the California Verbal Learning Test (CVLT) or the Hopkins Verbal Learning Test (HVLT). In the CVLT verbal learning the participant was asked to repeat a list of 16 words that was read a total of five times. The key score used was total number of words immediately recalled (sum of trials 1-5). In HVLT verbal learning the list consists of 12 words and is read 3 times. The key score used was also here total number of words immediately recalled (sum of trials 1-3). Verbal memory represent

the delayed free recall from the CVLT verbal memory or HVLT verbal memory, where the key score used is the number of words remembered 20 minutes after the immediate recall.

"Verbal fluency" was measured with the Category Fluency Test in the D-KEFS battery or the Category Fluency Test from the MCCB. In the category fluency in the D-KEFS, the participant is asked to name as many words as possible in one minute in the category *animals* and then in the category *furniture*. The key score used was total accepted words from the category *animals*. The category fluency test in the MCCB includes only the category *animals*, and the time limit is the same; one minute.

"Working memory" was measured with the Letter-Number Sequencing test from the Wechsler Adult Intelligence Scale (WAIS) or with the Letter-Number Sequencing Test from the MCCB. In the letter number sequencing test the participant is presented orally to a list of digits and letters. The task is to sort the digits in ascending order and the letters in alphabetical order. The key score represent total number of correctly sorted trials.

"Inhibition" and "Set-shifting" were measured with the Color-Word Interference Test from the D-KEFS battery. The key score for inhibition represent the time used when performing the third condition of the test; name the color of the ink of written words of incongruent colors. The key score for set-shifting represent the time used when performing the fourth condition of the test; alternate between naming the color of the ink on written words without a frame and reading the words framed.

Current IQ was measured with the abbreviated scale WASI with the subscales *similarities* and *block design.* In *similarities* the participant is given two words or concepts and has to describe how they are similar. In the *block design* subtest the participant is presented with identical blocks with surfaces of solid red, surfaces of solid white, and surfaces that are half red and half white. Using an increasing number of these blocks, the participants are required to replicate a pattern that the test administrator presents to him/her – first as a physical model, and then as a two-dimensional picture.

Higher scores reflect better performance on all tests, except for the Color-Word Interference test where lower scores reflect better performance.

4.5   Statistics

All data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA, version 22.0). Analyses were performed with a significance level < 0.05, two sided (confidence interval of 95%). Preliminary analyses were conducted to examine the distribution of each variable which included inspection for skewness and outliers. Several variables did not have normal distribution, and were transformed to be able to use parametric analyses as the main analytic strategies. Duration of untreated psychosis (DUP), the Positive and Negative Syndrome Scale (PANSS) factors, and Premorbid Adjustment Scale (PAS) scores were skewed; however, they showed good model fit when logarithmic transformed as evaluated by studying the residual plots. The score from the Calgary Depression Scale for Schizophrenia (CDSS) was square root transformed for better model fit. For the immune variables, the CRP showed satisfying model fit when it was logarithmic transformed. For the remaining immune variables however, non-parametric analyses were applied.

Descriptive statistics for the whole sample were obtained using proportions, standard deviations, means, medians, or range according to the measurement type and distribution. Independent sample t-tests were used to assess potential differences between groups on demographic and symptom variables for continuous variables, and chi square tests were used for categorical variables. Pearson correlation coefficients were used to show how the variables were correlated within the groups for normally distributed variables and with Spearman's rho for skewed distributions. Significance level was set to $p < .05$ and all tests were two-tailed. Differences between multiple groups in normally distributed continuous variables were analyzed with factorial One-Way Analysis of Variance (one-way ANOVA) with post-hoc Tukey tests.

Hierarchical multiple linear regression analysis was conducted to control for possible confounders and explore the proportion of variance explained for continuous variables in study I, III, and IV. In study III, a hierarchical multiple logarithmic regression analysis was conducted for one of the dependent variables. As a main rule, independent variables with known associations to the dependent variable from the literature were entered in the first step, followed by entering variables that had shown correlations or associations with the dependent variable in our initial correlation matrices and bivariate analyses in the second step, and the independent variable our hypotheses were based on in the final step.

In study II we conducted ANCOVA to examine the vitamin D distribution in three different groups, controlling for possible confounding variables. This model also allows us to do interaction analyses, and in our follow-up analyses we did inspect interactions.

Variables that did not show associations with either the dependent variable or the hypothesized independent variable in the initial bivariate analyses were not entered in the multiple regression models or in the ANCOVA.

Residual plots from the regression models were evaluated to test model fit.

5 RESULTS/ SUMMARY OF ARTICLES

Article I: Migrant background and ethnic minority status as predictors for duration of untreated psychosis

The aim of the study was to explore if patients with migration- and/or ethnic minority background have longer duration of untreated psychosis (DUP) than the patients from the majority population, and in case; -to what extent this is best explained by ethnic minority status or migration history, including age at migration. Health service access is for practical purposes without costs for the patients in our catchment area, making it possible to disentangle effects of migration and ethnic minority status from the effects of economic disadvantage.

Methods: 462 patients with a first episode psychosis were included. The sample consisted of non-immigrants (NI), ethnic minorities (EM) and migrants resembling the majority population (MM). Instead of discriminating between first and second generation immigrants we operationalized migration background into having migrated before or after the age of six. Multiple regression models were performed to evaluate ethnic minority status and migration background respectively.

Results: The sample consisted of NI= 312 (median DUP 26 weeks), EM=100 (Median DUP 52 weeks) and MM= 50 (median DUP 28 weeks). There were no significant differences in age, age at onset, gender or diagnosis distribution between the groups. EM had significantly lower premorbid academic adjustment than MM and lower education than MM and NI. In multiple regressions age at onset, premorbid social and academic adjustment and schizophrenia diagnosis retained a significant influence on DUP. In the last block, neither migration per se (t=1.6, p=0.11, Total model F= 11.8 (df 5, 461), adjusted R^2= 0.12) nor being ethnic minority (t=1.8, p= 0.07, Total model F=12.6 (df 5, 461), adjusted R^2=0.11, p< 0.001) had a statistically significant association with DUP. Migration after the age of six however had a statistically significant association with prolonged DUP (t=2.46, p= 0.01, Total model F= 13.3 (df 5, 461), adjusted R^2= 0.12, p<0.001).

Conclusions: Age at migration has a moderate, but statistically significant effect on DUP. The findings indicate that migrating after start of compulsory schooling is associated with a longer DUP in immigrant populations.

Article II: Vitamin D status in psychotic disorder patients and healthy controls – The influence of ethnic background

Background: We aimed in this study to investigate serum concentrations of vitamin D in first episode patients compared to patients with longer duration of illness (multi episodes) and healthy controls. Secondly we wanted to investigate the influence of ethnic minority status on vitamin D levels across the diagnostic groups and healthy controls.

Methods: A total of 284 participants were included. First episode patients were matched on age, gender and ethnicity to participants from a multi episode patient sample (1:1) and healthy controls (1:2). To investigate the potential influence of confounders, variables that were either statistically significantly associated with vitamin D or differed across groups (i.e. FEP, MEP or HC) or ethnicity (majority population or ethnic minority) in bivariate analyses were entered as covariates in an ANCOVA with vitamin D as the dependent variable; in which group membership (FEP, MEP or HC) and ethnicity were fixed factors in the model.

Results: The FEP sample had higher age at onset than the MEP (mean age 25±7 vs. 22±7, p= 0.03) and shorter duration of illness (2.8±4 vs. 6.3±7 years). There were no significant differences in medication or hospitalization status. MEP had vitamin D measured significantly more often during summer than HC (chi^2= 10.6, p =0.01). MEP had higher BMI than both FEP and HC (F= 10.4, p < 0.01). Vitamin D was higher during summer vs. winter (t= 3.96, p<0.01) and in females vs. males (t=2.16, p = 0.03). In the ANCOVA with gender, BMI, season and ethnicity as covariates, group (FEP, MEP or HC) did not contribute to the variation in vitamin D (F= 0.02, p=0.98). We did not find any differences in vitamin D levels between FEP (40.6 nmol/L, 95%CI 35.9, 45.3), MEP (39.9 nmol/L, 95%CI 35.0, 44.8) or healthy controls (40.2 nmol/L, 95%CI 36.8, 43.7). However, in both FEP, MEP and in HC, vitamin D was significantly lower in ethnic minorities than in the corresponding majority population (F= 11.85, p= 0.001 in FEP; F= 4.48, p = 0.04 in MEP and F=39.95, p< 0.001 in HC). Furthermore low vitamin D was associated with depressive symptoms in the FEP group (Pearson's r = -0.25, p = 0.04).

Conclusions: There were no differences in vitamin D levels between patients and healthy controls, neither between first episode patients and patients with longer duration of illness. Participants with ethnic minority background however had significantly lower vitamin D than corresponding patient- and control groups from the majority population, and low vitamin D was associated with depressive symptoms in first episode patients.

Article III: Low vitamin D is associated with negative and depressive symptoms in psychotic disorders

Background: Our first aim in this study was to investigate the relations between low vitamin D and symptomatology in a large sample of psychotic disorder patients. Due to the close relation between vitamin D and the immune system and findings indicating an association between the immune system and clinical symptoms, we also wanted to explore if the associations between vitamin D and clinical symptoms were influenced by selected immune markers.

Methods: Participants (N=358) with a medical history of one or more psychotic episodes were recruited. Current symptomatology was assessed by the PANSS analyzed by a five factor model including a positive factor, a negative factor, an exited factor, a disorganized/concrete factor. Instead of the depressive factor from this model we used The Calgary Depression Scale for Schizophrenia for assessment of depressive symptoms and suicidality. We performed bivariate correlations and multiple regression models to evaluate the associations between vitamin D and the outcomes.

Results: Low vitamin D was bivariate significantly associated with negative symptoms (r= -0.18, p=0.001) and depressive symptoms (r= -0.12, p=0.02) and on a trend level with positive symptoms (r= -0.09, p=0.09) and suicidal ideation (t=1.9, p=0.06). There were no bivariate correlations between vitamin D and excited (r=0.03, P=0.6) or disorganized (r= -0.06, p=0.3) symptoms. In multiple regressions, the association between vitamin D and negative symptoms (t=-2.27, p < 0= 0.02) and depressive symptoms (t = -2.71, p= 0.01) remained significant when adjusting for possible confounding factors (i.e. gender, education, diagnosis, hospitalization status, ethnicity, season and thyroid status). CRP was correlated with both vitamin D (rho=-0.12, p= 0.03) and negative symptoms (rho=0.12, p=0.03), but did not mediate the association between vitamin D and negative symptoms in multiple regression analyses. The correlations between vitamin D and the inflammatory markers sTNF-R1, IL-Ra and OPG were not significant (rho= 0.10, p=0.15; rho= -0.03, p=0.66; rho=0.09, p= 0.19 respectively)

Conclusion: There were associations between low vitamin D and higher negative and depressive symptoms in psychotic disorders that remained significant after controlling for possible confounding factors. Vitamin D's associations with these symptoms were not mediated by CRP.

Article IV: Vitamin D deficiency associated with cognitive functioning in psychotic disorders

Background: The aim of this study was to investigate the potential associations between from vitamin D deficiency (defined as S-25(OH)D ≤ 25 nmol/L) and impairments in key cognitive domains in a large sample of psychotic disorder patients.

Methods: This cross-sectional study included 225 patients and 159 randomly selected healthy controls assessed by a cognitive test battery, a clinical protocol (including SCID-I and PANSS), and by a physical examination including vitamin D measurements. Multiple regression models were performed to evaluate the effect of vitamin D deficiency on key cognitive domains: Processing speed, verbal learning, verbal memory and executive functioning including verbal fluency, inhibition, set-shifting and working memory.

Results: The patient sample had more vitamin D deficiency (chi^2= 13.9, p<0.001) and more ethnic minorities (chi^2 =13.9, p<0.001) than the healthy control sample. There were no significant differences in age or gender distribution. Vitamin D deficiency was significantly associated with all cognitive domains except verbal learning in bivariate analyses. In multiple regressions controlling for age, ethnicity, IQ, and patient versus control status vitamin D deficiency remained significantly associated with decreased processing speed (i.e. "Digit symbol coding") (t=-2.7, p=0.01) and decreased fluency (i.e. "Verbal fluency") (t=-2.1, p=0.03). In a subsample including only the patients (N=225) there was a significant bivariate association between "Processing speed" and "Verbal fluency" and the negative symptom factor from the PANSS (Pearson r= -0.18, P= 0.01/ r= -0.27, p <0.001 respectively). Additional analyses in the patient subsample indicated that vitamin D had a trend level association (t=-1.85, p= 0.07) with processing speed when controlling for negative symptoms, while negative symptoms diluted the association with verbal fluency (t=-1.30, p=0.19). Depressive symptoms were not associated with processing speed (r= -0.04, p= 0.58) or verbal fluency (r= -0.03, p=0.70).

Conclusion: The current study shows that there is an association between vitamin D deficiency and decreased processing speed (measured with digit symbol coding test) and between vitamin D deficiency and decreased verbal fluency (measured by category fluency test) across patients with psychotic disorders and healthy controls.

6 DISCUSSION

6.1 Main results

Our main results are that migration background, ethnicity, and vitamin D are associated with important clinical and cognitive features in established psychotic disorders, both at first treatment and later in the course of the disease. Migration after the age of six was significantly associated with prolonged duration of untreated psychosis (DUP), while ethnic minority status only had a trend level significance for the same. Moreover, being an ethnic minority with ancestry from Asia, Africa or Latin-America, has a great impact on the vitamin D levels. Ethnic minorities had lower vitamin D levels than the majority population across diagnostic groups; we found significantly lower levels both in first episode psychosis, in a sample of patients with a longer duration of illness, as well as in healthy controls.

We also found that low vitamin D may have clinical significance, as it was associated with more severe symptoms, negative and depressive symptomatology in particular. Furthermore, vitamin D below a critical level, defined as vitamin D deficiency, was associated with impaired processing speed and verbal fluency. Both negative and depressive symptoms and cognitive impairments are considered important for the patients' function, quality of life and long term outcome.

In the following sections I will discuss the specific findings one by one, followed by a general discussion (6.2), and then a discussion of methodological issues (6.3)

6.2 Discussion of separate research findings

6.2.1 Migrant background associated with duration of untreated psychosis

The main finding of study I was that migration after the age of six was significantly associated with a longer DUP in a catchment area based on the Norwegian public health care system. Consistent with previous studies (Bechard-Evans et al., 2007), we also found that poor premorbid adjustment, low age at onset and diagnosis within the schizophrenia spectrum were associated with a longer DUP. Our findings are in line with a Dutch study focusing on

migration background where first generation immigrants and individuals from highly urbanized areas had prolonged DUP compared to other patients (Boonstra et al., 2012). In our study, ethnic minority status did not have a significant association with DUP; however, there was a trend level association. Other studies have found ethnicity to have a significant contribution. In another Dutch study, ethnic minorities, in this case individuals with Surinamese, Ghanaian, or Moroccan background, had longer DUP than Dutch natives (Sterk et al., 2010). In a UK based study DUP in African-Caribbean minorities did not differ from the DUP in native-British, however there were indications that Black-Africans had shorter DUP (Morgan et al., 2006). The ambiguous findings in these studies may result from a complex interaction between characteristics affiliated with the different ethnic minority groups as well as characteristics of the residence country and health care system. These results probably need to be investigated locally (in each country) to be able to recognize local challenges.

In our study, we did not include patients that needed an interpreter, and may have missed very recent immigrants in our sample. There is thus a possibility that low functioning patients with little contact with the Norwegian society and limited ability to adapt to a new culture and language are excluded from our sample. Undocumented immigrants are neither presented in our sample. We cannot rule out that other factors associated with both immigrants background and help-seeking behavior, such as language skills, could confound the DUP results. However, our study is conducted within a public health care system, thus minimizing the influence from socioeconomic status. The distribution of ethnic minorities in the current sample is at the same level as in the general population, and previous findings with equal rates of admissions (Berg and Johnsen, 2004) and consultations (Ayazi and Bogwald, 2008) due to mental illnesses in both ethnic minorities and the reference population in this catchment area, support the generalizability of our findings.

6.2.2   The influence of ethnicity on vitamin D levels

In study II we did not find any statistically significant differences in vitamin D status levels between a group of first episode patients and multi-episode patients with longer duration of illness and to healthy controls, respectively. There were however significant lower vitamin D

levels in ethnic minorities compared with participants from the majority population across all three groups.

This first finding is in contrast to earlier case-control studies on vitamin D levels including patients with established psychotic disorders (Itzhaky et al., 2012; Jamilian et al., 2013; Partti et al., 2010; Rey-Sanchez et al., 2009). These previous studies however, have important methodological limitations, including lack of adjustment for ethnicity (Doknic et al., 2011; Jamilian et al., 2013; Partti et al., 2010; Rey-Sanchez et al., 2009), comparison between hospitalized patients and health care workers (Itzhaky et al., 2012), or comparison of hospitalized patients and healthy controls recruited by advertisements, without control for place of residence (Crews et al., 2013). The healthy controls in the current study were randomly recruited from the same catchment area as the patients, and matched for ethnic background, gender, and age. We were also able to control for potential confounding variables like BMI and season. A review of reported vitamin D levels from previous studies actually show remarkably similar vitamin D levels for different patient groups, but with considerable variations in the levels of control groups. Our analyses also showed that vitamin D levels in healthy controls from the majority population varied more between winter and summer than in the corresponding patient groups. Larger seasonal variation in healthy controls compared with patients is also observed by others (Crews et al., 2013). This could be explained by contingent factors, such as reduced outdoor activities, that might be secondary to illness behavior in the patient group during summer, compared to healthy controls.

The current findings are in contrast to a previous study from our research group finding lower vitamin D levels in a Norwegian patient sample compared to a Norwegian population based control sample (Berg et al., 2010). This can be explained by different study design. In the previous study Berg et al. used a control group where data on vitamin D, age and season for blood sampling were provided from the population cohort as means and standard deviations at group level. The current study has a control sample with individual data for each participant, thus enabling us to match directly on important background variables. Since psychotic disorders have onset in adolescence or early adulthood, clinical samples can often have lower average age than a population based control sample, and this is of importance as there is a presumed age gradient in vitamin D levels. Older and more chronic patient groups are more prone to be influenced by illness related lifestyle factors, and it is possible that investigations of this patient group will show differences between patients and controls independent of

ethnic background. The clinical sample in Berg's study had longer duration of illness than the current.

The main finding from our study was that ethnic minority status was a strong predictor of low vitamin D levels both in patients and in healthy controls. The crude observed difference in vitamin D between ethnic groups could be inflated, because a large proportion of the control group for administrative reasons had their vitamin D measured during the winter season. However, ethnicity still had a strong and statistically significant effect on vitamin D levels also after adjustment for season. These findings are in line with previous research showing high levels of insufficient vitamin D in visible ethnic minorities in Northern hemisphere (Andersen et al., 2007; Holvik et al., 2005).

6.2.3   Vitamin D associated with symptoms

Our main finding from study III was that low vitamin D was associated with higher levels of negative symptoms and of depression. The associations remained when controlling for the potential confounding factors gender, ethnic minority background, diagnosis, education, season, and thyroid metabolism represented by T4.

The significant association between low vitamin D and higher negative symptoms expand the knowledge from two previous small studies finding the same association in a frst epiosode sample and in males (Cieslak et al., 2014b; Graham et al., 2014). The findings are of clinical relevance since negative symptoms have an even higher impact on impaired quality of life than positive symptoms (Faerden et al., 2009; Fervaha et al., 2014) and we lack effective treatment strategies (Tsapakis et al., 2015).

There was a significant correlation between vitamin D and positive symptoms in bivariate correlations, but this finding was no longer significant after controlling for potential confounders, in this case education and having a diagnosis within the schizophrenia spectrum. We did not find associations with excited or disorganized symptoms. Associations between low vitamin D and positive psychotic symptoms have been found in studies of youths with psychiatric disorders (Gracious et al., 2012), and for inpatients with psychosis (Yuksel et al., 2014). The samples from these particular studies however, may represent a subgroup of patients with more severe symptomatology or other confounders, as they only included

inpatients. Associations with florid positive symptoms and atypical syptoms were found in a Canadian study which hypothesized that this was due to a recent drop in vitamin D levels in immigrants with recent refugee background (Dealberto, 2013). In this particular study however, the patients were not yet diagnosed, and education level was not taken into account. According to our studies, these factors are confounders of the association between vitamin D and positive symptoms. We did control for gender in our multiple regression models, as previous studies have found gender to affect the relation between vitamin D and symptomatology (Cieslak et al., 2014a). We also performed additional analysis straftified by gender and found a trend for bivariate correlation between low vitamin D and higher score on the disorganized symptom factor in women (Pearson's r=-0.14, p=0.06), however, in multiple regression this association was non-significant (t=-0.13, p=0.90). We did not find any correlation with excited symptoms in males or females.

We also found a significant association between low vitamin D and higher scores for depressive symptoms. This is in line with results from samples of psychotic disorder (Berg et al., 2010) and depressive disorders (Milaneschi et al., 2014). In line with another study (Grudet et al., 2014), suicidal ideations were also associated with low vitamin D in the current study, and the multiple regression analyses showed that this association was mainly mediated by depression. In a clinical setting, this could support vitamin D as adjuvant therapy in treating co-morbid depressions in psychotic disorders.

We hypothesized that inflammation was a mediating factor for the associations between low vitamin D and higher scores on negative and depressive symptoms. We found that CRP was associated with vitamin D and negative symptoms through bivariate correlation. Adding CRP, as additional independent variable, did however not mediate the association between vitamin D and negative symptoms. In line with earlier findings linking IL-1Ra to disease activity (Hope et al., 2011; Hope et al., 2013), the pro-inflammatory marker IL-1Ra was associated with negative symptoms in our study. This marker however, had no significant association with vitamin D. Our results imply that the observed associations between vitamin D and symptomatology are more likely due to other mechanisms than inflammatory pathways. The immune system is however very complex, and there could be other interactions between vitamin D and inflammations, that is not covered by our analytic strategy or choice of inflammatory markers.

6.2.4 Vitamin D associated with cognition

The main findings from study IV indicate an association between vitamin D deficiency and decreased processing speed (digit symbol coding test) and between vitamin D deficiency and decreased verbal fluency (verbal category fluency test) for both patients with psychotic disorders and healthy controls.

The association between vitamin D deficiency and processing speed is in line with results from previous studies of older individuals (Brouwer-Brolsma et al., 2013; Darwish et al., 2015). However, our study is the first to show this association also in a young population (mean age 30±9 years). This is of interest since impairment in processing speed is a consistent finding in psychotic disorder compared to healthy controls, despite different assessment methods and cultural differences (Green, 2006b; Schaefer et al., 2013). Processing speed is essential for all cognitive demands, and daily functioning, and has been proposed to be a specific marker for cognitive deficits in psychotic disorders, especially in schizophrenia (Dickinson et al., 2007). The impaired processing speed appears to be stable over time in longitudinal studies (Bonner-Jackson et al., 2010). The association between reduced processing speed and vitamin D deficiency was however not patient specific in the current study. The findings were observed across the sample (vitamin D deficiency associated with impaired processing speed), both for patients and healthy controls and remained significant after controlling for patient versus control status in multiple regressions.

Vitamin D deficiency was also associated with impaired verbal fluency. The association between vitamin D deficiency and impaired fluency is in line with findings from a multi ethnic cohort with older participants (Miller et al., 2015). A longitudinal study of the general population that found very high vitamin D levels (>100 nmol/L) to be significantly associated with better verbal fluency (Pettersen, 2016). Furthermore, the association, between vitamin D and verbal fluency, has previously been shown in a small study of patients with psychotic disorders (Graham et al., 2014), but in this particular study, involving 40 participants, results appeared to be confounded by gender differences. This was not the case in the current study which included larger sample. The finding that association with vitamin D deficiency was not patient specific indicates that the link between vitamin D deficiency and cognitive tasks are not directly influenced by disease mechanisms, but instead may represent common biological pathways. The effects on functioning might however be larger in groups with already compromised cognitive functioning (Assmann et al., 2015).

The current study did not find the expected associations between vitamin D deficiency and verbal memory as demonstrated in other clinical samples. There was a bivariate association, but this was explained by differences in current IQ levels and patient versus control status in the multiple regressions. A link between vitamin D deficiency and impaired memory has been suggested, notably in clinical samples with impaired memory (Vicente et al., 2015), and high vitamin D levels have been found in relation to better memory performance in other clinical samples (Koven et al., 2013). Very high vitamin D levels have, however, also been found to be related to poorer verbal memory in healthy populations (Lam et al., 2015; McGrath et al., 2007). Prospective studies have not found a consistent association between vitamin D and memory (Kuzma et al., 2016). The lack of association is in line with a comparable study of psychiatric patients assessed by Mini-Mental-State (MMS) (Folstein et al., 1975), a cognitive test focusing on orientation and memory, where no association between vitamin D and these cognitive measures were found (Leedahl et al., 2013). Vitamin D deficiency has earlier been related to cognitive flexibility, but not significantly associated with inhibition (Annweiler et al., 2014b). In a study of frail elderly, executive function including a combined measure of interference tests, fluency and a reaction time task, was associated with vitamin D in terms of better performance with higher vitamin D (Brouwer-Brolsma et al., 2013). Our study indicates no significant associations between vitamin D deficiency and interference and/or set-shifting.

We performed additional analyses stratified by patient versus control status and found that the association between processing speed and verbal fluency with vitamin D deficiency in the patient subsample could be partly mediated by negative symptoms. The reduction of sample size by removing the non-symptomatic healthy controls reduced statistical power however, thereby hampering interpretations.

6.3 General discussion: Migration and vitamin D in psychotic disorders

From the studies included in the current thesis we have learned that migration background and vitamin D are two closely entangled factors with implications in psychotic disorders, both together and separately, and our findings have relevance on different levels. On administrative level our findings from study I and II indicate that there are challenges related to provide information and make advices and treatment options available for some immigrant groups. On a clinical level our findings from study III and IV have added knowledge on how vitamin D levels are associated with important clinical and cognitive features, and how this may be especially important in immigrant groups of ethnic minority background.

We found that patients with migration background experienced delay in their pathway into the treatment clinics when experiencing psychotic symptoms, and we have indications from previous literature that such delay is associated with more severe symptomatology, and a worse long term outcome (Chang et al., 2012; Friis et al., 2016; Melle et al., 2008; Wang et al., 2016). In addition to belief and confidence in the healthcare system, knowledge about how and where to find help may differ based on migration background and time spent in the residence country. Improved health education in this group may be one potential way to intervene, as health literacy has associations to the use of health services (Gabriel, 2010; Grace and Christensen, 1998). In a non-systematic review of immigrants in European countries, the immigrants tended to be unfamiliar with the local health care system in terms of navigating services needed (Lindert et al., 2008). We propose that migration after school-age may influence knowledge about the local health care system and thus help-seeking behavior in immigrants, as an explanation for our findings. Low levels of literacy in general adds barriers to using and assessing mental health services (Grace and Christensen, 1998), and low levels of mental health literacy in particular have been found to delay treatment for depression in immigrants (Gabriel, 2010). Low mental health literacy may thus partially mediate the association between low premorbid academic adjustment and shorter education with longer DUP. These two characteristics were significantly more compromised for ethnic minorities in our study sample. When controlling for premorbid adjustment and diagnosis, ethnic minority status only had a trend for prolonged DUP.

Cultural background may influence on how symptoms are experienced and how they are interpreted, and this again may influence on help-seeking behavior. A recent study showed similar clinical insight in immigrants compared to the reference group; however first generation immigrants were less likely to recognize psychotic symptoms, and found hospitalization or treatment by a psychiatrist less beneficial than the majority (Berg et al., 2015). Ethnic minorities with traditions related to healing and spiritualism are found to be less satisfied with treatment in psychiatric clinics (Sexton and Sorlie, 2008). There may also be differences in openness about psychiatric symptoms, and help-seeking for these groups, depending on the degree of stigma related to such symptoms and help-seeking behavior in different ethnic groups (De Luca et al., 2016; Mantovani et al., 2016; Sadeghieh Ahari et al., 2013). This could explain why ethnic minority status appears to have an effect on DUP regardless of age at migration in some studies (Boonstra et al., 2012; Sterk et al., 2010).

In our measurements of DUP we cannot estimate where the delay is, as the period from first psychotic symptoms to appropriate treatment involves both patient delay, referral delay and mental health care delay, where the two latter are depending of the organization and availability of treatment options. Boonstra and colleagues found that the prolonged DUP in first generation immigrants was due to the patient delay (Boonstra et al., 2012).

We found that immigrants from ethnic minorities had alarmingly low vitamin D levels and that low vitamin D levels were associated with more severe symptoms and impaired cognitive function. Initiatives to reduce duration of untreated psychosis and increase vitamin D levels in immigrant groups may therefore have a potential beneficial effect in terms of reduced symptom burden. People living in Norway have limited access to vitamin D from the sun, because of high latitude and long winter seasons (Wacker and Holick, 2013). In the absence of sun exposure through winter, diet and supplements become all the more important, but natural sources are few (mainly fatty fish and cod liver oil). Thus, cultural differences in diet can be one of the reasons for low vitamin D levels both in patients and healthy controls from ethnic minorities. Possibly, language barriers could also lead to a failure in reaching the ethnic minority population with guidance regarding use of supplements. The authorities encourage all inhabitants to take vitamin D supplements (Helsedirektoratet, 2011), especially during winter season, however according to our findings this message is most probably not received in ethnic minority groups, as they had very low vitamin D levels. This could be due to how, where and in which format the information is given, or it could be due to this group's trust and beliefs in such advices. Another explanation is that this group may need higher doses of

supplements to achieve the same levels as the majority population; however the recommended doses do not discriminate between groups.

Taken together having migration background, ethnic minority background in particular, might cause both more severe mental disease, and more somatic co-morbidity, due to both migration background and prolonged duration of untreated psychosis, and insufficient vitamin D levels in ethnic minorities.

Low vitamin D levels had associations with more severe symptomatology and cognitive impairments, independent of migration background or ethnic minority status. Ethnic minorities with the lowest levels, are most likely to suffer from clinical features associated with low vitamin D levels, however in our analyses, vitamin D had significant associations with negative symptoms, depressive symptoms, impaired processing speed and impaired fluency, also when controlling for ethnic background. The association between vitamin D deficiency and impaired cognitive function was significant, also when controlling for patient versus healthy control status, indicating an independent association between vitamin D and processing speed and verbal fluency.

One explanation for the associations between vitamin D and symptoms is that disease behavior may influence vitamin D levels (Belvederi Murri et al., 2013). It is possible that illness behavior from both negative and depressive symptomatology includes spending more time indoors and having less focus on diet, thus the low vitamin D could be interpreted as secondary to the symptomatology. In our analyses we have controlled for diagnosis, hospitalization status, and ethnic background, but our data are cross sectional, and we cannot conclude regarding direction of the associations.

The association between low vitamin D and depressive symptoms was demonstrated both in first episode patients in study II and in a larger sample in study III. The same association has consistently been found in clinical samples including patients with depression (Anglin et al., 2013). Depressive symptoms have a large impact on patients' quality of life (Gardsjord et al., 2016; Romm et al., 2010) and are also affiliated with a more severe course of illness in a long term perspective (Sonmez et al., 2014).

Negative symptoms in psychotic disorders are common and difficult to treat (Aleman et al., 2016). Low vitamin D was associated with more severe negative symptoms both in study III and IV. Negative symptoms are affiliated with increased malaise and malfunctioning for the

patients (Faerden et al., 2009), and a worse prognosis for the course of the illness (Austin et al., 2015; Evensen et al., 2012). Our results from study IV also indicated that the impaired cognitive function was partly mediated by negative symptoms in the patient sample, and this underlines the influence of negative symptoms on function.

Negative and depressive symptoms can be difficult to discriminate from each other; however we assessed depressive symptoms by a depression scale developed just for this purpose (CDSS), and we analyzed negative symptoms as part of a validated five-factor model of the PANSS (Wallwork et al., 2012). Our findings indicate that the negative symptom factor and depressive symptoms, as assessed by our choice of instruments, do describe different symptom dimensions. Negative symptoms in study IV was associated with impaired cognitive functioning (negative symptoms vs. processing speed r = -0.21, p< 0.001; negative symptoms vs. verbal fluency r =-0.26, p<0.001) while depressive symptoms did not show the same associations with cognition (CDSS score vs. processing speed r = -0.03, p= 0.65; CDSS score vs. verbal fluency r = -0.13, p= 0.06). This finding is in line with a review suggesting negative symptoms and cognitive symptoms as one cluster, as opposed to affective symptoms and positive psychotic symptom as a different cluster (Dominguez Mde et al., 2009).

The negative symptom factor includes N6 (Lack of spontaneity and flow of conversation) and G7 (Motor retardation) from the PANSS (Wallwork et al., 2012). The lack of motivation and motor retardation inherent in the negative symptom syndrome might disturb test performance in patients with prominent negative symptoms. How negative symptoms and cognition interact with each other is however difficult to disentangle.

Affective symptoms like depression have been proposed to have other etiologies than cognitive and negative symptoms (Dominguez Mde et al., 2009). The reasons for us finding low vitamin D associated with both negative/cognitive, and depressive components, could be because low vitamin D is secondary to the symptoms and impairments, not the other way around. Another possibility is that vitamin D, due to its multifunctional properties, can influence different biological pathways (Christakos et al., 2016) (see 6.5 Possible mechanisms).

6.4 Methodological discussion

6.4.1 Sample representability and generalizability

The Norwegian Health Care system is catchment area based and publicly funded. This should diminish the possibility of sample recruitment bias based upon geographic or socioeconomic differences. However, patient participation in the TOP-study is based on referral to the project by clinicians from the psychiatric clinics.

There are several reasons why this may have caused a selection bias. Individuals severely impaired by their psychotic symptoms, depression or cognitive deficits were probably not asked to participate because their clinician found it unethical to expose them for several hours of assessment. On the other hand, it is possible that very well -functioning patients with a first episode psychosis did not want to identify with a socially stigmatized group, and therefore declined to participate. This would imply that we are generalizing from a group representing the majority, but with a bias towards loss of information regarding patients with a very low or a very high level of functioning. There is also a possibility that the best functioning patients were not referred as involvement of the research recruitment team might delay the discharge from the clinic, while the patients with a more severe picture and more co-morbid conditions were referred as they probably would be available for the research team within the unit for a longer period of time. This could bias the sample into more low functioning participants.

To motivate the clinicians to refer all eligible participants, great effort was put on providing both written and verbal information about the project to the management, the clinicians, and the patients in participating clinics. Furthermore, research fellows from the recruitment team, like me, regularly participated in meetings at the different units to identify individuals suitable for recruitment. After the clinical assessments, a clinical report was provided the clinician and the recruiter offered to meet with the patient and his/her clinician to be able to provide answers to questions about the clinical report or the diagnosis.

Recruitment from in- and outpatient clinics from a catchment area provide a broad spectrum of psychotic disorder with participants from all parts of the society, and despite the issues discussed about the referral of patients into the study, we believe that our sample represent the patient population. The proportion of participants with immigrant background compares to the

overall demographics in the catchment area indicates good representability; however, our sample did not include immigrants without sufficient understanding of a Scandinavian language.

6.4.2 Strengths and limitations

The major *strengths* in our study are the large sample sizes and the very thoroughly characterization of every individual in terms of social variables, premorbid function, current symptomatology, somatic screening, and cognitive functions, as well as validated diagnoses from a broad spectrum of psychotic disorders. This allows us to do multiple analyses controlling for many potential confounding factors.

There might however be both advantages and disadvantages linked to including a broad spectrum of psychotic disorders. Large samples in psychiatry research are often heterogeneous due to potential overlap of clinical symptoms, and the heterogenic nature of categorical symptom syndromes. Notably in first episode or early phases of the disorders, the clinical picture is heterogeneous, and the diagnoses are not stable. In this case, inclusion of a broad spectrum is necessary, when aiming to capture the true first episode patients. However, there might be subgroups with more severe or less severe disease, and when all these patients are included in one big sample, one might risk that the great variation is blurring important associations. We have tried to disentangle these issues by using symptom specific outcomes, and focusing on cognitive domains rather than diagnosis. We did also control for diagnosis in our analyses.

In the TOP study protocol the clinical recruitment team were trained extensively and calibrated against each other and gold-standard ratings. Thus, there was a high overall agreement for diagnostic evaluations and the inter rater reliability for symptom scores was high. The main clinical instruments were validated in similar clinical samples and have shown to have good overall reliability. The five factor model we used for analyzing the PANSS scores is validated both in first episode samples and in clinical samples with diverse ethnic groups represented (Langeveld et al., 2012; Wallwork et al., 2012). The CDSS is developed especially to find depressive symptoms in patient groups with prominent negative symptoms (Addington et al., 1992), and the PAS also have good psychometric properties (Cannon-Spoor et al., 1982).

The advantages of studies in first episode samples are, as mentioned, that this patient group is considered less influenced by treatment and behavioral changes caused by the disease than more chronic patients. We have a high proportion of first episode patients in our sample. In addition the participants in our studies, not defined as first episode, are still relatively young (mean age 30 ± 9 years) and have relatively short duration of illness (mean 5 ± 6 years).

We used two different control groups, one randomly selected from national registry and one from a population based study including age cohorts. Both approaches are considered to provide representative control groups.

An overall ***limitation*** for the study was its cross-sectional design which offers no explanation concerning causality. Furthermore, we cannot rule out that the associations presented are influenced by confounding factors not taken into account.

Complex social phenomena like migration are difficult to operationalize. People with migration background may or may not be considered to be ethnic minorities, while ethnic minorities may or may not have personal migration background. The ethnic minority group in our studies also comprises a large diversity of participants. Norway has a long history in accommodating immigrants from Pakistan. The first immigrants from Pakistan came in the 1970s and the majority of migrants from Pakistan these days, are people with relatives in Norway applying for family reunion. More recently, immigrants from Somalia started to come to Norway, as asylum seekers or refugees (from late 1990s) due to acts of war in their home country. We know from other countries that there are differences related to recent or longstanding immigration history, and refugee versus non-refugee immigrants (Dealberto, 2010; Hollander et al., 2016). We have not been taken this into account in our studies, as we have focused only on being visible ethnic minority or not, and grouped people with Asian, African or Latin-American ancestry into one category in our analyses.

We have also used visible ethnic minority as a proxy of skin color when evaluating ethnic background in relation to vitamin D levels. There are available kits to assess skin color, which would be a much more accurate and objective measurements of this variable; however, we did not have these available in our study. As seen in many other studies, we also had fewer ethnic minorities in our randomly selected control group than one would expect from the demographic variables in our catchment area. To deal with this, we applied for the use of data

from a population based health study, focusing especially on immigrants, giving us available measures for a large group of immigrants within a specified age cohort. However, this study only included participants with Asian (including Turkey) ancestry, excluding people with African or Latin-American ancestry. We have participants from African and Latin-American countries in our clinical sample, so the control groups are not corresponding entirely with the clinical sample.

We also lacked reliable information about the use of vitamin D supplements and time spent outdoors, factors that could influence vitamin D levels in all participants. Another limitation is that two different methods for vitamin D measurements were used during the study period. A regression equation (LC-MS/MS = 1.16 x (RIA) -9) was obtained at the laboratory during method comparison to control for the contribution from 3-epi-25(OH)D to the total from RIA measures. The equation was used to convert all S-25(OH)D concentrations obtained by RIA to equivalent concentrations obtained by LC-MS, and these calculated measures are used in the analyses. However, when studying the distribution of the different metabolites in the sample evaluated by LC-MS/MS, this equation might appear to overcompensate for the possible contribution from 3-epi-25(OH)D from the RIA, as this metabolite appears rarely as measured by LC-MS/MS.

Another important limitation is, as in other clinical studies, missing values. Sometimes missing values are few and can easily be replaced by mean, or by the most common score for the group; like replacing a few missing values on BMI or other variables only evaluated as covariates or possible confounders. The issue is more serious when there are missing values on important outcome variables, or if there are so many missing values that you risk bias the results with replacements. We had many missing values on CDSS in study III. However, we had the opportunity to impute the missing values based on another correlated depression scale, by calculating a regression equation based on a subsample that was assessed with both scales. In the same study we only had immune data on a subgroup, and we could not replace or impute them in any way. We therefore had to investigate one of our research aims in a smaller study sample than we initially expected for and the results may be influenced by this decrease in sample size and loss of statistical strengths.

Retrospectively one may say that the possible influence from medication could have been more emphasized. However, there were no significant associations between vitamin D and the use of medication in our sample. When analyzing vitamin D as a continuous variable in

relation to use of psychoactive medication or not, there was no significant group differences (t=0.31, p= 0.76), nor were there differences between the medicated and non-medicated groups, when vitamin D deficiency was defined as serum level $\leq$ 25 nmol/L (chi^2= 0.90, p= 0.64). In additional analyses for specific medication groups vitamin D, as a continuous variable, did not correlate with the use of antipsychotics (r = -0.06, p= 0.31), or the use of antidepressants (r = 0.16, p= 0.10). Vitamin D deficiency (serum level $\leq$ 25 nmol/L) did not have a significant association with antipsychotics (chi^2= 2.33, p = 0.31), or antidepressants (chi^2= 0.98, p= 0.91). Thus adding medication into our analyses would most likely not change the main results.

6.5 Clinical implications

Age at migration has a moderate, but statistically significant effect on DUP. Information about how to recognize psychotic symptoms and how and where treatment for these symptoms can be provided should be encouraged as a public health initiative, and this information should not only be easily accessible for the general population, but also for immigrant groups less familiar with the health care system. The Norway a public health care system is organized with the intentions to treat every inhabitant equally and provide the same health care for everybody. Both patients and healthy controls with ethnic minority background had inadequate vitamin D levels, thus initiatives to increase vitamin D levels should be applied for whole group of ethnic minorities, not only for people examined in the clinics. These are challenges for the public health care system.

Our study design does not allow us to conclude about the direction of the associations between vitamin D and symptomatology nor vitamin D and cognition. Low vitamin D could certainly be a result of depressive and negative symptoms, as these symptoms may cause the patients to be less exposed to sun, or care less about diet. It is less intuitive how impaired processing speed and impaired fluency would cause vitamin D deficiency; however there might be confounding factors that we did not take into account in our analyses. Our findings nevertheless provide arguments for planning large scale randomized controlled trials, to evaluate the potential beneficial effect from vitamin D supplements in patients with low vitamin D levels, and further investigate clinical symptoms or cognitive impairments within the areas we found associations.

Another point of importance is that the risk of cardiovascular diseases and metabolic syndrome has been found to be associated with psychotic disorders (Johnsen et al., 2011; Ringen et al., 2014). Increased cardiovascular risk is also related to inadequate vitamin D levels (Choi et al., 2014; Menezes et al., 2014; Ruwanpathirana et al., 2014). Elevated risk of cardiovascular disease and metabolic syndrome in psychotic disorder in ethnic minorities has been demonstrated in long-term follow-up samples (Henderson et al., 2005). It is thus of interest that, in our age and gender matched sample from study II, ethnic minorities also had significantly higher BMI than the group recruited from the majority population, as well as lower vitamin D. Ethnic minorities may thus also have increased risk of somatic co-morbidity as low vitamin D levels and high BMI are associated with increased risk of cardiovascular diseases. People suffering from psychotic disorders have high risk of premature death which might be partly explained by cardiovascular co-morbidity (Dieset et al., 2016). This may be especially pronounced in ethnic minorities, and related to low vitamin D levels (Chiang et al., 2016; Das-Munshi et al., 2016; Lally et al., 2016). Clinicians should routinely measure vitamin D in psychotic disorder patients, in ethnic minorities in particular, and offer supplements if vitamin D is found to be below the reference value.

6.6 Possible mechanism

Prolonged DUP is associated with a poor short and long term outcome (Friis et al., 2016; Melle et al., 2005). Some researchers have hypothesized that psychosis is being toxic for the brain (Wang et al., 2016). The immune system is perceived to have an important role in the pathogenesis of psychosis (Goldstein et al., 2009; Potvin et al., 2008). Vitamin D may have neuroprotective properties due to close relation to the immune system (Garcion et al., 2002), and vitamin D in sufficient amounts has in animal models found to have neuroprotective effects (Christakos et al., 2016; Wrzosek et al., 2013). These suggest a potential beneficial effect from vitamin D in preserving brain function in psychotic disorder.

We found that low vitamin D level was associated with increased negative symptoms and cognitive impairments in our studies. Both cognitive impairments and negative symptoms are considered to have a neurodevelopmental etiology (van Os and Kapur, 2009), and imbalance in the excitation-inhibition systems involving glutamate and GABA have been proposed as neuronal correlates for both these disease components (Aleman et al., 2016; Coyle, 2006).

Furthermore oxidative stress has been proposed as a possible mechanism influencing the dysregulation of the inhibitory GABA response (Sullivan and O'Donnell, 2012). Vitamin D on the other hand has been found to protect against the adverse effects from oxidative stress (Nikooyeh et al., 2014; Wrzosek et al., 2013). Animal models have shown a neuroprotective role and enhanced cognition from vitamin D supplements (Landel et al., 2016). From clinical studies sufficient vitamin D is found to preserve cognitive function in the elderly (Miller et al., 2015).

There was also an association between low vitamin D levels and increased depressive symptoms in our studies. Insufficient vitamin D levels are found to disrupt serotonin activation (Patrick and Ames, 2015), suggesting a possible influence of vitamin D in the pathogenesis of depression. The observed seasonality in affective disorders also suggests an important role for sun exposure and vitamin D in depression (Akhter et al., 2013; Geoffroy et al., 2014). Clinical trials with vitamin D supplementation in depressive patients have shown diverse, however promising results (Li et al., 2014; Spedding, 2014).

Neuroimaging studies encompass a possible area of research for investigation of how vitamin D affects the brain in psychotic disorders. Vitamin D deficiency is found to be associated with lower brain volume and, more consistently, larger ventricles in cross-sectional studies of both animals and in clinical samples of Alzheimer's disease (Annweiler et al., 2014a). Larger ventricles and reduced total brain volume are among the most consistently reported structural imaging findings in schizophrenia (Haijma et al., 2013; Rimol et al., 2010b; Shenton et al., 2001). In addition, a recent longitudinal study found higher vitamin D levels to be associated with less regional cortical thinning over a three year period (Walhovd et al., 2014). These findings support the hypothesis for a neuroprotective effect of vitamin D.

A suggestion is thus, that low vitamin D accelerate neurodegeneration through loss of neuroprotection, specifically due to oxidative stress, and that this is of importance especially in disorders with already compromised CNS functioning. Another possibility is that vitamin D is more directly involved as a mediator of neurotransmitters.

While we did not find any differences in vitamin D between adult patients with psychotic disorders and healthy controls, prospective studies have suggested vitamin D deficiency as a contributing factor to higher risk of developing psychotic disorders in visible ethnic minorities in the Northern hemisphere (Dealberto, 2007; McGrath, 1999; Veling, 2013). Since the main negative effect of vitamin D would be on brain development in earlier phases of life, our

findings neither support nor contradict this hypothesis. However, the consistent findings of low vitamin D in ethnic minorities, maintain the need to explore the role of vitamin D deficiency as one possible contributor to the higher risk of psychosis in ethnic minorities.

6.7 Implications for future research

Pathways into the health care system need to be investigated and mapped in detail, in order to gain more knowledge of how duration of untreated psychosis can be reduced in immigrant groups with a short history in the residence country. We propose that interventions aimed at increasing health literacy, specifically in terms of recognizing pathological symptoms, may reduce DUP in immigrant populations. Also of interest is the development of more beneficial treatment options for the immigrant population in Norway. However, in which arenas and in what format this should be done, is not obvious. We would need to know more about where individuals from these groups meet, and if they are eligible for interaction with the health care system. Another factor is that ethnic minorities in cases where a severe symptom is recognized, report less belief in that contacting a psychiatrist or admission to a clinical ward would help (Berg et al., 2015). Also there might be more stigmas related to help-seeking behavior in some groups. Qualitative investigations could enhance knowledge around these issues, and provide information about how the health care system can develop customized treatment, early intervention in particular, for individuals with diverse migration background.

Randomized controlled trials with vitamin D supplements in adequate doses should be conducted to investigate if vitamin D substitution has a beneficial effect on the clinical and cognitive symptoms and impairments in patients with low vitamin D levels. Such studies could also provide information regarding directions of the associations. Randomized controlled trials have been conducted in relation to depression and meta-analyses of the results are published, yielding ambiguous results. However, if the samples are clinically depressed and the vitamin D intervention is sufficient in amount and length to increase vitamin D to adequate levels, vitamin D appears to have an anti-depressive effect (Li et al., 2014; Spedding, 2014). No intervention studies have assessed the possible beneficial effect of vitamin D supplement on negative symptoms, and should be an aim in future research.

Randomized controlled trials of the effect of vitamin D supplements on cognitive functioning in geriatric patients, report conflicting findings, but do support a beneficial effect in processing speed (Dhesi et al., 2004). Other studies have found no differences between the intervention group and the control group, on other cognitive domains (Corless et al., 1985; Rossom et al., 2012; Stein et al., 2011). A randomized placebo controlled study with young healthy adults did not reveal any effect of vitamin D supplements on either cognition or emotions (Dean et al., 2011), still, there were neither any adverse effects of supplementation.

Uncontrolled clinical trials have shown that few weeks of oral vitamin D supplements, give an adequate increase in vitamin D (Przybelski et al., 2008). However an intervention study of exposure to the sun with refractory schizophrenia patients compared to staff members, found increased levels of vitamin D in the staff members, but not in the clinical sample, despite the study being conducted during a sunny spring/summer with Caucasian participants (Bogers et al., 2016). In conclusion maybe vitamin D supplements are better to use in intervention than sun exposure. Vitamin D supplements are also considered safe to use (Jagannath et al., 2010), are well tried out and readily available. This, combined with the substantial negative effects of cognitive dysfunctions on daily living is a good argument for planning large scale randomized controlled studies in target populations, in order to conclude about vitamin D's potential beneficial effect on cognition in psychotic disorders.

The relations between vitamin D and structural changes in the brain found in imaging studies are not investigated in psychotic disorder samples. Vitamin D may also be associated with subcortical structures of particular interest in psychotic disorders. Reduced hippocampal volume compared with healthy controls is a strong finding in psychotic disorders (Rimol et al., 2010a) and a small study found vitamin D deficiency to be associated with reduction in hippocampal volume in patients with schizophrenia (Shivakumar et al., 2015). This should be further investigated in a bigger sample.

Recent animal studies have found vitamin D to prevent metabolic adverse effects induced by antipsychotics (Dang et al., 2015; Nagashima et al., 2016). These relations should be further investigated in humans. The increased risk for cardiovascular disease in psychotic disorders, and the association between cardiovascular risk and inadequate vitamin D levels (Choi et al., 2014; Menezes et al., 2014) in ethnic minorities in particular (Das-Munshi et al., 2016; Ruwanpathirana et al., 2014) will also need further research. The immune system is considered to play an important role linking psychotic disorders to cardiovascular risk (Dieset

et al., 2016). The immune factors in our study III did not appear to influence the relations between vitamin D and clinical symptomatology, but this may be an important pathway related to somatic health, metabolic syndrome and cardiovascular diseases involved in the response to antipsychotic medication (Nagashima et al., 2016). Bigger sample sizes and more comprehensive investigations can provide answers to these issues.

7. CONCLUSIONS

In a first episode sample of psychotic disorders, patients with immigration background had longer duration of untreated psychosis (DUP) compared to non-immigrants.

- Migration after the age of six was significantly associated with prolonged DUP
- Ethnic minority status was only associated with DUP on a trend level after controlling for the possible confounding factors premorbid adjustment, age at onset and having a diagnosis within the schizophrenia spectrum.
- Ethnic minorities had significantly lower premorbid adjustment than migrants from European and North-American countries (migrant majority) and shorter education than migrant majority and non- immigrants.

Compared to the majority population, ethnic minorities had significantly lower vitamin D levels

- Ethnic minorities had lower vitamin D than the majority in first episode patients, in multi episode patients and in healthy controls.
- There were no significant differences between vitamin D levels in patients compared with matched controls.
- In the Norwegian subsample, the healthy controls had larger seasonal variation in vitamin D level than patients.
- Low vitamin D levels were associated with increased depressive symptoms in first episode patients.

In a psychotic disorder sample low vitamin D levels were associated with more severe symptoms; however these associations were not mediated by inflammatory markers

- Low vitamin D was significantly associated with increased depressive symptoms
- Low vitamin D was associated with increased negative symptoms
- The association between low vitamin D and suicidality was mediated by depression
- There were no association between vitamin D and excited or disorganized symptoms
- Increased CRP was correlated with low vitamin D and increased negative symptoms, however CRP did not mediate the association between vitamin D and negative symptoms
- There were no correlations between vitamin D and the inflammatory markers sTNF-R1, IL-Ra and OPG.

In a psychotic disorder and healthy controls sample, vitamin D deficiency was associated with cognition.

- Vitamin D deficiency was associated with impaired processing speed and impaired verbal fluency
- The associations between vitamin D deficiency and verbal memory, working memory, inhibition and set-shifting were not significant when controlling for current IQ and patient versus control status
- In the patient subsample negative symptoms was significantly associated with processing speed and verbal fluency.
- When controlling for negative symptoms in multiple analyses in the patient sample, the association between vitamin D deficiency and processing speed was only on a trend level and there was no association between vitamin D deficiency and verbal fluency.

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Appendix

Errata

	Line	Original text		Corrected text
24	19	(relative risk of 2.7 (95% CI 2.3, 3.2)	cor	(relative risk of 2.7, 95% CI 2.3, 3.2)
24	20	(relative risk of 4.5 (95% CI 1.5, 13.1)	cor	(relative risk of 4.5, 95% CI 1.5, 13.1)
24	21	(relative risk of 4.8 (95% CI 3.7, 6.2)	cor	(relative risk of 4.8, 95% CI 3.7, 6.2)
36	13	The collecttion and handling of	cor	The collection and handling of
53	18-19	In the following sections I will discuss the specific findings one by one, followed by a general discussion (6.2), and then a discussion of methodological issues (6.3)	cor	In the following sections I will discuss the specific findings one by one (6.2), followed by a general discussion (6.3), and then a discussion of methodological issues (6.4)
63	27-28	(see 6.5 Possible mechanisms)	cor	(see 6.6 Possible mechanisms)