

Lipid effects during antipsychotic drug treatment and their relevance for clinical outcomes

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SCIENTIFIC ENVIRONMENT

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SUMMARY

Schizophrenia is a devastating mental disorder with disease mechanisms that are still poorly understood. Evidence has emerged that lipid dysregulations and myelination abnormalities might contribute to the pathophysiology of schizophrenia. Antipsychotic drugs often induce severe metabolic adverse effects, such as weight gain, dyslipidemias, and diabetes. However, several studies in chronic patients have indicated that some antipsychotic drug-related metabolic changes may be associated with improvements in psychotic symptoms. The main aim of this doctoral thesis was to combine clinical, biological, and imaging data to increase our current understanding of the relationship between serum lipid changes and various outcomes in antipsychotic-treated patients earlier in their illness course with emphasis on first-episode psychosis (FEP) patients. The clinical samples included FEP patients using antipsychotic drug treatment, olanzapine-treated, and unmedicated patients with broad schizophrenia spectrum disorders, along with a group of healthy controls from the Thematically Organized Psychosis project in Oslo. The participants underwent a thorough clinical evaluation, structural imaging, analyses of serum lipids, and physical examination, including assessment of body mass index (BMI). The severity of positive and negative symptoms and cognitive performances were assessed at inclusion and after a one-year follow-up, along with serum lipids. Linear mixed-effects models were used to examine associations between changes in serum lipids versus changes in positive, negative, and cognitive symptoms. General linear models were used to investigate associations between serum lipids and cortical thickness and gray/white matter intensity contrast, which were used as proxy measures for intracortical myelin. Our results indicate that an increase in serum HDL-C during antipsychotic drug treatment is associated with improvements in negative symptoms and verbal learning, independent of changes in BMI. Moreover, OLZ treatment was linked to normalized cortical intensity contrast, and a higher serum level of HDL-C in OLZ-treated patients was related to thicker cortices suggesting a lipid-mediated effect on intracortical myelin. Together, our results may indicate that the therapeutic effect of antipsychotic drug treatment could in parts be linked to lipid biosynthesis.

LIST OF PUBLICATIONS

Paper 1: Increase in serum HDL level is associated with less negative symptoms after one year of antipsychotic treatment in first-episode psychosis.

Gjerde PB, Dieset I, Simonsen C, Hoseth EZ, Iversen T, Lagerberg TV, Lyngstad SH, Mørch RH, Skrede S, Andreassen OA, Melle I, Steen VM.

Schizophr Res. 2018, Volume 197, Pages 253-260.

<https://doi.org/10.1016/j.schres.2017.10.042>

Paper 2: Improvement in verbal learning over the first year of antipsychotic treatment is associated with serum HDL levels in a cohort of first episode psychosis patients

Gjerde PB, Simonsen C, Lagerberg TV, Steen NE, Ueland T, Andreassen OA, Steen VM, Melle I.

Eur Arch Psychiatry Clin Neurosci. 2019.

doi: 10.1007/s00406-019-01017-w. [Epub ahead of print]

Paper 3: Association between olanzapine treatment and brain cortical thickness and gray/white matter contrast is moderated by cholesterol in psychotic disorders.

Gjerde PB, Jørgensen KN, Steen NE, Melle I, Andreassen OA, Steen VM, Agartz I.

Psychiatry Res Neuroimaging. 2018, Volume 282, Pages 55-63.

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ABBREVIATIONS

BBB The blood–brain barrier
BMI Body Mass Index
CLZ Clozapine
CNS Central Nervous System
CVLT-II California Verbal Learning Task
D-KEFS The Delis-Kaplan Executive Function System
D2-receptor Dopamine receptor D2
DDD Defined Daily Dose
DSM Diagnostic and Statistical Manual for Mental Disorders
DTI Diffusion Tensor Imaging
DUP Duration of untreated psychosis
EPS Extrapyramidal symptoms
FA Fractional Anisotropy
FEP First-episode psychosis
FGA First Generation Antipsychotic
GLM General linear models
HDL-C High-density lipoprotein cholesterol
LDL-C Low-density lipoprotein cholesterol
MRI Magnetic Resonance Imaging
OLZ Olanzapine
PANSS Positive and Negative Syndrome Scale for Schizophrenia
PUFA Polyunsaturated fatty acids
RCT Randomized Controlled Trial
SANS Scale for the Assessment of Negative Symptoms
SGA Second Generation Antipsychotic
SREBP Sterol Regulatory Element Binding Protein

TG Triglycerides

TOP Thematically Organized Psychosis study

WAIS Wechsler Adult Intelligence Scale

1. INTRODUCTION

First, I will give a general overview of the literature on schizophrenia and related psychotic disorders, focusing on patients with first-episode psychosis (FEP). Then I will go on to introduce more thesis-specific issues, concentrating on antipsychotics and metabolic disturbances, primarily dyslipidemia and changes in weight/body mass index (BMI). The literature search for this thesis was completed in May 2019.

1. GENERAL INTRODUCTION

1.1 Schizophrenia and related psychotic disorders

1.1.1 A walk down history lane

Psychosis is defined in the Oxford Dictionaries as: “A severe mental disorder in which thought and emotions are so impaired that contact is lost with external reality.” Amongst the psychotic disorders, schizophrenia is the severest form. It is a chronic multifactorial disorder depicted by several symptom dimensions and impairments in cognition and functioning.

It was the Swiss psychiatrist, Eugen Bleuler, who first suggested the term “Schizophrenia” for the disorder described by the German psychiatrist Emil Kraepelin in the late 19th century as “Dementia Praecox.” Dementia Praecox was characterized by the early onset of disease with subsequent cognitive deterioration and poor outcome. Bleuler, on the other hand, posited that the symptoms of schizophrenia could be explained as an inevitable split in patients’ affect and behavior, hence the term (from Greek *skhizein* ‘to split’ + *phrēn* ‘mind’). Bleuler further argued that the disease was, in fact, a group of clinical conditions with different etiologies and not a single disease entity. In contrast to

Kraepelin, Bleuler also noted that some patients could recover from the disease, which was an argument against a “neurodegenerative” disease model.

1.1.2 Epidemiology

The lifetime prevalence of schizophrenia is estimated to be around 0.7 %¹. Evensen et al.² reported a twelve-month prevalence of 0.17 % in the Norwegian population. According to the World Health Organization report on the global burden of disease, schizophrenia is classified amongst the most common conditions associated with a high rate of years lived with disability³, and among the ten most costly illnesses worldwide⁴.

1.1.3 Diagnostic criteria

Psychosis entails an impaired relationship with reality, including symptoms of delusions and hallucinations. Psychosis is a central symptom criterion for the Diagnostic and Statistical Manual of Mental Disorders 4th (DSM-IV) and 5th (DSM-V) diagnoses of schizophrenia, schizophreniform-, schizoaffective-, delusional-, and brief psychotic disorder, and in psychosis not otherwise specified (psychosis NOS). We have focused on patients with schizophrenia, schizophreniform-, schizoaffective-, and psychosis NOS, which is termed as “broad schizophrenia spectrum disorders” in the following thesis.

In the DSM-IV edition, schizophrenia is defined by having at least two 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 patient’s thoughts or behaviors, or two or more voices communicating with each other (“Schneiderian first-rank symptoms”). There must, additionally, be a marked reduction in work or social function (Criterion B). Continuous signs of the disorder must last for six months or more. This period must also include at least one month of active phase symptoms meeting Criterion A (or shorter if

treated adequately). For the schizophrenia criteria to be fulfilled, schizoaffective disorder and mood disorder with psychotic features must have been ruled out. Moreover, the disturbance must not be due to the physiological effects of substance abuse or a medical condition. Finally, if there is a history of pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if protuberant delusions or hallucinations are also present for at least a month (or less if successfully treated). Recently, there has been a change in the definition of schizophrenia with the publication of the latest diagnostic manual, DSM-5. In this latter manual, the presence of Schneiderian first-rank symptoms alone is not sufficient to satisfy Criterion A, and patients are required two out of five groups to meet Criterion A independent of the nature of the symptoms ⁵.

In schizophreniform disorder, signs of the disturbance are present for more than one month, but less than six months and functional decline does not have to be present. All other criteria described for schizophrenia must otherwise be met. In schizoaffective disorder, there is a major depressive episode, manic episode, or mixed episode concurrent with the characteristic symptoms in schizophrenia. Furthermore, during the same period of illness, there must have been delusions or hallucinations for at least two weeks in the absence of protuberant mood symptoms.

While we did not include patients with delusional disorder or brief psychotic disorder in our studies; delusional disorder is characterized by non-bizarre delusions for at least one month, without meeting criterion A for schizophrenia and function is not markedly impaired. In brief psychotic disorder delusions, hallucinations, disorganized speech or disorganized/ catatonic behavior has to be present for at least one day but less than one month, with eventual full return to premorbid level of functioning.

Finally, the diagnosis “psychosis NOS” is used when psychotic symptoms are present but do not meet the full criteria for any of the formal diagnoses for schizophrenia, schizophreniform-, schizoaffective-, delusional-, and brief psychotic disorder.

1.1.4 Clinical characteristics

Schizophrenia and other related psychotic disorders are heterogeneous in terms of symptomatology, neurocognitive, and functional outcome⁶. This heterogeneity is clinically displayed in many ways, with afflicted individuals varying in symptom severity and treatment response. The different symptoms in psychotic disorder are typically grouped into symptom dimensions. Along with positive symptoms and negative symptoms, cognitive impairments are often considered as core deficits⁶. I have thus focused on these three core symptoms in the present thesis.

Positive symptoms are denoted as such because they constitute an addition to normal experiences, and include delusions and hallucinations. Delusions are beliefs that persevere despite evidence that the beliefs are not logical or accurate. Hallucinations are sensory experiences in any modality that are perceived without an actual external stimulus. The most common type experienced is auditory hallucinations, which can range from simple sounds to fully formed voices, which may for example comment on the patient's thoughts and actions. Positive symptoms are the most frequently manifested symptoms of schizophrenia⁷. These symptoms usually fluctuate with time, being most severe in first-episode patients and during exacerbation of the disorder. While they often respond well to antipsychotic drug treatment⁷, they are not strongly associated with prognosis or functional outcome⁸.

Negative symptoms are denoted as such because they constitute an absence or marked reduction of normal experiences or behaviors, and include alogia (reduced speech content or meaning), anhedonia (loss of pleasure), and avolition (decreased motivation or ability to initiate or perform self-directed purposeful activities). Patients with these symptoms show decreased initiative, poor self-care, social withdrawal, and reduced expressivity. Negative symptoms are often the first symptoms to develop in patients with psychotic

disorder⁹. They are independent of the positive symptoms¹⁰, and tend to be stable over time in contrast to positive symptoms^{11,12}, although there are also reports of a more fluid course¹³. Furthermore, negative symptoms may persist after positive symptoms have been successfully treated, and as such, they are found to have a higher impact on functioning and recovery^{12,14,15}. Negative symptoms are often divided into primary and secondary symptoms, where primary symptoms are considered to be intrinsic to schizophrenia, and secondary symptoms to be a response to positive or affective symptoms, medication side effects or to environmental deprivation¹⁶. In epidemiological studies, primary negative symptoms are reported in 15–20% of the patients¹⁷.

While not a formal part of the current diagnostic criteria, acknowledgment of cognitive impairments dates back to Kraepelin. It is estimated that approximately 60–80% of schizophrenia patients manifest a significant level of cognitive deficit¹⁸, reaching between 1 and 2 standard deviations below the same aged control groups^{19,20}. These impairments are reported across all cognitive domains, but the severity is most significant in the domains of processing speed, attention, working memory, verbal learning, and problem-solving^{21,22} with impairment already present at the start of first treatment²³. People with ultra-high-risk of developing schizophrenia and young people with a family history of schizophrenia have reduced cognitive functioning compared to healthy controls, adding support to a neurodevelopmental origin²⁴. As with negative symptoms, cognitive impairment often precedes the presentation of positive symptoms²⁵, and may endure after the positive symptoms have been successfully treated¹. The presence of cognitive impairments is further associated with a more severe course of illness and a higher rate of use of health services^{2,26}. Interestingly, a mild to moderate correlation between negative symptoms and cognitive deficits have been found^{21,27}. Moreover, both cognitive symptoms and negative symptoms have been associated with structural dysfunction in similar brain regions^{27,28} and evidence indicates that they may have a common neurodevelopmental origin²⁹.

1.1.5 Onset and illness course

In the majority of all cases, the disorder emerges slowly with so-called prodromal symptoms. The term “first psychotic episode” is used when the symptoms succeed a given level of symptom severity. The further course of the disorder is heterogeneous³⁰, but characteristically relapsing-remitting between psychotic episodes and more stable phases in the absence of active phase symptoms³¹.

The initial years of the disorder are the most symptomatic and often include considerable psychosocial deterioration³². The rate of relapse within the first years after illness onset has been estimated to be around 35%³³, while the lifetime risk of relapse has been estimated to be up to 70%³⁴, irrespective of pharmacological treatment. That said, approximately 40 % of individuals with first-episode psychosis (FEP) experience relatively long periods with limited or no active phase symptoms as well as a decent level of functioning after undergoing their first psychotic episode³⁵. Systematic reviews based on meta-analyses of clinical trials have revealed that the risk of relapse in schizophrenia decreases with antipsychotic medication use³⁶, and some even argue that the leading risk factor for relapse is antipsychotic therapy discontinuation³¹.

The importance of studying patients with FEP

In the last decades, researchers have become more interested in patients in the early stages of the disorder. Studying patients with an FEP could also uncover risk factors less biased by antipsychotic drug treatment, drug side effects, and long-term effects of a detrimental lifestyle. Early illness phase and response to treatment during the first years after onset are further believed to be important predictors for future progression³⁷. Therefore, studying patients with an FEP could provide valuable information about the illness course and help to uncover prognostic predictors.

1.1.6 Etiology and pathophysiology

Although fastidious efforts have been made to identify the precise etiology and pathophysiological mechanisms of schizophrenia, it still remains an unresolved puzzle²⁵. Schizophrenia is currently believed to be multifactorial with complex gene-environment interactions³⁸. The heritable component has been estimated to be between 60-80%^{39,40}. While genetic research has exploded over the years, and international collaborations have aided in large sample Genome-Wide Association Studies (GWAS) with identification of a vast number of susceptibility genes for schizophrenia⁴¹, genetic findings so far have only explained a small fraction of the heritability⁶. In addition to these genetic risk factors, environmental factors such as high paternal age, obstetric complications, childhood trauma, infectious agents, urbanization, migration, and use of cannabis increase the risk of a chronic disease course^{6,42}.

Abnormalities in brain structure have repeatedly been found in post-mortem^{43,44}, and *in vivo* magnetic resonance imaging (MRI) studies⁴⁵⁻⁴⁷. Based on such findings, schizophrenia is currently regarded to be a neurodevelopmental disorder, in which the normal brain development is altered due to genetic and environmental factors during gestation and early life with the onset of clinical symptoms later in life⁴⁸. Structural neuroimaging studies have frequently reported brain volume changes in schizophrenia patients compared to healthy controls⁴⁵⁻⁴⁷. These include enlargement of the ventricles and smaller total brain volume, reduced cortical gray matter volume (particularly in frontal and temporal regions), and reduced hippocampal volume. A reduction in thickness has also been demonstrated in schizophrenia and related psychoses in comparison to healthy controls^{45,49}; most consistently in frontal and temporal regions. Several diffusion tensor imaging (DTI) studies have, moreover, reported of various white matter aberrations (i.e., lowered white matter integrity) typically assessed by fractional anisotropy (FA) reductions (for a review see⁵⁰⁻⁵³). These white matter abnormalities have been associated with positive symptoms (hallucinations)⁵⁴, negative symptoms⁵⁵⁻⁵⁷, as well as cognitive symptoms (executive function, memory, processing speed)⁵⁸.

In addition to the aforementioned brain structural pathologies, disturbances in neurotransmission have also been implicated in the pathophysiology of schizophrenia (see review ⁵⁹). Neurochemical imaging studies have indicated that in the active phases of the illness, an increase in dopamine synthesis and release in specific brain areas (striatum), as well as a higher concentration of synaptic dopamine compared to steady-state concentrations, could be found ⁶⁰. These changes in dopamine transmission have further been related to symptoms such as delusions and hallucinations ¹.

As the underlying pathophysiology of schizophrenia is still not clear, we do not have medication or other treatment options that as of today target the *cause* of the disorder. Treatment is primarily symptomatic and aimed at reducing psychotic symptoms, where treatment options include medication and psychosocial interventions such as cognitive therapy and community-based psychosocial interventions.

2. SPECIFIC INTRODUCTION TO THE THESIS

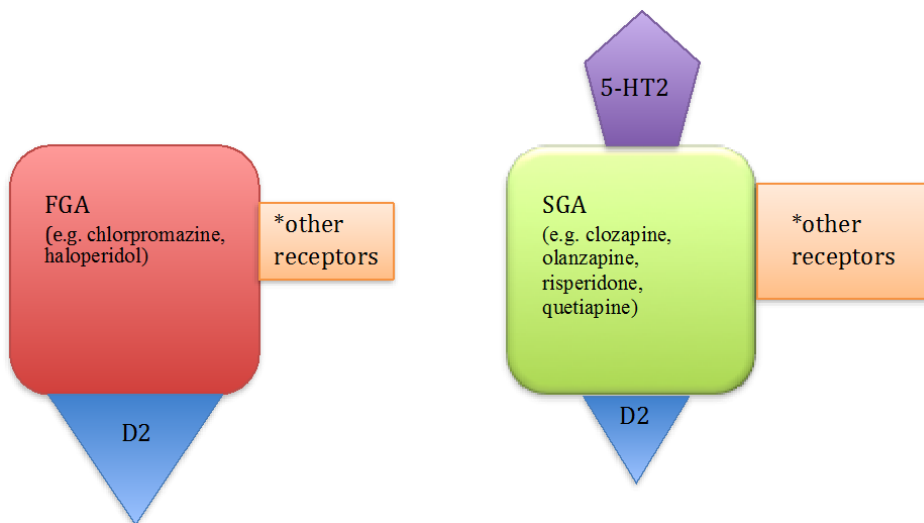
2.1 Antipsychotic drugs

2.1.1 A brief history of antipsychotic drug development

During the first half of the 20th-century patients with schizophrenia were confined to specially designed psychiatric hospitals: “mental asylums.” The “cures” of the pre-neuroleptic era included lobotomy, cold baths, and insulin comas, causing many unnecessary deaths. With the introduction of antipsychotics, the care of schizophrenia was revolutionized, allowing a significant number of institutionalized patients to be discharged and successfully reintegrated into the community. Antipsychotics are now a cornerstone in the treatment of schizophrenia.

Chlorpromazine is considered the prototype antipsychotic agent, and the first of the “first-generation antipsychotics” (FGAs) introduced as a treatment for psychiatric disorders more than 60 years ago. The serious adverse effects associated with FGA, including motor symptoms from the extrapyramidal system and hyperprolactinemia, however, encouraged the search for new antipsychotics. Clozapine (CLZ), the first “second-generation antipsychotic” (SGA) agent, was synthesized in the late 1950s and introduced clinically in Europe in the early 1970s⁶¹. While the ability of antipsychotic drugs to block dopamine D2-receptors is considered pivotal for symptom relief, there are general differences in the receptor binding profiles of FGAs and SGAs (Figure 1). SGAs, in general, have lower affinity for dopamine D2-receptors and a higher affinity for serotonergic (5-HT)- receptors as well as a more diverse receptor binding profile⁶².

Figure 1: A simplified receptor binding profile of first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), along with their therapeutic and adverse effects. Adopted from Stahl, S. M. (2008) Essential Psychopharmacology Online (<https://stahlonline.cambridge.org>)



Receptors		Therapeutic and Adverse Effects
Dopaminergic (D2)		Antipsychotic (therapeutic) effects, hyperprolactinemia, extrapyramidal symptoms
Serotonergic (5-HT2)	5-HT2A	Modulation of nigrostriatal dopamine binding (decreased extrapyramidal symptoms)
	5-HT2C	Metabolic complications and weight gain
*Other receptors	Histaminergic	Weight gain and drowsiness
	Muscarinic	Constipation, urinary retention, and dry mouth
	Alpha adrenergic	Orthostasis and drowsiness

2.1.2 Antipsychotics and effects on psychotic symptoms

With antipsychotic treatment, symptomatic remission is achieved by as many as 80% of patients affected by an FEP⁶³. In the acute setting, the early introduction of an SGA at the minimal effective dose is the standard recommendation in most guidelines⁶⁴.

While both FGA and SGA have proven to be able to treat positive symptoms leading to symptom reduction effectively, and even recovery in some patients^{6,65}, cognitive deficits and negative symptoms that better predict long-term outcome do not seem to show a similar response rate^{6,66,67}. In a meta-analysis by Leucht and colleagues⁶⁸, some SGAs (amisulpride, CLZ, olanzapine (OLZ), and risperidone) were found to be more efficient than FGAs for treatment of negative symptoms. Conversely, other SGAs (quetiapine, aripiprazole, sertindole, ziprasidone, and zotepine) were only as effective as FGAs. With that said, few of the studies included in this meta-analysis had explicitly examined the effect of SGAs on primary negative symptoms. Some SGAs may be useful for

secondary negative symptoms since they show greater effects on symptoms such as depression and anxiety and because they have a lower risk of extrapyramidal symptoms (EPS) ⁶⁹. Nevertheless, a relatively recent study examining FGAs and SGAs found that OLZ was more effective in treating schizophrenia patients with predominantly negative symptoms compared to the other antipsychotic agents ⁷⁰. The latter is also supported by a recent systematic review ⁷¹, that found some SGAs (including amisulpride and OLZ) to be more effective in treating patients with predominantly negative symptoms.

Despite a large number of studies that have evaluated the effects of antipsychotic medications on cognition, this relationship remains somewhat controversial ⁷². While there are studies that have shown that SGAs in comparison to FGAs may improve specific cognitive domains (see review ⁷³), there has also been work that has challenged such findings. Perhaps the most known one is The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study ⁷⁴, which indicated that regardless of the grouping (FGA or SGA), the antipsychotics had similar effects on cognition. The authors further argued that the effect size for cognitive improvements was small ⁷⁴ and that they were of questionable clinical significance ⁷⁵.

With that said, other studies have reported a beneficial effect of certain SGAs in relations to specific cognitive domains. For example, OLZ treatment has been found to significantly improve several cognitive domains, including vigilance, attention, verbal learning and memory, verbal fluency, as well as executive functioning ^{76,77}. CLZ has likewise shown a large to moderate positive effect on verbal fluency, attention, and executive functioning ⁷⁶. Still, as with the debate on the possible superiority of SGAs, there are also those who have not found a specific SGA agent having a uniform positive effect on cognitive functioning (for a review see ⁷⁸). It is further unclear whether the improvement observed with SGAs in the studies mentioned above epitomize actual cognitive enhancement or only represent a relative reduction in anticholinergic- and EPS-

related cognitive effects ⁷⁹. It is also possible that the improvements may, at least in part, be explained by practice effects ⁸⁰.

Lastly, it is estimated that up to 30% of patients with schizophrenia do not respond to treatment with currently available antipsychotic agents ⁸¹.

2.1.3 Antipsychotics and effects on brain structures

The majority of studies in patients with FEP as well as in patients with chronic schizophrenia have linked antipsychotic drug exposure to decreases in prefrontal and parietal lobe volumes, gray matter loss, and increases in basal ganglia volumes ^{82–86}. However, there are also authors who report no significant association between antipsychotic drug treatment and brain structures, both in adolescents ⁸⁷ as well as in chronic patients ^{88–90}. DTI studies examining treatment-related changes in white matter in patients with schizophrenia have likewise been inconsistent. Some report reduced white matter integrity during antipsychotic treatment ^{91,92}; while others report an increase in FA and an improvement in white matter integrity ^{93,94}.

Several studies that have examined subgroups of antipsychotics have found a differential effect of FGAs and SGAs on brain volume changes in schizophrenia. SGAs have for example been putatively associated with a lesser decrease in cross-sectional and longitudinal gray matter volume studies than has been found for FGAs ^{85,95–99}. In a five-year MRI study of schizophrenia patients, Van Haren et al. ⁸⁵ examined cortical thickness and change in cortical thickness. They reported significant correlations between antipsychotic medication and cortical thickness change although with difference in the nature of these associations: for FGAs, correlations were negative (i.e., higher intake was associated with more pronounced decreases in cortical thickness), whereas correlations with SGAs were positive (i.e., higher intake was related to less decrease in cortical thickness). In another study, Lieberman et al. ⁹⁶, examined the differential effects of OLZ and haloperidol on brain volumes in FEP patients. They found that haloperidol was

associated with significant reductions in gray matter volume after 12 and 52 weeks in comparison to healthy controls, whereas OLZ treatment was not. In compliance with these studies, a relatively recent meta-analysis concluded that the instrumental role of antipsychotic treatment in decreasing cortical gray matter volume cannot be generalized, but appears to be less for SGAs than for FGAs⁸⁶.

The biology underlying such differential effect of antipsychotics is yet to be understood, but Liebermann et al.¹⁰⁰ postulated that some SGAs might be able to reverse the morphological brain changes observed in patients with schizophrenia, including gray matter volume reductions, and decrease in dendritic spine density observed within the prefrontal cortex. Others have hypothesized that SGAs might have a neuroprotective effect, either increasing the expression of neurotrophic factors¹⁰¹ or by stimulating neurogenesis¹⁰². A cumulative number of studies, by Bartzokis and colleagues, have further indicated that some SGA might promote and/or improve myelination of the cortex^{103,104}, possibly through stimulating lipid pathways¹⁰⁵⁻¹⁰⁷. Such a notion is further supported by animal studies where SGAs have been shown to promote myelination¹⁰⁸⁻¹¹¹.

2.2 Lipid disturbances in patients with a psychotic disorder

2.2.1 Evidence of lipid disturbances in schizophrenia

Metabolic disturbances such as weight gain, dyslipidemia, and abnormal glucose metabolism are widely found in patients with schizophrenia, but also amongst other psychotic disorders. These disturbances increase the risk for diabetes, metabolic syndrome and cardiovascular diseases, and have been found to contribute to increased mortality in these patients¹¹²⁻¹¹⁴.

As reviewed in the preceding sections, substantial efforts have been made in the search for etiological and pathophysiological factors. Interestingly, several clinical observations, as well as genetic studies, are now providing evidence for a “lipid hypothesis” of

schizophrenia. First, the genes encoding the Sterol Regulatory Element Binding Proteins, SREBP1 and SREBP2, transcription factors involved in lipid biosynthesis, have been associated with schizophrenia ^{115,116}. Secondly, Andreassen et al. ¹¹⁷ demonstrated overlap in genetic susceptibility factors between schizophrenia and various cardiovascular risk factors, including BMI, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) in the blood ¹¹⁷.

Considering that schizophrenia is a neurodevelopmental brain disorder, and lipids (especially cholesterol) are crucial for proper brain development and neuron cell communication ^{118,119}, other genetic and non-genetic studies have likewise indicated an abnormality in lipid biosynthesis and metabolism in the pathophysiology of schizophrenia ^{120–126}. For example, the onset of schizophrenia in late adolescence or early adulthood ¹²⁷ coincides with a period of neuronal development when significant changes in fatty acid composition are taking place in the cerebral cortex ¹²⁸.

Lipids are also essential for myelin formation and functioning ¹²⁹, which has been found to be deficient in patients with schizophrenia ¹³⁰. Indeed, a meta-analysis of DTI studies in schizophrenia found decreased FA in white matter tracts interconnecting the prefrontal cortex and hippocampus ¹³¹. Such white matter disruption and other myelin abnormalities, hampering efficient communication between distinct brain regions, are known to play a crucial role in cognition and negative symptoms ¹³². Recently, researchers have started to focus more on the cerebral cortex as it is highly myelinated and such cortical myelin abnormalities are demonstrated in several neuropsychiatric disorders including schizophrenia ^{133,134}. The degree of intracortical myelination is also considered to be critical for the optimization of brain function ¹³⁵, and it is found to be highly associated with cognitive performance ¹³⁶.

Other lipid abnormalities, such as lower levels of membrane lipids, have also been demonstrated in drug-naïve patients and patients treated with antipsychotic drugs ^{137,138}.

There are, for example, studies showing alterations in the levels of polyunsaturated fatty acids (PUFAs), phospholipids and TGs in prefrontal and frontal cortex of schizophrenia patients ^{124,125}. PUFA disturbances have, in particular, been related to negative symptoms ^{139,140} and, to a lesser degree, to cognitive symptoms ¹⁴¹. Having in mind that negative symptoms and cognitive symptoms may have a common neurodevelopmental origin and be related to more structural brain changes, studies show that higher membrane PUFA concentrations may be associated with better brain white matter integrity ^{51,140}. Intriguingly, the membrane lipid abnormalities are not only observed within the central nervous system (CNS) but are also widely displayed in cells in the peripheral system ^{141,142}.

Finally, disturbances related to serum lipids have been exhibited in the early phases of the disorder ^{120,143,144}. According to two recent meta-analyses, FEP patients with minimal or no exposure to antipsychotics show differences in serum lipid profiles compared to healthy controls ^{120,145}. These serum lipid differences include lower levels of total cholesterol and LDL-C and higher TG levels in FEP. The meta-analysis by Misiak et al. ¹²⁰ also found lower levels of HDL-C in their FEP patients. Correspondingly, studies in at-risk patients have reported a subthreshold lipid dysregulation with reduced HDL-C levels ¹⁴⁴.

2.2.2 Metabolic effects following antipsychotic drug treatment: focusing on lipids and weight measures

Patients with schizophrenia, in comparison with the general population, have a 4-fold higher prevalence of metabolic syndrome, a constellation of features: abdominal obesity, dyslipidemia, abnormal glucose metabolism, and hypertension ¹⁴⁶. Whereas a sedentary lifestyle and lack of physical activity may be partially at fault ¹⁴⁷; antipsychotic drug treatment is considered the leading cause ^{148–150}. A meta-analysis determined that patients with severe mental disabilities, who were treated with an antipsychotic drug, had a

substantially higher risk of metabolic syndrome than antipsychotic-naïve individuals¹⁵¹. The risk was far greater with OLZ and CLZ than with other antipsychotics such as aripiprazole, and much larger in patients on polypharmacotherapy than in those on monotherapy¹⁵¹. Our focus has been on serum lipid changes as, along with weight gain; these are considered by many to be the most frequent metabolic changes following antipsychotic drug treatment^{113,152}. As serum lipids and BMI may be correlated¹⁵³; I will also review the literature on antipsychotic-related weight changes.

Most antipsychotics have an increased risk of causing weight gain and disturbances in lipid metabolism¹⁵⁴. However, there are reported differences in the extent of these disturbances. Meta-analyses have repeatedly shown CLZ and OLZ to induce more weight gain than other antipsychotic agents^{155,156}. Weight gain, mainly caused by enhanced appetite and food intake, may indirectly increase lipid levels, but it has also been shown that dyslipidemia can occur independently of weight gain in antipsychotic-treated patients^{157–159}. A specific concern was raised by a recent meta-analysis¹⁶⁰, which revealed that about 40% of patients with schizophrenia and related disorders treated with an antipsychotic had lipid disturbances and that dyslipidemia (i.e., high levels of TG and lower levels of HDL-C) might be the most prevalent cardiovascular risk factor in schizophrenia; another important argument for directing focus on this metabolic feature.

As adolescents¹⁵² and young schizophrenic patients^{150,161} are more prone to adverse metabolic effects with increases in TG levels, weight gain and metabolic syndrome following antipsychotic treatment, addressing metabolic concerns in patients earlier in their disease course may be imperative. Correll et al.¹⁵⁰ in their baseline data from Recovery After an Initial Schizophrenia Episode–Early Treatment Program (RAISE-ETP) study uncovered dyslipidemia in about half of their FEP patients with limited prior drug exposure, which is comparable to adults averaging 20 years older in the general US population¹⁶². Several studies also report that the adverse metabolic effects seem to prevail in as short as three months after initiation of pharmacotherapy^{163,164}, with the risk

of further weight gain and worsening of lipid profile during continued drug treatment^{156,163–165}.

In previously drug-naïve patients and patients with limited prior antipsychotic drug exposure, the weight gain and lipid disturbances have been even more pronounced^{166,167}. For example, Perez-Iglesias¹⁶⁷ found that after only 12 weeks of antipsychotic drug treatment (haloperidol, risperidone or OLZ), previously drug-naïve FEP patients experienced a marked weight gain (mean = 5.7 kg) leading to overweight in about 40 % and a worsening in lipid profile (increase in total cholesterol, LDL-C, and TG). Additionally, in drug-naïve patients contra more chronic patients, all antipsychotics (i.e., FGAs and SGAs alike) have been found to induce weight gain^{161,164,168,169} and dyslipidemias¹⁶⁷, although with some differences in magnitude as demonstrated in the European First Episode Schizophrenia Trial (EUFEST)^{148,170} and in the “Evaluation of METabolic disordERs in schizOphRenic patients” (METEOR) study¹⁶⁹.

2.2.3 Possible therapeutic implications of the metabolic adverse effects

While the metabolic side effects may impose a serious burden on the somatic health, it has also sparked some debate as two of the most metabolically potent drugs, CLZ and OLZ,¹⁷¹ are also the most efficacious drugs^{69,172}. This issue gets further complicated as there is a growing body of studies reporting an association between antipsychotic-related weight gain and clinical improvement (to name a few: ^{173–179}) and remission status¹⁸⁰, especially during OLZ and CLZ drug treatment. In relation to these studies, Sharma et al.¹⁷⁹ raised some key questions: “are metabolic side effects a necessary evil with the use of antipsychotic medication?” and ““is there a metabolic threshold for antipsychotics?””.

The answer appears to be complicated, as amisulpride, which has a lesser propensity for weight gain, has in some studies shown better long-term efficacy compared with more conventional serotonin-, dopamine- or multireceptor-SGAs^{69,179}. Furthermore, studies are

indicating a general link between weight gain and clinical improvement independent of the *type* of antipsychotic drug used¹⁸¹. These issues raise the question that perhaps other metabolic pathways, e.g., lipid-related pathways, might be mediating the previously observed link between antipsychotic-related weight gain and therapeutic efficiency. Indeed, weight gain during antipsychotic drug treatment may be a *proxy* for serum lipid changes¹⁵³.

Studies have found an association between elevated TG and treatment response (mostly reduction in overall and positive symptoms) in patients receiving antipsychotic drug treatment^{159,181–183}. For example, Procyshyn et al.¹⁵⁹ reported that risperidone-treated patients who improved in total and negative symptom PANSS scores had increased TG and total cholesterol levels when controlling for weight gain. In another study with 372 chronic schizophrenia patients treated with antipsychotics for more than two years, Chen et al.¹⁸⁴ established a link between the increase in TG levels and improvements in negative symptoms. There are also studies reporting a link between higher levels or increases in total cholesterol, HDL-C, and LDL-C levels, and improvement in cognitive symptoms^{185,186}. Lancon et al.¹⁸⁵ examined 168 schizophrenia outpatients and found an association between metabolic syndrome and memory impairment on measures of verbal learning, and short- and long-term memory. When examining the different components of metabolic syndrome, they discovered that low HDL cholesterol was associated with memory impairment (along with hypertriglyceridemia and abdominal obesity).

However, in the post-hoc analysis of the CATIE trial, Hermes et al.¹⁸¹ could not find an association between serum lipids and improvement in psychosis, even when each antipsychotic drug was analyzed separately. Likewise, a link between serum lipids and cognition during antipsychotic usage has not consistently been observed^{187,188}. One cause for the discrepancies between these studies may be sample differences, with the latter three studies including mostly chronic patients, where illness- and lifestyle-related factors might have intertwined with direct medication effects. Also, lipid synthesis in the brain

during antipsychotic drug treatment is hard to study in an *in vivo* setting, but there may be some indications for studying serum lipids as a proxy for the lipid availability in the CNS.

2.2.4 Lipids in the brain and the peripheral system

2.2.4.1 From a general perspective

Lipids constitute a large group of molecules involved in numerous essential processes and structures in the human organism¹⁸⁹. TGs are the primary storage form of lipids in the body, composed of a glycerol backbone and three esterified fatty acids. Fatty acids, TG, cholesterol may be absorbed from the diet or synthesized *de novo*.

De novo synthesis of cholesterol is a complex pathway where cholesterol is synthesized via the isoprenoid biosynthetic pathway (for details see¹⁹⁰). Altogether, a minimum of 20 enzymes is involved for manufacturing cholesterol, where the hydroxymethyl glutaryl-Coenzyme A reductase is the rate-limiting enzyme¹⁹⁰. For transport and storage, cholesterol is usually esterified, i.e., linked to fatty acids through an ester binding.

The brain is the most cholesterol-rich organ, containing about 20% of the whole body's cholesterol pool¹⁹¹. Nearly 80% of the cholesterol in the adult brain is in myelin sheaths formed by oligodendrocytes to insulate the axons; the rest is made up by plasma membranes of neurons and astrocytes to maintain their morphology and synaptic transmission¹²⁹.

Cholesterols, as well as the receptors for cholesterol-containing molecules, are pivotal signaling molecules for brain morphology during embryonic development¹²⁹. Sufficient availability of cholesterol is crucial for the physicochemical properties of cells within the CNS and an absolute requirement for synapse development, synapse formation, dendritic differentiation, axonal guidance, and long-term potentiation^{192–194}. The highest rate of cholesterol synthesis in humans occurs during the first postnatal weeks¹⁹⁵. This window

of time corresponds with the peak of the myelination process, where deficiencies in cholesterol biosynthesis can severely delay the myelination process ¹⁹⁶.

During the maturation of neurons, the endogenous synthesis of cholesterol is impaired, and the neurons depend on cholesterol provided by astrocytes ¹⁹⁷. Sufficient availability of cholesterol is necessary for all normal neuronal function and morphology, but there are marked differences in the cholesterol content in different brain regions as indicated by the differences in the expression of cholesterol-synthesizing enzymes and lipoprotein receptors in various regions of the brain ¹⁹⁸.

Most of the CNS cholesterol is recycled. However, for adequately maintaining homeostasis, mechanisms to export cholesterol into the circulation are mandatory. CNS cells, in particular astrocytes, can shed HDL-like lipoproteins composed of cholesterol and phospholipids and apolipoprotein E into the cerebrospinal fluid ¹²⁹. Another pathway for cholesterol excretion, which is quantitatively more important, is the export of cholesterol as 24(S)-hydroxycholesterol and 27-hydroxycholesterol ¹²⁹. Oxysterols, with hydroxylated side chains, can cross the lipophilic membrane of the blood-brain barrier (BBB) at a much faster rate than “normal” cholesterol ¹⁹⁹.

In plasma, the above-mentioned oxysterols are transferred on lipoproteins such as LDL and HDL ¹²⁹. The proportion of 24(S)-hydroxycholesterol to cholesterol in plasma is relatively constant, and patients with hypercholesterolemia also show higher plasma concentration of 24(S)-hydroxycholesterol ²⁰⁰. Interestingly, 27-hydroxycholesterol can pass the BBB, and the daily *influx* of this oxysterol into the brain has been estimated to be around 5 mg, depending on the concentration in the circulation and on the integrity of the BBB ²⁰¹. On the latter matter of the integrity of BBB: there is growing clinical and experimental evidence that vascular endothelial dysfunction and BBB hyperpermeability occur in a subset of individuals with schizophrenia ²⁰². Together, these studies may at

least in parts support peripheral (i.e., serum) lipids to be used as a proxy for cholesterol metabolism in the CNS.

2.2.4.2 From an antipsychotic drug perspective

Studies by our research group were the first to demonstrate that weight-inducing antipsychotic drugs also up-regulate the expression of genes involved in the biosynthesis of cholesterol and fatty acids²⁰³. These genes are controlled by the SREBP transcription factors, SREBP1 and SREBP2 (for a review, see²⁰⁴). These transcription factors bind to a specific DNA sequence called the sterol regulatory element and increase the transcription of enzymes involved in cholesterol and fatty acid biosynthesis²⁰⁵. Examinations of various antipsychotics in cultured CNS-cells have further revealed that CLZ is one of the most potent SREBP activators¹⁰⁷, and experiments in cultured liver cells have shown that CLZ activates SREBP potently²⁰⁶.

As previously mentioned, CLZ and OLZ have the highest disadvantage regarding adverse metabolic effects (including dyslipidemia and weight gain); however, these drugs are also the most effective ones^{68,207}. Fernø et al., hence proposed that the SREBP-mediated activation of cellular lipid biosynthesis may represent a new mechanism of antipsychotic drug action, involved in both therapeutic efficacies^{107,203} (through the enhanced synthesis of lipids in CNS) and metabolic side effects^{203,208} (through increased production of lipids in peripheral tissues such as the liver). Indeed, there seems to be some correspondence between SREBP activation in the *in vitro* experiments mentioned above and their association to weight gain reported in the clinical setting.

Remembering that myelin deficits are repeatedly found in schizophrenia, and that myelin is constituted of mainly lipids, there are several studies using MRI and DTI showing a beneficial effect (e.g., increasing FA) of antipsychotics on myelin and other brain structures, which may also support a lipid-link to psychosis, although indirectly. While

subcortical myelin has been studied extensively, in recent years focus has shifted to intracortical myelin. Some authors even argue that deficits in intracortical contra subcortical myelin may be more pronounced in patients with schizophrenia²⁰⁹. Following this train of thoughts, studying peripheral (i.e., serum) lipids as a proxy measure for central lipid synthesis during antipsychotic drug treatment and relating it to intracortical myelin, may aid in investigating possible *in vivo* lipid effects of antipsychotics on brain structures and perhaps increase our understanding of the link between serum lipids and psychosis as outlined in section 2.2.3.

2.3 Knowledge Gaps

Summarizing the literature hitherto, there are some essential knowledge gaps in our understanding of antipsychotic-related lipid disturbances and their link to outcomes, thus compiling the rationale for the current PhD thesis.

There is evidence supporting an association between BMI, TG, and positive symptoms, but few have studied such associations to the other psychotic symptoms, herein negative symptoms and cognitive symptoms. Prior studies have focused mostly on chronic patients where long illness duration, multi-pharmacy, and lifestyle are harder to control for.

Moreover, studies assessing the cognitive changes during antipsychotic drug treatment in relation to metabolic changes have in general lacked a healthy control group to control for practice effects and also for addressing the impact of current obesity trends in the society.

While DTI studies have been widely used to study antipsychotic-related subcortical myelin changes; the intracortical myelin has just recently gained interest. Additionally, most imaging studies have not included an unmedicated patient group, which may be important to differentiate the subtle changes related to illness versus the potential effects of antipsychotic drugs.

3. AIMS OF THE STUDY

The overall objective of this thesis was to combine clinical, biological and brain imaging data to increase our current understanding of the relationship between serum lipids and clinical, cognitive, and brain structural outcomes in antipsychotic-treated patients with broad schizophrenia spectrum disorders, emphasizing on patients with FEP.

The following questions were raised:

- 1) Is there an association between antipsychotic-related change in serum lipids and clinical outcome defined in terms of reduction in positive or negative symptoms? If so, are these associations independent of concomitant changes in BMI?
- 2) Is there an association between change in serum lipids and improvement in cognitive function? If so, are these associations independent of concomitant changes in BMI?
- 3) Does treatment with a metabolically potent antipsychotic agent (i.e., OLZ) influence intracortical myelin, assessed indirectly via cortical thickness and gray/white matter intensity contrast in patients with a broad schizophrenia spectrum disorder? Moreover, is there an association between such structural changes, if any, and changes in serum lipid levels?

4. MATERIALS AND METHODS

The patient sample and corresponding data that were used in this PhD project had been collected by others as part of the Thematically Organized Psychosis (TOP) Study in Oslo (see below).

4.1 Ethical aspects

Thorough information about the study was given, and the participants' ability to give informed consent was evaluated. The participants were also informed that participation

was voluntary and that they could withdraw at any point, and request all their collected data to be deleted. All participants gave written informed consent prior to their inclusion in the study. The Regional Ethics Committee and The Norwegian Data Inspectorate approved the study.

4.2 Clinical samples

The three articles in this thesis include results from two one-year cohort studies (with the same FEP sample: Study 1 and Study 2) as well as a cross-sectional MRI study (Study 3). For sociodemographic and clinical characteristics of the samples, see Table 1 and Table 2.

Participants in the three studies were recruited consecutively during 2003-2014 from in- and out-patient psychiatric units in the catchment areas of the four major hospitals within the South-Eastern health region in Norway, as part of the TOP Study.

General inclusion criteria for the TOP Study: Being in a stable psychosis phase and having a DSM-IV diagnosis of broad schizophrenia spectrum disorder or bipolar spectrum disorder. Age between 18 – 65 years old, speaking and understanding a Scandinavian language well enough to complete the assessments, and being able and willing to give informed consent.

General exclusion criteria: Presence of a pronounced cognitive deficit (IQ below 70), or severe brain damage. Patients were also excluded if their diagnosis was considered to be alcohol- or substance-induced disorder instead of a primary psychiatric disorder. Presence of alcohol- or substance-related disorders was not in itself an exclusion criterion for the patients.

FEP patients (Study 1 and Study 2)

In addition to the general criteria of TOP, in Study 1 and 2 we had some additional criteria for the FEP sample, which constituted of the following DSM-IV diagnoses: N =

87 (66%) with a diagnosis of schizophrenia, N = 5 (4%) schizophreniform disorder, N = 16 (12%) schizoaffective disorder and N = 24 (18%) psychosis NOS. The rationale for including wider diagnoses was that the diagnoses in the early phases are less stable than later on²¹⁰. FEP was defined as the onset of first-episode positive psychotic symptoms (i.e., PANSS score of 4 or higher on positive scale items P1-delusions, P3-hallucinatory behavior, P5-grandiosity, P6-suspiciousness, or General scale item G9-unusual thought content), and not having received adequate prior treatment for psychosis. Adequate treatment was defined as antipsychotic medication in doses over 1 Defined Daily Dosage (DDD) for > 12 weeks or briefer if this treatment was followed by symptomatic remission. DDD is the anticipated average maintenance dose per day for a drug used for its primary purpose in adults (https://www.whooc.no/ddd/definition_and_general_considera/). In general, the patients were recruited in the early phases of treatment but were most often not treatment-naïve.

OLZ-treated and unmedicated patients with broad schizophrenia spectrum disorders (Study 3)

For study 3, we selected a subsample of patients with broad schizophrenia spectrum disorders (from the TOP main study) who were either on stable OLZ monotherapy (n=33) or were unmedicated (n=19). Stable monotherapy was defined as using a constant daily dose of OLZ (minimum 5 mg) at the time of blood sampling and on the day of MRI. Being unmedicated was defined as the absence of any antipsychotic drug at the time of blood sampling and at the time of MRI scanning. Patients were excluded if the time interval between MRI scan and blood sample surpassed 90 days (mean interval= 38.8 days, SD= 28.6).

The distribution of DSM-IV diagnoses was for the OLZ group: schizophrenia, N = 12 (36%); schizophreniform disorder, N = 5 (15%); schizoaffective, N = 4 (12 %); and psychosis NOS, N = 12 (36%). For the unmedicated group, the diagnoses were:

schizophrenia, N = 9 (47%); schizophreniform disorder N = 1 (5 %); psychosis NOS, N = 9 (48 %).

Of the 19 unmedicated patients, six were antipsychotic-naïve, whereas ten patients had used antipsychotics previously. Data on previous medication were missing for three participants. Among the ten patients who had received antipsychotics earlier, the average time since treatment with an antipsychotic agent was 18 months (SD: 16 months, range 3-47 months, data was missing for one patient). Six of these patients had previously used OLZ (mean dosage 10 mg, SD: 6.1 mg, data missing for one patient). For more details, we refer to the Methodological section in Study 3.

Healthy controls in the TOP study

Healthy controls from the TOP database were used in Study 2 (N=83 subjects) and Study 3 (N=76 subjects). These individuals were aged 18-45 years and invited to participate based on a random selection from the National Registry in Norway. The controls were interviewed with Primary Care Evaluation of Mental Disorders (PRIME-MD)²¹¹ to ensure no history of a severe psychiatric disorder in controls or any of their first degree relatives. Controls with somatic conditions interfering with brain functioning or history of drug abuse/dependency (or use of cannabis within the last three months), head trauma, neurological disorders, or pathological neuroradiological findings were excluded. For study 2, we matched for age and gender. For Study 3, we did not match for age or gender; however, there were no significant differences between the OLZ and unmedicated group in comparison to healthy controls regarding these demographic variables.

Table 1: Sociodemographic and clinical characteristics of the first-episode psychosis (FEP) patients and healthy controls (HC).

	FEP (<i>n</i>)	HC (<i>n</i>)	FEP, mean (SD)	HC, mean (SD)	<i>t</i>	<i>p</i> -value
Age (years)	132	83	26.7 (7.6)	29.0 (6.8)	-2.6	0.01
Education (years)	132	83	12.9 (2.8)	14.2 (2.0)	-4.43	<0.001
Alcohol use (AUDIT scores)	120	71	7.3 (7.4)	5.9 (3.0)	1.89	0.06
DUP (weeks), median (range)	132		40.0 (1-1040)			
Total PANSS scores	132		63.2 (13.9)			
PANSS positive subscores	132		2.6 (1.0)			
PANSS negative subscores	132		2.2 (1.0)			
Depressive symptoms (CDSS scores)	128		6.2 (4.5)			

	FEP (<i>n</i>)	HC (<i>n</i>)	FEP, <i>n</i> (%)	HC, <i>n</i> (%)	χ^2	<i>p</i> -value
Gender (male)	132	83	85 (64.4)	80 (59.7)	0.62	0.45
Ethnicity (Caucasian)	132	83	87 (65.9)	132 (98.3)	52.32	<0.001
Smoking (daily)	132	86	60 (45.5)	17 (19.8)	15.04	<0.001
Hospitalization at inclusion	132		30 (22.7)			
Change in diet ("better diet") [†]	132		20 (15.2)			
Change in exercise ("increased exercise") [‡]	129		21 (15.9)			
Continuous antipsychotic drug use [§]	132		100 (76)			
Intermittent antipsychotic drug use [¶]	132		32 (24)			
Antipsychotic monotherapy	132		91 (69)			
Antipsychotic polypharmacy	132		41 (31)			

FEP= first episode psychosis, HC= healthy controls, SD= standard deviation, *n*= number of subjects, %= percentage, AUDIT=Alcohol Use Disorder Identification Test, DUP= duration of untreated psychosis, PANSS= Positive and Negative Syndrome Scale, CDSS= Calgary Depression Scale for Schizophrenia. P-values are obtained from T-tests and Chi-square test.

[†] Diet was divided into "similar or poorer" and "better" compared to diet habits at baseline.

[‡] Exercise was divided into "similar or reduced" and "increased" compared to exercise habits at baseline.

[§] "Continuous antipsychotic drug use" refers to the continuous use of any antipsychotic agent during the study period.

[¶] "Intermittent antipsychotic drug use" refers to the use of any antipsychotic agent, either at baseline or 12 months.

Table 2: Sociodemographic and clinical characteristics among olanzapine-treated (1) and unmedicated patients (2) and healthy controls (3).

	1.OLZ N= 33	2.Unmedicated N= 19	3. Healthy controls N=76	p-values	Post-hoc tests
Age (years), mean (SD)	31.0 (11.2)	33.1 (11.1)	31.9 (9.6)	NS	
Gender (male), <i>n</i> (%)	18 (55)	14 (74)	45 (59)	NS	
Ethnicity (Caucasian), <i>n</i> (%)	28 (85)	14 (74)	74 (97)	$\chi^2 (8, N = 128) = 18.09, p=0.02$	2 vs. 3
Education (years), mean (SD)	13.2 (3.2)	12.2 (2.4)	14.2 (2.4)	$F (2,115) = 3.54, p= 0.03$	2 vs. 3
Handedness (right), <i>n</i> (%)	25 (96)	13 (81)	65 (86)	NS	
Smoking (daily), <i>n</i> (%)	20 (62.5)	8 (47.1)	12 (22)	NS	
Diet, <i>n</i> (%)	H: 23 (71.9) MH: 8 (25.0) UH: 1 (3.1)	H: 10 (58.8) MH: 7 (41.2) UH: 0	NA NA NA	NS	
Exercise, <i>n</i> (%)	L: 21 (70) M: 7 (23.3) F: 2 (6.7)	L: 6 (46.2) M: 5 (38.5) F: 2 (15.4)	NA NA NA	NS	
Alcohol use (AUDIT), mean (SD)	8.0 (8.9)	9.8 (8.4)	NA	NS	
Substance use (DUDIT), mean (SD)	5.7 (10.3)	6.5 (8.1)	NA	NS	
Diagnosis, <i>n</i> (%)	SZ=12 (36), SF=5 (15), SA= 4 (12), NOS=12 (36)	SZ=9 (47), SF=1 (5), SA= 0 (0), NOS=9 (48)	NA	NS	
DUP (weeks), median (range)	16.5 (1-468)	104.0 (1-1040)	NA	$U= 104.5, Z=-2.64, p=0.01$	1 vs. 2
Duration of illness (years), mean (SD)	2.9 (4.0)	7.6 (7.2)	NA	$t(34)=-2.53, p=0.02$	
Currently hospitalized, <i>n</i> (%)	6 (18.2)	1 (5.3)	NA	NS	
Previous admissions due to psychosis, mean (SD)	1.3 (1.0)	0.7 (1.1)	NA	NS	
OLZ dosage (mg/day), mean (SD)	11.82 (4.98)	NA	NA	NA	
OLZ treatment duration (months), mean (SD)	19.2(33.3)	NA	NA	NA	
Total PANSS, mean (SD)	54.6 (15.0)	57.1 (10.2)	NA	NS	
Positive PANSS subscores, mean (SD)	11.9 (4.1)	15.3 (4.7)	NA	$t(50)=-2.67, p=0.01$	1 vs. 2
Negative PANSS subscores, mean (SD)	14.5 (7.4)	11.2 (3.3)	NA	NS	
Global functioning, function (GAF-F), mean (SD)	47.4 (12.1)	47.5 (12.6)	NA	NS	
Global functioning, symptoms (GAF-S), mean (SD)	47.8 (12.2)	44.0 (11.6)	NA	NS	

Groups: 1=Olanzapine-treated patients (OLZ), 2=unmedicated patients, 3=healthy controls. Diet was classified as H= healthy, MH= moderately healthy, and UH=unhealthy. Exercise was classified as L=little, M=moderate, and F=frequent. AUDIT=Alcohol Use Disorder Identification Test, DUDIT= Drug Use Disorder Identification Test, DUP= duration of untreated psychosis, was defined as the number of weeks from the first occurrence of a psychotic symptom above clinical threshold to the first adequate treatment. PANSS=Positive and Negative Syndrome Scale, GAF-F= Global Assessment of Functioning- functions, GAF-S= Global Assessment of Functioning-symptoms, SZ= schizophrenia, SF= schizophreniform, SA= schizoaffective, NOS= psychosis not otherwise specified, N= number of subjects, NA= not applicable, NS= non significant, SD = standard deviation, F= F-test, T=t-test. P-values are obtained from one-way ANOVA, T-tests, Chi-square test and Mann-Whitney U test. Post-hoc tests (t-tests) were performed for the F-tests that were significant and we only report the significant group differences

4.3 Clinical assessments

Information about demographic variables (age, gender, ethnicity, education), clinical variables (age at onset, history of psychosis, hospitalizations, symptom severity and functioning), and lifestyle-related variables (smoking, alcohol, drug use) was collected as part of a clinical interview and by using standardized structured interviews and rating scales. For healthy controls in the TOP study, demographical information (age, gender, ethnicity, education) and lifestyle variables (smoking, alcohol, drug use) were obtained.

A clinical assessment team of clinical psychologists, psychiatrists, and medical doctors performed the diagnostic and clinical assessments. A satisfactory inter-reliability was achieved with an overall agreement of 82%, $\kappa = 0.77$ (95% CI: 0.60-0.94) for DSM-IV diagnostics. Senior psychiatrists and specialists in clinical psychology continuously supervised the clinical assessment.

The Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS)²¹² assessed current symptomatology. This interview assesses the patient's symptom burden over the last week. The original PANSS scale is divided into three sections, positive symptoms (7 items), negative symptoms (7 items), and general pathology (16 items). Likert scale ranging between 1-7; where each item is defined and scored according to it being absent or present in the following way: 1=absent, 2=minimal, 3=mild, 4=moderate, 5= moderately severe, 6=severe, 7=extreme.

Since a variety of factor analyses have revealed other factor structures to have better clinical validity in different cultural background²¹³ and for assessment of FEP²¹⁴, we used the five-factor model proposed by Wallwork et al.²¹³ in Studies 1 and 2. Here the positive and negative symptom factors are reported, as these two symptom factors are considered to be most relevant in testing our hypotheses. 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),

N6 (lack of spontaneity and flow of conversation) and G7 (motor retardation). Because each five-factor subscale includes a different number of items, and to avoid confusion with the original three-scale PANSS, Studies 1 and 2 report mean item scores for the five-factor PANSS positive and negative subscales.

Duration of untreated psychosis (DUP) was defined as the number of weeks from the first occurrence of a psychotic symptom above the clinical threshold to the first adequate treatment (for details see ²¹⁵). Remission was defined as at least one week with no score of ≥ 4 on any of the following five PANSS items: P1, P3, P5, P6, or G9. Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) ²¹⁶, as it has been found to differentiate well between depression and negative symptoms. Global functioning was assessed with the Global Assessment of Functioning (GAF) split version (with separate scales for symptoms (GAF-S) and functioning (GAF-F)) ²¹⁷.

Smoking was coded based on the self-report of the participants as current smokers and non-smokers. Alcohol and substance use was measured with the Alcohol Use Disorders Identification Test (AUDIT) ²¹⁸ and the Drug Use Disorders Identification Test (DUDIT) ²¹⁹. In patients' interviews, information regarding diet (classified as healthy, moderately healthy or unhealthy) and exercise habits (classified as light, moderate or frequent) was obtained at baseline and 12 months. In Studies 1 and 2, diet was divided into "similar or poorer diet" (including patients who did not change their diet habits from inclusion to 12 months, as well as patients who reported a poorer diet at 12 months) and "better diet" (consisting of patients who reported a beneficial change in diet). Exercise was, likewise, divided into "similar or reduced exercise" and "increased exercise" at 12 months.

4.4 Cognitive assessments

Current IQ was measured with the Wechsler Adult Intelligence Scale (WAIS) subscales similarities and block design ²²⁰. The cognitive test battery comprised of five cognitive domains (verbal learning, processing speed, working memory, verbal

fluency, and inhibition) on the basis of previous findings related to cognitive dysfunction in FEP ²²¹. To minimize the number of statistical tests, one subtest within each test was selected. All participants showed satisfactory neuropsychological test effort marked by two errors or less on the forced recognition trial of the California Verbal Learning Task (CVLT-II) ²²². Higher scores indicated better performance on all tests apart from the inhibition subtest, where higher scores indicated a poorer functioning. Raw scores were reported for all tests in order to be able to calibrate the cognitive performance of the FEP patients as compared to a representative age- and gender-matched healthy control group from the same catchment area as the patients.

Verbal learning was measured with the California Verbal Learning Test (CVLT-II) ²²², verbal learning subscore. Participants were asked to repeat a list of 16 words that were read a total of five times. The key score used was the total number of words immediately recalled (sum of trials 1-5).

Processing speed was measured with the Digit Symbol Test (WAIS) ²²⁰. Numbers paired with symbols comprises the test, and the task is to fill in blank spaces with correct symbols within the time limit of 90 seconds. The total number of correct symbols was used as a measure of processing speed.

Working memory was measured with the Letter-number Sequence Test (WAIS) ²²⁰. 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 represents the total number of correctly arranged trials.

Verbal fluency was measured with the Verbal Fluency Test, phonetic subscore from the D-KEFS ²²³. The subtest consists of three trials, requiring the production of as many words as possible beginning with the letters 'F', 'A,' and 'S' within the time frame of 60 seconds each. The number of words generated in each of the trials was used as measures of verbal fluency.

Inhibition was measured with the Color-Word Interference Test from the Delis Kaplan Executive Function Scale (D-KEFS)²²³, inhibition subscore. The key score for inhibition represents the time used to name the color of the ink of written words of incongruent colors.

4.5 Antipsychotic drug treatment and use of other medication

A detailed record of the patient's current medication was obtained through medical records and self-reports (see Appendix Tables 1- 2 for details). None of the patients used lipid-lowering prescription or antidiabetic drugs. Due to the extent of switching between different antipsychotic agents, current antipsychotic drug treatment was defined as continuous antipsychotic use and intermittent antipsychotic use in Studies 1 and 2. Continuous use was delineated as using any antipsychotic agent at baseline and 12 months (not necessarily the same antipsychotic drug at both time points), while intermittent use was delineated as using whichever antipsychotic agent at either baseline or 12 months. All patients who used FGAs also used SGAs. Due to insufficient data on switches and duration of antipsychotic treatments during the follow-up period, it was not feasible to calculate cumulative drug exposure. In Study 3, medication information from the day of MRI was used.

4.6 Somatic examination

The patients were asked about comorbid somatic diseases. Heart, lungs, and the abdomen were evaluated by clinical examination, and a short neurological status was conducted. Digital weights were used to weight all the participants, and BMI calculated accordingly: weight (in kilograms) divided by height (in meters squared) (kg/m^2).

Blood was drawn from the antecubital vein in the morning after overnight fasting at baseline and 12 months, on the day the neuropsychological testing took place. The Department of Clinical Chemistry at Oslo University Hospital, using standard enzymatic methods from Roche Diagnostics Norge AS (Oslo, Norway), analyzed

cholesterols (total, HDL-C, LDL-C) and TG. All blood samples were sent immediately after gathering and analyzed unremittingly as routine samples.

4.7 Brain imaging data

The MRI is a non-invasive technique for *in vivo* brain visualization without the use of ionizing radiation. This technique takes advantage of the magnetic assets of hydrogen. In short, the patient is placed in a magnet tunnel, which uses radio waves in pulses to polarize and excite hydrogen protons in the tissue. Termination of the pulse returns the protons to their original spin (relax) and emit radiofrequency waves, which are used to reconstruct images of the tissue. The relaxation process can be divided into different aspects, such as the T1 and T2 relaxation time constants. Simplified, the T1 tells more about the tissue properties, while the T2 tells more about the internal factors of the magnetic spin of the protons. The tissue contrast is dependent on T1 and T2 relaxation times, the number of affected protons, flow, and temperature. In T1 weighted imaging, fat has a high signal (appears white on the image) and water a low signal (appears black on the image). In T2 weighted images, tissues with high fat content show weak signals (appears black on the image), while tissues with high water content show high signals (appears white on the image).

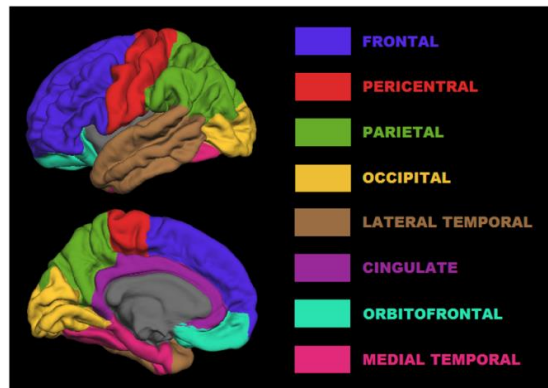
In the present thesis, structural T1 weighted MR images were obtained to investigate quantitative measures (morphometry) of brain structures as our focus was on cortical structures and because a significant determinant of this intensity signal is the cholesterol in myelin^{224,225}. Moreover, strong correlations are reported between T1 signal intensity and myelin content^{226,227}.

4.7.1 MR scan acquisition and data processing

Patients and healthy controls in Study 3 were scanned consecutively at the Department of Neuroradiology, Ullevål University Hospital in Oslo, on the same 1.5 T Siemens Magnetom Sonata scanner equipped with a standard eight-channel head coil. A neuroradiologist evaluated all scans to exclude subjects with brain pathology from the

studies. During the study period, there was no major scanner up-grade or change of hardware. Before undergoing post-processing, scans were visually inspected, and poor quality scans were excluded. T1-weighted data from all subject samples were processed using FreeSurfer version 5.3.0 (freely available from the website <http://surfer.nmr.mgh.harvard.edu/>). All surfaces were inspected, and manual editing was performed according to standard FreeSurfer quality control procedures. From the reconstructed surfaces, cortical thickness was measured as the shortest distance from the white area to the pial surface at each vertex. For the primary analyses, we extracted average cortical thickness for each label in the Desikan-Killiany atlas (34 regions)²²⁸ and merged 33 of these labels (all except the insular cortex) into eight bilateral lobar areas, as shown in Figure 2. Average cortical thickness across the cortical surface was also extracted.

Figure 2. The eight bilateral lobar regions used in our analyses.

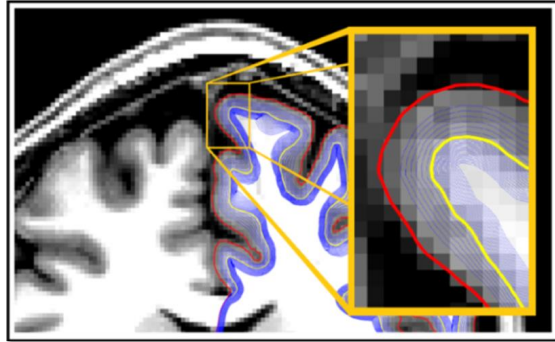


4.7.2 Calculation of the gray/white matter contrast

FreeSurfer was used to sample intensity values at each vertex along the gray/white boundary. Sampling distances were set at 0-60% into the cortical ribbon and 0-1.5 mm into subjacent white matter (see Figure 3). Values from gray matter were averaged to form a single gray matter intensity value for each vertex; similarly, values from white matter were averaged to form a single white matter value. The difference between these values (i.e., averaged gray and white matter intensity values at each vertex) was then computed and normalized by the average of the gray and white matter intensity

values at each vertex. For more details, we refer to the Methodology section in Study 3.

Figure 3. Illustration of gray/white matter intensity contrast. The yellow line represents the gray/white matter boundary. The blue lines represent different sampling distances used to obtain gray/white matter intensity values.



4.8 Statistical analyses

All data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA). Analyses were performed with a significance level < 0.05 , two-tailed (confidence interval of 95%). All variables were checked for deviations from a normal distribution and logarithmically transformed if necessary, before being entered into the analyses.

The main analyses consisted of the following: To examine which outcome variables were associated with longitudinal changes in serum lipids and BMI, mixed-effects regression modeling was used in Studies 1 and 2. In these mixed models, we controlled for age, gender, and antipsychotic usage. Of note, antipsychotic usage was controlled for in the main analyses in Study 1 and in the post-hoc analyses in Study 2. In Study 3, we employed a general linear model (GLM) controlling for age, gender, and group (OLZ, unmedicated, and healthy controls).

Missing variables were treated pairwise. Preliminary analyses (Little's Missing Completely at Random (MCAR) test) showed that the missing variables were

randomly distributed. For more details on the statistical approaches and details on missing variables, we refer to the Statistical sections of the individual studies.

5. SUMMARY OF RESULTS

Study 1: Increase in serum HDL-C level is associated with less negative symptoms after one year of antipsychotic treatment in FEP.

In Study 1, we aimed to examine whether changes in serum lipids are associated with improvement of psychosis symptoms following one year of antipsychotic drug treatment in a cohort of 132 FEP patients included through the TOP project. Data on antipsychotic usage, serum lipids (total cholesterol, HDL-C, LDL-C, and TG), BMI and clinical state using PANSS were obtained at baseline and after 12 months. Mixed-effects models were used to examine the relationship between serum lipids and psychotic symptoms while controlling for potential confounders, including BMI.

Our results indicate that during the one-year follow up, the FEP patients experienced a significant reduction in PANSS positive and negative subscores, ($B = -0.48$, $p < 0.001$) and ($B = -0.17$, $p = 0.03$), respectively.

Concerning the serum lipids, there was a significant decrease of 0.07 mmol/L (SD = 0.27) in mean HDL from baseline (1.39 mmol/L; SD = 0.38) to 12 months (1.32 mmol/L; SD = 0.37) at the group level ($p = 0.02$), but on an individual level 49 subjects (54%) experienced a decrease and 41 subjects (46%) an increase in their HDL-C levels. Group comparison between patients with an increase in HDL levels versus those with a decrease during the follow-up period displayed no significant differences in sociodemographic or illness-related factors except that the HDL increase group had higher mean PANSS negative subscore at baseline, 2.5 (SD = 1.1) vs. 2.0 (SD = 1.0) ($p = 0.04$) and a higher mean AUDIT score at 12 months, 8.8 (SD = 7.0) vs. 5.1 (SD = 5.2) ($p = 0.01$), respectively. There were no significant changes in

serum total cholesterol, LDL-C, or ln TG. Also, there was no significant difference in the direction of lipid change between continuous versus intermittent antipsychotic use.

At baseline, regression analyses showed a negative association between HDL level and PANSS negative subscores when controlling for age, gender, and antipsychotic use ($B = -0.67$, $p = 0.02$). After one year of antipsychotic treatment, the mixed-effects model demonstrated a significant association between an increase in HDL-C and a decrease in PANSS negative subscores ($B = -0.48$, $p = 0.03$). Moreover, the association between change in HDL-C and change in negative symptoms remained significant after controlling for BMI change ($B = -0.54$, $p = 0.02$). No significant associations were found between changes in total cholesterol, LDL-C, ln TG, BMI, and changes PANSS positive and negative subscores.

Post-hoc mixed model analyses further showed that neither illness (including diagnosis subgroup, DUP, hospitalization, concurrent changes in PANSS positive subscores and CDSS scores) nor lifestyle-related factors (including smoking, alcohol use, changes in diet and exercise) significantly influenced the relationship between HDL-C and PANSS negative subscores.

In conclusion, we found that an increase in HDL-C level during antipsychotic treatment was related to improvement in negative symptoms, independent of BMI changes.

Study 2: Improvement in verbal learning over the first year of antipsychotic treatment is associated with serum HDL-C levels in a cohort of FEP patients.

As a follow-up to Study 1, we investigated in Study 2 whether changes in serum lipids are associated with cognitive performance in FEP patients during the first year of antipsychotic drug treatment. The same antipsychotic-treated FEP sample was used along with 83 age- and gender-matched healthy individuals to control for practice effects and naturally occurring changes in metabolic measures in the general

population. Information regarding cognitive performance, psychotic symptoms, lifestyle, BMI, serum lipids, and antipsychotic treatment, were obtained at baseline and after one-year follow-up. The cognitive test battery comprised assessments for verbal learning, processing speed, working memory, verbal fluency, and inhibition. Mixed-effects models were employed to examine the relationship between changes over time in serum lipids and cognitive domains, controlling for potential confounders.

For group differences in demographic-related variables we refer to Table 1. Regarding the cognitive measures, our results indicate that the FEP patients exhibited marked impairments in cognitive functioning for all domains at baseline ($p < 0.001$). During the one-year follow-up, there was a group by time interaction for verbal learning ($F = 6.86, p = 0.01$), with a steeper change in FEP than in the control subjects ($B = 3.54, p = 0.01$), signifying that practice effects alone cannot explain the relatively more marked improvement in patients compared to healthy controls. The mixed-effects model analyses also revealed a group by time interaction for verbal fluency ($F = 6.38, p = 0.01$); here, the FEP group displayed a negative change in comparison with the healthy control group, ($B = -3.15, p = 0.01$), respectively.

Regarding the serum lipids, the FEP patients had significantly higher levels of total cholesterol and LDL-C compared to the healthy controls at baseline, ($F = 8.94, p = 0.003$) and ($F = 11.54, p = 0.001$), respectively. At the one-year follow-up, there was no significant change in mean levels of serum lipids among the FEP patients when compared to the healthy controls at the group level. Still, at the individual level, FEP patients displayed the following changes in their serum lipids: 47 patients (47%) experienced a decrease and 52 (53%) an increase in their total cholesterol levels; 49 patients (54%) experienced a decrease and 41 (46%) an increase in their HDL-C levels; 43 patients (50%) experienced a decrease and 43 (50%) an increase in their LDL-C levels; 40 patients (45%) experienced a decrease and 49 (55%) an increase in their TG levels.

When investigating the two cognitive domains that showed a group by time interaction (verbal learning and verbal fluency) for associations with serum lipid levels, we discovered that there was a significant group by HDL-C interaction effect for verbal learning ($F = 11.12, p = 0.001$): an increase in HDL-C level was related to improvement in verbal learning among FEP patients compared to the healthy controls ($B = 10.32, p = 0.001$). Verbal fluency, in contrast, did not evidence any significant group by lipid interactions.

The post-hoc mixed models adjusting for antipsychotic usage (i.e., continuous use versus intermittent use), and positive and negative symptoms demonstrated that the group (i.e., FEP) specific link of HDL-C to verbal learning remained highly significant ($F = 7.45, p = 0.007$). Similarly, adjusting for remission status did not considerably impact the observed link between serum HDL-C and verbal learning in the FEP group ($B = 8.42, p = 0.002$). Moreover, while there was a main effect of BMI on verbal learning ($F = 4.88, p = 0.03$), the group by HDL-C interaction remained significant ($F = 9.86, p = 0.002$) indicating that the link between HDL-C and verbal learning was independent of BMI. Lastly, ethnicity, hospitalization, depressive symptoms, smoking habits, diet, exercise, and alcohol use demonstrated no attenuation of results for the observed link between HDL-C and verbal learning.

In conclusion, the current study of antipsychotic-treated FEP patients revealed that during the first year of follow-up, an increment in serum HDL-C was associated with better cognitive performance in verbal learning, independent of BMI changes.

Study 3: Association between OLZ treatment and brain cortical thickness and gray/white matter intensity contrast is moderated by cholesterol in psychotic disorders.

In a sample of patients with broad schizophrenia spectrum disorders, we investigated the relationship between treatment with OLZ and cortical thickness and gray/white matter intensity contrast, and the relationship between these measures and serum lipid

levels. A total of 33 OLZ users, 19 currently unmedicated psychotic patients, and 76 healthy controls were included. Data on serum lipids (total cholesterol, HDL-C, LDL-C, and TG), BMI, clinical state and functioning were acquired through clinical assessments and interviews. Cortical measures were obtained by MR brain images. GLMs analyses were, thereafter, used to assess any group differences, as well as to investigate possible associations between serum lipids and cortical measures.

For group differences in demographic- and illness-related variables we refer to Table 2. Regarding the cortical measures, our results indicate that the OLZ users had similar cortical gray/white matter intensity contrast measures as the healthy controls ($p < 0.05$, corrected). Although the unmedicated patients had higher nominal intensity contrast compared to the healthy controls (frontal, cingulate, lateral temporal, and medial temporal regions) ($p < 0.05$, uncorrected), they did not remain significant after correction for multiple comparisons.

OLZ users also displayed significantly thinner cortices compared to the healthy controls in frontal, orbitofrontal, and medial temporal regions ($p < 0.05$, corrected), while there were no significant differences in cortical thickness between unmedicated patients and the healthy controls. Of note, the cortical thickness and intensity contrast were correlated in all regions except for cingulate and pericentral cortex.

Regarding the serum lipids, there was a group difference in mean serum HDL-C levels and LDL-C levels, ($F = 3.28$, $p = 0.04$) and ($F = 3.51$, $p = 0.03$), respectively. The post-hoc tests revealed that the OLZ-group exhibited a lower mean HDL-C value and a higher LDL-C value compared to the healthy controls.

Examining any group-specific interactions between serum lipids and cortical measures, we found that OLZ-treated patients with higher HDL-C levels had thicker cortices in frontal, orbitofrontal, cingulate, occipital, and pericentral regions, as well as a thicker mean cortex ($p < 0.05$, uncorrected). However, only the pericentral region remained significant after correcting for multiple comparisons ($p < 0.05$, corrected).

For the gray/white matter intensity contrast, a group-specific interaction with LDL-C for occipital lobe contrast was observed, where higher LDL-C levels were associated with higher intensity contrast in OLZ users specifically ($p < 0.05$, uncorrected). However, this interaction did not remain significant after corrections for multiple comparisons were applied ($p > 0.05$, corrected).

The group effects, concerning cortical measures, found in the main analyses remained significant when controlling for potential confounders, including ethnicity, education, DUP, illness duration, and positive symptoms ($p < 0.05$, uncorrected). Moreover, the HDL-interaction with cortical thickness demonstrated in the main analysis, remained significant when controlling for BMI, positive and negative symptoms ($p < 0.05$, uncorrected).

In conclusion, the cortical gray/white matter intensity contrast was found to be similar among users of the SGA OLZ and the healthy controls, suggesting comparable cortical myelin content. Despite the general thinning of the cortex in the OLZ users, there was a moderating effect of HDL-C on cortical thickness, which may indicate a lipid-related increment in cortical myelin among the OLZ users.

6. DISCUSSION

In the following sections, I will first discuss the main findings of each study (6.1), followed by a general discussion of our findings (6.2). Lastly, I will discuss methodological issues (6.3) and possible clinical and scientific implications of our results (6.4).

6.1 DISCUSSION OF THE SPECIFIC STUDIES

6.1.1 Study 1

The link between HDL-C and negative symptoms

The central finding from Study 1 was a specific link between HDL-C and negative symptoms, both at baseline and also after one year of antipsychotic drug treatment. To the best of my knowledge, there are no other comparable studies in FEP patients; there are however two studies in *chronic* schizophrenia populations, which report a link between serum HDL-C levels and negative symptoms^{184,185}.

In one of these publications, Chen and colleagues¹⁸⁴ found that negative symptoms (as measured with the Scale for the Assessment of Negative Symptoms (SANS)) were positively related to change in HDL-C levels (and negatively related to change in TG levels) in antipsychotic-treated patients. These authors reasoned that negative symptoms might have a distinct lipid profile. While on the surface the positive association between HDL-C and negative symptoms may seem to conflict with our results, the sample in Chen's study was different; the patients were chronic and treated for two years with different antipsychotic agents. HDL-C usually decreases with continued antipsychotic usage and also with multiple psychotic episodes¹¹³, which could explain the positive correlation between negative baseline symptoms and subsequent change in HDL-C levels. Possible differences in the percentage of CLZ users between the studies, differences in ethnicity (Caucasian versus Asian) and other demographic variables (e.g., outpatients versus inpatients), as well as which negative symptoms are measured (e.g., PANSS negative subscores versus SANS scores) may additionally have contributed to the apparent differences in the link between HDL-C and negative symptoms.

In our study, both serum HDL-C and negative symptoms decreased during the study period. As already outlined, several studies report of a decrease in serum HDL-C levels during antipsychotic drug treatment with an SGA drug^{150,160,229}, and SGAs are reported to be more effective in reducing negative symptoms compared to FGAs^{70,71}.

Still, in our study we found a significant *inverse* association between serum HDL-C and negative symptoms. At first glance, this may seem counterintuitive, but one possible reason for the disparity may be the differences between examining something at a group level contra an individual level.

We found that while on a group level the mean HDL-C decreased amongst the FEP patients, on an individual level, 46% experienced an increase in HDL-C levels after antipsychotic treatment. This indicates that both increases and decreases may occur at the individual level, being “hidden” within the mean levels of the group. Indeed, there may be a subgroup of individuals who experience an increase in HDL-C even during treatment with an SGA. For example, Wirshing et al.²³⁰ found that treatment with risperidone resulted in an increase in mean HDL-C levels by 5% and minimum HDL-C levels by 11%. In our FEP sample, the patients whose HDL-C levels increased did not differ from those who experienced a decrease concerning sociodemographic, lifestyle- or illness-related factors, except for reporting higher alcohol consumption at 12 months. It is, however, unlikely that the increase in HDL-C levels may be solely due to higher alcohol consumption as there was no significant increase in alcohol use during the follow-up period.

While we did not assess medication side effects in details, which could be linked to secondary negative symptoms as previously delineated, we used the five-factorial PANSS (instead of PANSS three-scale), which is more specific to the various symptom dimensions in psychosis, differentiating better between general symptoms and more secondary negative symptoms due to antipsychotic drug treatment. Additionally, we controlled for antipsychotic usage (continuously versus intermittent use) to see if the symptom trajectory differed, as using medication continuously is more likely to cause adverse side effects than intermittent use. Our results indicated that whether one uses antipsychotics continuously or intermittently had a limited effect on the negative symptom trajectory.

As studies indicate that concomitant positive symptoms may lead to periods of hospitalization and social isolation – both of which are circumstances that might evoke secondary negative symptoms¹¹ – we controlled for positive symptoms in the post-hoc analyses, obtaining similar results as in our main analyses. Moreover, as depressive symptoms may sometimes disguise themselves as negative symptoms (i.e., secondary negative symptoms), we also controlled for this in the post-hoc analyses, again obtaining similar results as in our main analyses. These additional analyses may denote that the link between HDL-C and negative symptom improvement could reflect an improvement not only in secondary symptoms but perhaps also to some extent in primary negative symptoms. Remembering that negative symptoms may be related to impairment in myelin⁵⁵⁻⁵⁷ and that myelin primarily consists of lipids¹²⁹, it may be possible that increasing availability of HDL-C could be beneficial in improving negative symptoms by addressing the myelin deficits. The possible link between HDL-C, myelin, and psychosis is further discussed under “General discussion” (see below).

While a link between HDL-C levels and reduction in negative symptoms conveyed via myelination may be intriguing, the observed link between HDL-C and PANSS negative subscores could also represent an indirect effect of successful treatment that reduces the negative symptoms, leading to subsequent changes in lifestyle and diet, and improving HDL-C levels. A recent study by Jakobsen et al.²³¹ may support such an interpretation; they found that negative symptoms at baseline were associated with worse metabolic outcomes including higher BMI values and lower HDL-C levels in their two-year follow-up study of antipsychotic-treated patients with schizophrenia. The authors argued that negative symptoms, with apathy and avolition, might have led to inadequate diet and cardiorespiratory fitness and consequently to higher BMI and lower levels of HDL-C.

In our study, patients who experienced an increase in HDL-C had more pronounced negative symptoms at baseline. Moreover, there was a link between higher HDL-C levels and lower negative symptoms at baseline, implying that having a higher HDL-C by some means might be beneficial for reducing negative symptoms. The patients in

our studies were also receiving standard treatment according to recent guidelines. The clinical changes were thus not due to a different quality of treatment. In addition, as the Norwegian outpatient clinics and the hospitals are mostly government-sponsored and catchment area based, the socioeconomic difference is unlikely to explain the displayed changes in serum HDL-C levels and negative symptoms.

As mentioned in the Introduction section 2.2.3, most prior studies have found an association between an increase in serum TG levels and a reduction in positive symptoms during treatment with antipsychotics^{159,183,232}. It is therefore relevant to discuss why we did not find a similar link to positive symptoms in our FEP sample. One possible explanation is that most prior studies were performed on chronic patients treated with CLZ, an antipsychotic agent with known TG increasing potential. In our relatively young sample, there were only three CLZ users (Studies 1 and 2 see Appendix Table 1). Differences in the number of patients using antidepressants may also have affected the results, as antidepressants can also increase TG levels²³³, although their effect on positive symptoms is disputed. None of our patients were using medications for dyslipidemia (nor diabetes); hence, the lack of significant increase in TG was not due to such medications. Lastly, it is essential to acknowledge the differences in the PANSS three-scale versus the five-factorial PANSS that we used. The five-factorial PANSS has shown to be more specific to the various symptom dimensions in psychosis.

6.1.2 Study 2

A link between HDL-C and verbal learning

The main finding of Study 2 was the positive association between serum HDL-C and verbal learning, which is in line with two prior studies in chronic patients^{185,234}. Lancon et al.¹⁸⁵ established a link between HDL and verbal learning and memory in a cross-sectional sample of chronic schizophrenia patients. Lindenmayer²³⁴ and colleagues found that HDL-C levels were positively associated with scores on attention/vigilance in their sample of 159 patients with schizophrenia and

schizoaffective disorder. Notably, in the latter study, the authors also reported that higher levels of TG were associated with lower scores on attention/vigilance.

Our study, however, is the first to report on an association between HDL-C and cognition in a cohort of FEP patients with limited prior antipsychotic drug exposure while controlling for practice effect. The young age amongst our patients and the lack of long-lasting effects of poor lifestyle choices and multi-pharmacy is a major strength of the study as it may be easier to differentiate illness chronicity from treatment effects.

That being said, an important follow-up question is why a similar link was not demonstrated amongst the healthy controls. One plausible explanation is that there may be higher interindividual variability in brain structures, cognitive measures, and metabolic measures between patients with schizophrenia than between healthy controls, increasing the probability of detecting statistical relationships. In support of this, DTI studies have shown that neurocognitive functioning may correlate with impaired connectivity in patients with schizophrenia but not in healthy controls²³⁵. Unfortunately, due to our study design and sample composition, we cannot determine whether any differences in interindividual variability between patients and healthy controls are due to intrinsic factors or extrinsic factors such as antipsychotic drug treatment.

As pointed out in the Result section of Study 2, there was a significant decline in verbal fluency in FEP patients compared to the healthy controls, but no links to serum lipids were uncovered. It is possible that the relative decline may be partly due to an improvement in the control group, whereas patients with schizophrenia may not have shown *any* improvement²³⁶. Alternative explanations may include that the subgroup of patients who declined, might have struggled with higher symptom load with more positive symptoms such as hallucinations, and also experienced more negative symptoms with secondary effects on cognitive processes²³⁷. Lastly, it is essential to

consider the possibility that verbal fluency is not similarly linked to lipid metabolism as verbal learning.

Brain structures such as the hippocampus express high transcript levels of lipid biosynthesizing enzymes¹²⁹, are densely populated by synapses, and play a prominent role in verbal learning and memory^{238,239}. Several studies have found a link between performance on verbal learning and hippocampal volume^{240,241}. More importantly, there is evidence in the normal aging population and patients with neuropsychiatric disorders, which points to high serum HDL-C levels, in particular, being protective against hippocampal atrophy²⁴². This dependency of the hippocampus on intact cholesterol metabolism could at least in parts explain our finding of a distinct link between HDL-C and the hippocampus-based task of verbal learning.

As we found in the same FEP population a link between HDL and negative symptoms, and existing literature indicates a mild to moderate correlation between negative symptoms and cognition²⁷, and more specifically to verbal learning^{29,237}, we adjusted for negative symptoms in the post-hoc analyses while arriving at the same conclusion: a link between HDL-C and verbal learning.

Some of the inconsistencies in prior studies, pertaining to the nature of the relationship between negative symptoms and cognition, may be related to differences in methodology. The definitions and instruments used to assess negative and cognitive symptom constructs could be a source of significant variability. For example, the SANS or the original negative scale of the PANSS²¹² include items which may be closer to cognitive dysfunction than to negative symptoms, thus producing some measurement overlap²⁴³. In contrast, factorial analyses carried out in the last decades have generally yielded five-factorial constructs for the PANSS, which include a “Cognitive/Disorganized factor,” as well as a “Negative PANSS factor” with a more restricted composition than the original PANSS negative scale. We employed the five factorial PANSS construct.

Combined, our results may suggest related but partly independent mechanisms behind cognitive deficits and negative symptoms in schizophrenia²⁹. On the latter note, there are some newer studies which indicate disturbances in lipid metabolism as a plausible denominator for both these disease components^{56,103,244,245}. We found that the effect of HDL levels on verbal learning was more than that of negative symptoms on verbal learning, as indicated by a larger standardized beta coefficient.

6.1.3 Study 3

Cortical thinning

In Study 3, we observed a general cortical thinning (i.e., a reduction in mean cortical thickness) in OLZ-treated patients, but with specific regions located in frontal and temporal lobes showing more significant thinning²⁴⁶. Prior studies have reported of both a general cortical thinning in schizophrenia^{247,248}, and of a more regional specific thinning^{247,249}.

Contrary to our initial expectations, it was the OLZ-treated patients in our sample, and not the unmedicated patients, who exhibited a significant cortical thinning compared to the healthy controls. Negative findings have been reported in other studies with small sample sizes^{250,251}. Thus, we could have lacked sufficient power in our unmedicated sample as it consisted of only 19 patients. Still examining the mean values, the unmedicated patients were more or less similar to the healthy controls.

An alternative explanation may, therefore, be that the exhibited cortical thinning in the OLZ-treated group and the seemingly "normal" cortical thickness in the unmedicated group could be due to the MRI techniques applied in our study, which cannot differentiate pathologies in the cellular layers of the cortex. Along this line of thought, glial proliferation, a general marker for neuronal loss in neurodegenerative diseases, has not been found in the brains of patients with schizophrenia, and neuronal cell numbers appear to be similar in patients and healthy controls²⁵², indicating that neuronal death is not to be blamed for the displayed cortical thinning.

The clinical correlates of the detected brain changes following antipsychotic drug treatment are yet to be studied in depth^{253–255}. In our sample, the OLZ group had significantly thinner cortices, but it was the unmedicated patients who experienced a higher positive symptom load. Perhaps shedding some light on this matter are studies that demonstrate thicker cortices in patients in non-remission compared to those who are in remission²⁵⁶. One may therefore wonder whether the apparently “normal” cortical thicknesses in the unmedicated group could dissimulate illness severity.

Increased anisotropy has, for instance, been reported in patients experiencing hallucinations compared to healthy controls and other patients without active hallucinations²⁵⁷. This might also open up for the possibility that dynamic changes wherein increases in signals from myelin-related structures might reflect reactive processes of the disease such as swelling of myelin or remodeling of connections associated with psychosis²⁵⁸. Given the foregoing, we found a nominally increased gray/white matter intensity contrast (possibly suggesting impaired intracortical myelination) along with higher positive symptoms in the unmedicated patient group.

Gray/white matter intensity contrast

As already mentioned, we found that the OLZ-treated patients had comparable gray/white matter intensity contrast to the healthy controls. While the unmedicated patients did not differ significantly from the healthy controls, their contrast measures were nominally higher than those for OLZ and healthy controls. In a larger sample (including our patients) Jørgensen et al.²⁵⁹ found increased gray/white matter contrast in sensory and motor regions of the cortex in patients with schizophrenia compared to healthy controls. The regions showing differences were found to overlap with heavily myelinated regions of the cerebral cortex as evidenced by both MRI-based myelin maps and post-mortem studies²⁶⁰. Since signal intensity in both gray and white matter is closely related to myelin content, the gray/white-matter intensity contrast, although not a direct measure of myelin, could, in theory, reflect illness-related alterations of myelination. Accordingly, the increased tissue contrast in our unmedicated patients

could be a result of lower gray matter signal intensity indicative of reduced intracortical myelin.

Contrary to our findings, Kong et al.²⁶¹ reported *decreased* gray/white matter contrast in frontal, temporal, and parietal regions in patients with schizophrenia. One possible explanation for the discrepancy in the findings may be that Kong et al.²⁶¹ recruited older inpatients (48 years) with longer duration of illness (25 years), and the sample sizes differed considerably. Additionally, they did not include an unmedicated group nor examine the specific effects of one antipsychotic agent. In particular, the influence of aging is essential to consider, since increasing age correlates with tissue contrast reductions to a larger degree than does increasing age with, for example, cortical thickness alterations²⁶².

It is, furthermore, essential to mention that we cannot exclude the probability that an intense regional thinning of the cortex might have impacted the computation of gray matter intensity values, as there was a partial correlation (adjusted for age and gender) between thickness and contrast. Nonetheless, the strength of these correlations was weak, which may suggest some biological independence between the two cortical measures.

A link between serum lipids and cortical measures

Our second aim in Study 3 was to examine if there was a group dependent serum lipid interaction effect with cortical measures. The results indicated an OLZ-specific interaction with HDL-C for cortical thickness pertaining to pericentral regions, which also remained significant after correcting for multiple comparisons and testing for a range of other potential confounders. Similar findings were also demonstrated in the cortices mean, frontal, orbitofrontal, cingulate, occipital, and pericentral regions ($p < 0.05$, uncorrected).

There are some prior studies, which have demonstrated cortical thinning in the auditory regions in patients with a history of auditory hallucinations and thinner

prefrontal cortex in patients with negative symptoms; proposing that such cortical thinning may reflect underlying abnormalities in the cytoarchitecture in schizophrenia^{263,264}. As already stated, in our study it was the OLZ users who displayed a thinning of their cortices (including in the areas near auditory cortex and the prefrontal cortex), but it was the unmedicated subjects as a group who reported a higher positive symptom load while no differences were found in negative symptoms between the two patient groups. One could, therefore, wonder as to whether thicker cortices in OLZ users with higher levels of HDL-C could represent a subgroup with less psychotic symptoms (hallucinations) possibly related to improved myelination; unfortunately, we lacked sufficient statistical power to perform such subgroup analyses.

As outlined in the Introduction sections 2.2.2 and 2.2.4.2, a growing body of evidence points to OLZ (and other antipsychotics) inducing lipid biosynthesis^{107,203,265} and also up-regulation of cholesterol transport proteins²⁶⁵. It is further established that cholesterol is crucial for developing and maintaining lipid-rich brain structures, such as the myelin and for proper neuronal cell communication^{118,119}. Thus, one interpretation of our results may be that the specific link between serum HDL-C and increased cortical thickness during OLZ treatment reflects increased intracortical myelin related to the increased availability of specific lipid fractions²⁶⁶. In further support of such an idea, certain SGAs have been found to ameliorate the loss of gray matter in patients in the early stages of schizophrenia^{96,98}, and several studies from Bartizokis' research group have provided evidence of increased myelin (including intracortical myelin) during treatment with SGAs (risperidone)^{104,135,267}. Changes in body cholesterol balances have, likewise, been shown to alter myelin integrity²⁶⁸. Last but not least, a similar HDL-C x cortical thickness interaction was not observed amongst the healthy controls (indicating that it was not an overall improvement in myelin by some other means) or in the unmedicated group (indicating that the improvement was not solely related to patient status) giving additional support to an OLZ-mediated lipid effect on intracortical myelin.

6.2 GENERAL DISCUSSION

6.2.1 Is it the body weight or serum lipids that are related to clinical outcomes?

Several studies have pointed towards a link between antipsychotic-related adverse metabolic effects, such as weight gain, and improvement in positive and overall psychotic symptoms^{174,176,177,269}. Even though almost two-thirds of our patients experienced an increase in BMI, there were no significant associations between weight gain and improvement in positive or negative symptoms of schizophrenia. A similar lack of association has also been reported elsewhere in the literature for some SGAs^{270,271}, including in patients treated with a metabolically potent drug such as CLZ²⁷². Hence, our results do call into question the view that weight gain is a “necessary evil” for therapeutic benefit as proposed by Sharma et al.¹⁷⁹.

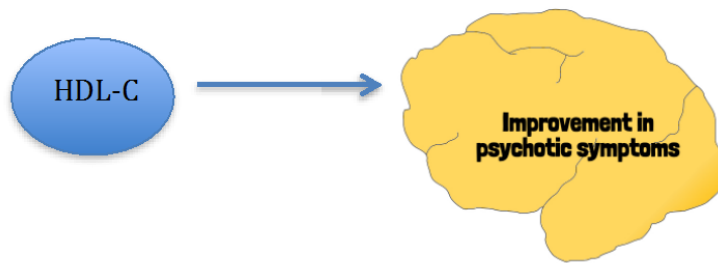
Also, other parts of the literature indicate that weight gain is not a “necessary evil”. For example, obesity and metabolic syndrome in the general population, as well as in schizophrenia, is related to impaired cognition and functioning^{234,273}. Moreover, lifestyle modification with weight gain prevention in patients treated with an SGA drug has not led to detrimental effects on psychopathology²⁷⁴. Also, switching strategies from high-risk metabolically potent antipsychotic to a low-risk agent has not unequivocally demonstrated an increased risk of clinical deterioration^{275,276}. Finally, those who spontaneously recover have not shown a consistent link between recovery and weight gain^{159,175}. One possible reason for the inconsistency in the literature may be due to a third variable effect. In our studies, we observed a *BMI-independent* link between serum HDL-C and outcome measures.

6.2.2 What does the link between serum HDL-C and symptom change imply?

In our two FEP cohorts, we found a link between an increase in serum HDL-C and clinical improvement, with a reduction in negative symptoms and an improvement in verbal learning. In Study 3, moreover, we found a link between HDL-C and thicker cortices possibly indicating increased intracortical myelination. While the causality cannot be determined due to the design and statistical methods used in our three

studies, I will outline some possible explanations for the exhibited HDL-C link with outcome measures.

Figure 4. A link between HDL-C and improvement in psychotic symptoms.



Examining the above relationship (Figure 4), one way of looking at it may be that having higher HDL-C levels *per se* is associated with a lesser symptom load. In support of this, higher levels of HDL-C have been linked to less transitioning to psychosis in high-risk patients²⁷⁷, and a worsening of HDL-C levels has been observed as the illness progresses into chronicity²²⁹.

Figure 4 could also be interpreted this way: increasing HDL-C levels by *any* means might be beneficial for psychotic symptom relief. Supporting such a notion, studies are reporting that improving diet, by for instance regular intake of fish oil or other substrates that may improve lipid profile, could be related to better cognitive performance²⁷⁸ and to a reduction in psychotic symptoms in general²⁷⁹. Nonetheless, there are also several studies which have disputed a beneficial effect of such supplementations^{280,281}.

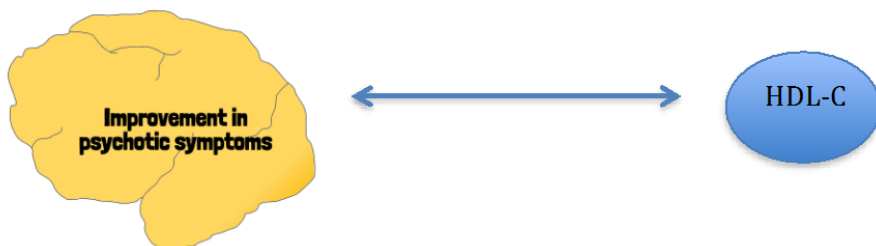
Along with an improvement in diet, exercise is often recommended for patients with dyslipidemia. Exercise therapy as an add-on to other treatment options in patients with psychotic disorders has demonstrated beneficial effects on brain structures, improvement in cognitive performance, and overall psychotic symptoms (for a review see^{282,283}). While it is possible that the observed link between HDL-C and clinical

improvements in our studies may be related to such lifestyle improvements, we did control for diet and exercise in the post-hoc analyses. Our results indicate that the association between HDL-C and clinical improvements were independent of such factors.

Also, less favorable lifestyle choices such as increased alcohol consumption have by some been found to increase serum HDL-C levels²⁸⁴, and there are even studies that report a reduction in negative symptoms with alcohol intake²⁸⁵. While the latter possibility may seem intriguing to some, it is most likely linked to a reduction in secondary negative symptoms such as anxiety. It is also important to remember that increased alcohol consumption has not been related to improved cognitive performances; on the contrary, it has often been associated with poorer performances on cognitive tasks^{286,287}. As a final note, in regards to alcohol, we controlled for alcohol use in Studies 1 and 2 without finding any significant effect on the observed link between HDL-C and outcome measures.

Other important aspects to consider is the possible bi-directionality of the HDL-C association witnessed in our studies as our results are based on regression analyses where directionality cannot be determined (Figure 5).

Figure 5. Bi-directionality of the HDL-C association with clinical improvements.



For example, the observed links between HDL-C and negative symptoms and verbal learning could represent an indirect effect of successful treatment that reduces the

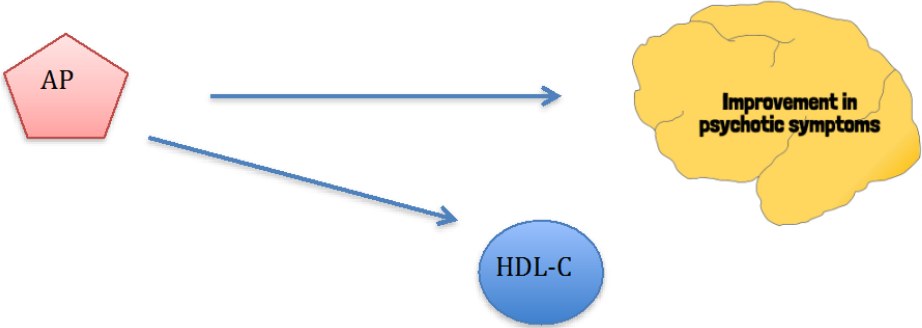
psychotic symptoms, leading to subsequent changes in lifestyle and diet while improving HDL-C levels (Figure 5). The study by Jakobsen²³¹ mentioned in section 6.1.1 may support such an interpretation. Still, if clinical improvements were to be significant determinants of the HDL-C increase, than patients in remission or recovery would be expected to have higher HDL-C levels. In our studies, there were no significant differences between the patients who were in remission versus those in non-remission with regards to their HDL-C levels. Besides, when controlling for remission status in the post-hoc analyses, we could not find any significant impact on the observed link between HDL-C and our outcome measures.

How does antipsychotic drug treatment fit into the puzzle?

Possibility 1:

As described in the Introduction section 2.2.2, most studies report an increase in LDL-C and TG levels during antipsychotic drug treatment, but the effects on HDL-C have been less uniform. Additionally, in the majority of psychotic patients and especially in patients with limited prior drug exposure (e.g., FEP), antipsychotics have been found to be highly effective⁶³. Hence, one possible explanation for the observed link between HDL-C and clinical improvement during antipsychotic drug treatment may be that antipsychotic drugs could cause both lipid changes and therapeutic benefits by *independent* pathways (Figure 6).

Figure 6. Antipsychotic (AP)-related effects on psychotic symptoms and serum HDL-C levels.



A possible independency between the pathways could also imply that the therapeutic efficiency of antipsychotics might be due to mechanisms not necessarily related to lipid pathways. There have, for example, been some studies related to other lipid moieties, which have demonstrated a reduction of LDL-C, and/or TG levels during lipid-lowering medications without deterioration in psychotic symptoms. The effects of lipid-lowering medications on HDL-C are, however, poorly understood²⁸⁸, but in clinical practice there seems to be little effect of these medications on serum HDL-C levels.

Possibility 2:

As reviewed in the Introduction sections 1.1.6 and 2.2.1, compelling evidence from different lines of research has implicated dysfunctional myelin and oligodendrocytes (i.e., the cells responsible for wrapping myelin around neuronal axons in the brain) in the pathology of schizophrenia and related psychotic disorders^{103,130}. Myelin is essential for controlling and regulating conduction velocities along axons and thus the synchronicity of brain signals across different brain regions, and for controlling synapse plasticity²⁸⁹.

The effect of antipsychotics on myelin structures has been increasingly studied in recent times. In a DTI study of schizophrenia patients in exacerbation, Garver et al.²⁵⁸ found increased diffusibility consistent with decreased myelin integrity during acute psychosis. After four weeks of treatment with the SGAs risperidone or ziprasidone, or the FGA haloperidol, they observed a partial restoration of myelin integrity in the subgroup that responded to treatment. Others, such as Bartzokis et al.²⁶⁷, have demonstrated higher volumes of intracortical myelin in schizophrenia patients treated with oral risperidone than in those treated with the FGA fluphenazine decanoate.

A recent study by Tishler et al.²⁹⁰ examined 93 patients with schizophrenia treated with SGAs (with medication exposures of 0–333 months) along with 80 healthy

control subjects. They found that the relationship between the length of exposure to SGAs and intracortical myelin was positive during the first year of treatment, but was subsequently negative. The authors hypothesized that such intracortical myelin trajectory might agree with the “clinically observed antipsychotic response trajectory with high rates of remission in the first year followed by progressively lower response rates.” They further argued that as postmortem evidence implicates intracortical myelin deficits in schizophrenia pathophysiology, “correcting these deficits may be an important mechanism of action for antipsychotics.”

As noted earlier, myelin consists primarily of lipids (particularly cholesterol), synthesized mainly *de novo* in the brain. Interestingly, several studies (both *in vitro* cell studies, *in vivo* animal and human studies) indicate that antipsychotics drugs could induce lipogenesis directly through activation of SREBP (for an overview see ¹²³) and that these lipogenic effects may be linked to the myelin-stimulating effects of antipsychotic agents ^{107,203}.

Revisiting the result from Study 1, we observed a significant link between the increase in HDL-C levels and improvement in negative symptoms during antipsychotic drug treatment. Additionally, though a comparable number of healthy controls and FEP patients experienced an increase in serum HDL-C levels, it was only amongst the FEP patients that an association between HDL-C levels and verbal learning was exhibited (Study 2). Moreover, in Study 3, we found an OLZ-specific link between higher serum HDL-C levels and thicker cortices, possibly related to increased intracortical myelin, which was not evidenced in the unmedicated patients or the healthy controls. Hence, an interesting (though speculative) way of interpreting our results is that antipsychotic drugs by inducing lipid pathways that increase the availability of certain lipid fractions in the brain, ^{107,230} may aid in “correcting” the defective myelin in schizophrenia, facilitating symptom relief (Figure 7).

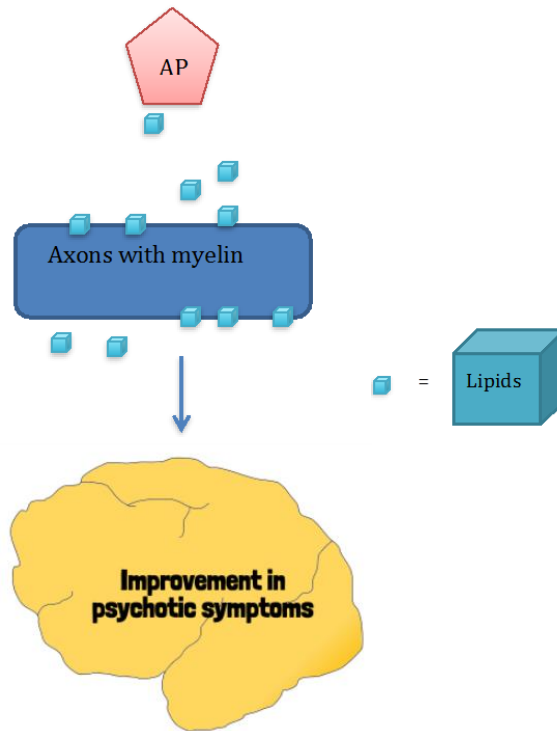
The latter view could also imply that antipsychotic drugs cause lipid changes and therapeutic benefit via *common/interdependent* mechanisms, and that the lipid changes

may be necessary for the therapeutic efficacy. Indeed, animal studies depict myelin-protecting and also oligodendrocyte-stimulating properties as therapeutically relevant mechanisms of antipsychotic drug action^{291,292}. Moreover, studies in schizophrenia patients have repeatedly demonstrated a correlation between the increase in serum lipid levels during antipsychotic drug treatment and clinical improvements^{69,159,183}, with differences in the effectiveness of antipsychotic drugs being reliant on their ability to induce metabolic changes.

Lastly, as mentioned in the Introduction, cholesterol is a key component of lipid rafts in the cell membrane. These lipid rafts are essential for proper signal transduction and cell communication²⁹³. While there are several studies that have indicated a dysfunctional cell membrane in patients with schizophrenia (section 2.2.1), there are also some authors who describe a "normalizing" effect of antipsychotics on the membrane lipid organization and metabolism^{137,141,294}.

Seen together, these findings may point to a shared lipid-related mechanism by which antipsychotics achieve their therapeutic properties^{107,203,295} (Figure 7). Further substantiating such a view is the fact that increased availability of cholesterol, especially HDL-C, has been related to improved synaptic plasticity and vesicle formation^{296,297} (crucial for neuronal communication) and also to increment of hippocampal structures (important in memory and learning tasks).

Figure 7. Hypothesized mechanism for antipsychotic (AP) therapeutic effect. An antipsychotic drug-induced activation of lipid biosynthesis in glial cells may increase the availability of lipid "building blocks" for repairing myelin, and as a result improving psychosis.



6.2.4 Representativeness of the FEP sample in light of the observed changes in lipids and clinical symptoms

Changes in serum lipids during follow-up

As reviewed in the Introduction, section 2.2.2, previous literature has often reported an increase in TG and LDL-C levels especially during treatment with an SGA^{298,299}, and more so in FEP patients with limited prior drug exposure^{165,300}. In our sample, there were no significant changes at a group level in serum total cholesterol or LDL-C, but there was a trend-wise increase in TG levels. While the lack of significant changes in serum TG, LDL-C, and total cholesterol during the one year on antipsychotic medication may question the representativeness of our FEP sample, there are similar studies in FEP patients which report non-significant changes in serum lipids during antipsychotic drug treatment³⁰¹. Nonetheless, there are some issues worth considering.

One may be that we had only two time-points, but TG and other serum lipids are likely to fluctuate during the one-year follow-up. Added to the fact that our patients had considerable antipsychotic switching during the follow-up period, this may have “neutralized” some of the initial serum lipid changes.

Changes in positive and negative symptoms during follow-up

In accordance with previous literature (Introduction section 2.1.2), there was a reduction in positive and negative symptoms over the first year of antipsychotic drug treatment^{302,303} where the decline in negative symptoms was quantitatively less than for positive symptoms^{302,303}. While the general view has been that negative symptoms are “stable” in the non-acute phase of the disorder¹¹, a recent meta-analysis found that negative symptoms may improve over time in outpatients with schizophrenia³⁰⁴. One possible reason for the different results in the clinical course of negative symptoms may be due to methodological issues. For instance, there are differences in the assessment tool concerning which negative symptoms that are measured. Also, the timeline may be different: the PANSS assesses the symptoms of the previous week; while the SANS assesses symptoms of the last month. Still, the improvements in negative symptoms found in our study and in the aforementioned meta-analysis³⁰⁴ may imply a greater potential for treatment responsiveness than previously anticipated.

Baseline cognitive deficits and changes during follow-up

Following previous literature on patients with an FEP, our patients showed generalized cognitive deficits^{305,306}. While the majority of prior studies have found a stable course for the cognitive impairments^{23,24}, we found that verbal learning improved amongst the FEP in comparison to the healthy controls. Also, other studies of patients early in their illness course have reported cognitive changes during the study periods; both deterioration and improvements (for a review see^{24,307,308}).

One possible reason for the conflicting results is that different cognitive domains are perhaps measured or summarized to composite scores, which may, in theory, give rise to different trajectories. For instance, Barder et al.³⁰⁹ showed that executive function,

impulsivity, and working memory did not change over the study period (up to five years), suggesting “stability,” while motor speed and verbal learning displayed trends towards significant decline. This introduces some nuance to the picture of cognitive stability. Also, in support of distinguishable cognitive trajectories, pharmacological interventions studies have reported specific effects on different cognitive domains (see Introduction section 2.1.2) designating a pharmacological dissociation of certain groups of cognitive processes. In our study, none of the patients were using medications for diabetes or dyslipidemia, nor did they have any known heart diseases or diabetes, which in theory could have affected the brain circulation and functioning, including cognitive performance.

6.3 METHODOLOGICAL ASPECTS: STRENGTHS AND LIMITATIONS

6.3.1 Study design and clinical sample

6.3.1.1 Naturalistic study design

The three studies encompassing this doctoral thesis are of naturalistic study design, permitting us to gather information on a representative sample of individuals receiving “treatment as usual.” A significant limitation with naturalistic designs, in general, is that we cannot rule out that confounding factors not taken into account might influence the associations presented.

6.3.1.2 Sample size and subgroups

We chose to include a broader diagnostic spectrum, i.e., patients with FEP not limited to first-episode schizophrenia. One benefit of such broader inclusion is that it increases the number of participants and thereby the statistical power. Nevertheless, there are some disadvantages also: when patient subgroups with more severe or less severe disease are included in the same sample; pronounced variation may blur important associations. We tried to address this issue by focusing on symptom-specific outcomes rather than diagnosis. Additionally, as patients in Studies 1 and 2 were followed as

part of a longitudinal study, information on diagnosis from the one-year follow-up visits was used to ensure some temporal stability.

For study 3, there were some additional concerns regarding the sample sizes within each group, and we cannot exclude that the analyses may have been underpowered to detect all real group differences. Still, the post-hoc-power analyses using G*Power showed that there were enough subjects within the different groups to find moderate to strong associations, but perhaps not to find weaker associations.

6.3.1.3 Possible selection biases

Participation in the project required the ability to give informed consent and to cooperate during clinical interviews and MRI scanning. Thus, the most severely ill patients would likely decline participation, or they may not be capable of completing the inclusion procedures. As the main bulk of inclusion took place in outpatient clinics, this could also bias the sample towards subjects with more factors promoting treatment adherence (e.g., having positive attitudes towards the treatment and its necessity). On the other hand, it is a well-known fact that a proportion of patients referred to further treatment in outpatient clinics from in-patient wards may fail to follow treatment and are therefore not recruited in the studies.

It is also likely that severely ill patients may be on more extensive antipsychotic regimes (which is more likely to increase TG and LDL-C levels) but due to the clinical situation, they may be non-compliant to a blood test and therefore not be included in the lipid analyses. This may have resulted in us “missing” possible associations between TG and LDL-C and clinical outcomes.

A particular concern with the patient samples in Study 3 was that the unmedicated group might have consisted of psychiatrically stable outpatients who either refused to take medication or were off medication for unknown reasons, thereby denoting that the observed differences cannot solely be attributed to antipsychotic drug treatment.

Future studies should, therefore, seek to better control for factors behind being unmedicated, including psychosocial determinants.

Finally, healthy controls were recruited by sending letters of invitation to a randomly drawn sample from the National Registry in Norway. There is likely to be some bias among the individuals who decided to participate (e.g., having higher education), resulting in a control sample not fully representative of the general population. Even so, we had age and gender-matched healthy controls in Study 2, and all healthy controls (in Study 2 and 3) were recruited from the general population of the same geographical and socio-cultural area and within a limited time-span. This procedure should limit falsely enlarged differences between patients and controls due to temporal trends, such as more overweight and metabolic disturbances in the overall population.

6.3.2 Issues related to antipsychotic drug treatment

6.3.2.1 Drug naïve patients

The studies included in this thesis (Studies 1 and 2) involved patients with limited prior drug exposure. Still, some antipsychotic-induced metabolic changes, especially weight gain could, in theory, have occurred before inclusion by the way we defined our FEP sample as not previously having received adequate treatment for psychosis. Adequate treatment was demarcated as antipsychotic medication in doses over 1 DDD for < 12 weeks or shorter if this treatment was followed by symptomatic remission.

6.3.2.2 Antipsychotic switching

There was a considerable amount of switching of antipsychotic medication in the two cohort studies (see Appendix Table 1). Thus, it is possible that patients who experienced weight gain or dyslipidemias switched to more metabolically neutral agents during the study period, reducing or reversing the initial metabolic effects. Having several time points between baseline and the one-year follow-up could have provided a better overview of these effects. Likewise, the remaining FEP patients at 12 months may be subjects tolerating antipsychotic drug treatment without gross

metabolic side effects, in particular weight gain, which is a known cause for discontinuation of treatment³¹⁰. Having said that, it is reassuring that the FEP (independent of the specific antipsychotic agent), were not statistically different from the age and gender-matched healthy controls at baseline; yet, they experienced a significant increase in BMI compared to the controls (Study 2), and that a considerable proportion (39%) experienced a clinically significant increase in BMI, i.e., $\geq 7\%$ of BMI at baseline. Similar percentages for FEP have been reported by others³¹¹.

In order to tackle some of the issues concerning antipsychotic drug switches, we merged the exposure to different antipsychotic drug types into a dichotomized variable (continuous use versus intermittent use). While it may be suboptimal, all naturalistic studies face this dilemma and to achieve sufficient statistical power; instrumental groupings are often needed. We did not group the treatment variable in the general matter of FGA versus SGA since all patients using FGA also used SGA. Grouping patients according to whether they used a metabolically potent drug (e.g., OLZ) or more metabolically neutral drugs also proved to be difficult due to vast switching between the drugs, and to insufficient subject numbers in each group. Also, in our cohort studies we were primarily interested in the serum lipid changes *per se* with relations to outcome measures, and not necessarily in relations to a specific antipsychotic agent. Nonetheless, as there may be differences in the serum lipid levels between monotherapy and polypharmacy, we did adjust for this in the post-hoc analyses. The latter analyses, showed that whether one was receiving monotherapy or polypharmacy did not significantly impact the observed relationships between serum HDL-C levels and clinical outcomes, corroborating findings from other studies of which antipsychotic polypharmacy was not independently associated with the occurrence of metabolic abnormalities³¹².

6.3.3 Issues related to clinical assessments

6.3.3.1 Clinical data

In the present thesis, we used standardized and widely accepted measures with good psychometric properties to study the phenomena at hand. Still, some aspects of assessment should be addressed. Assessments at baseline were not done before symptoms had stabilized. The consequence of this may be that the difference between the two assessment points on symptom level will be less, since patients may already be “stabilized” at the baseline assessment. On the other hand, it may also be considered as an advantage as it eliminates some of the acute phase changes, which is often “noise” in the statistical analyses. Furthermore, it is a well-known predicament that higher baseline psychopathology score may be associated with more significant improvement over time due to regression to the mean. In our sample, the initial PANSS scores were moderate, and we also adjusted for initial PANSS values by looking at the within-subject changes from baseline.

As indicated previously, negative symptoms are not a unitary construct but are made up of different symptoms. Different symptom scales, like the PANSS and SANS, differ on how they define the individual negative symptoms and what negative symptoms that are focused on and measured. This should be kept in mind when interpreting the results from Study 1, but also to some degree when interpreting the results in Study 2, as we adjusted for negative symptoms (i.e., PANSS negative subscores) in the post-hoc analyses.

An additional issue, which researchers may encounter, is that it is hard to differentiate the primary negative symptoms, which are part of the disease process itself, from the secondary negative symptoms that arise as a result of e.g., depression, side effects of antipsychotic medication, or psychotic withdrawal¹⁶. Being diagnosed with schizophrenia may in itself be an adverse life event causing stigma and functional impairments. Hence, the improvement in negative symptoms over the one-year follow-up could at least in parts be due to the alleviation of secondary negative symptoms.

6.3.3.2 Cognitive data

Assessment of each cognitive domain was based on one neuropsychological subtest to restrict the number of statistical tests. Thus, we might have overlooked associations with other potentially relevant cognitive functions. It is, however, debatable whether the differences between the individual subtests are *clinically* meaningful as it is likely to be smaller differences between subtests than differences between tests developed entirely separate from each other (due to their co-norming on a single patient sample). In order to reduce the number of tests and outcome measures, some researches may choose to use summary scores. A contentious issue with such summary scores is that they may “hide” variations in the contributions of each test. We believe that by using single tests from widely used neuropsychological tests, it is easier to reproduce our findings and for comparing them across studies.

We did not use the standardized Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery due to the fact that it had not been translated to the Norwegian language when the TOP-study started. Nonetheless, the domains chosen to be tested were based on a previous study in an FEP population by our colleagues²²¹ and overlap with many of the domains measured by the MATRICS test battery³¹³. Still, it is essential to recognize that different cognitive tests, while testing the same domain, may give rise to different results. Also, natural variations, e.g., the mood that day, the medication used may have affected our results. Moreover, we cannot exclude the possibility that other biological parameters and subclinical disease may have confounded the observed associations. We did nevertheless try to reduce the influence of the factors mentioned above by controlling for concomitant changes in positive, negative and depressive symptoms, and also for BMI in our studies; obtaining comparable results as in our main finding (i.e., a link between serum HDL-C and verbal learning).

An additional issue with Study 2 is that the controls were healthy, and could, in theory, be susceptible to a ceiling effect in the amount of change that can be achieved leading

to differences in the learning potential in the FEP and the healthy control group. While an untreated control group may have been ideal for addressing this matter, this is not always ethically advisable.

6.3.3.3 Biological data

All subjects were fasting on the day of blood sampling, which took place on the same day as the cognitive testing. Still, the serum lipid measures are “screenshots,” and it is possible that the patients during the 12-month period could have fluctuated in their serum lipids (Studies 1 and 2). It is also necessary to highlight that using blood as a proxy for the brain has limitations, and should be considered when drawing conclusions³¹⁴. Moreover, for the MRI study (Study 3) we set a limit of 3 months between blood sampling and brain scanning; still, we cannot be sure that the serum lipid levels are representative of the values measured on the day of brain scanning. In general, it is the serum TG levels that fluctuate the most, even on a day-to-day basis depending on the food intake and the composition of dietary intake. While the mechanism explaining the biological variation in serum lipid concentrations are not fully elucidated, they are most likely caused by intrinsic factors related to their biosynthesis and tissue use, as regulated by genetic factors, and their interactions with extrinsic factors. Tackling all of these problems in a naturalistic setting is, however, difficult.

6.3.3.4 Subjective measuring of diet and exercise

The assessment of self-rated diet and exercise (Studies 1 and 2) is associated with some challenges. For example, cognitive impairment may influence the ability to both remember and reflect on the statements regarding diet and exercise. On the other hand, social stigma and wanting to be perceived as healthy individuals may cause the participants to report a better diet and exercise than what may be the actual case. While it may not be feasible outside the confinement of an institution, more detailed description of diet and exercise by some means is desirable in future studies.

6.3.4 Issues related to brain imaging

Motion of the head is a potential confounder that could influence our findings in Study 3, mainly because patient populations tend to have more head motion than healthy controls³¹⁵. While we did not measure motion during scan acquisition, all scans were visually inspected, and poor quality scans were removed. Future studies should, nonetheless, consider prospective motion corrections during scan acquisitions³¹⁶ together with physical interventions (e.g., improved padding) to reduce actual motion.

Patients and healthy control subjects were scanned concurrently, which limits the possibility of scanner drift over time, affecting the results. Also, there were no scanner hardware upgrades during the inclusion period. Nevertheless, there may be variability in how cortical structures are measured, leading to difficulties in the interpretation of findings across studies. In the present thesis, the commonly used FreeSurfer software was used to define the cortical region boundaries. This method sections brain regions into cortical regions delineated by reliable anatomical landmarks (gyri and sulci) and is considered anatomically valid²⁴⁷. Employing a standardized procedure to retrieve brain regions of interest enables replication in future studies.

Another issue pertaining more to the selected cortical measures is that while the reliability of regional cortical volumes and thickness measures as well as subcortical volumes has been examined in several studies; the reliability of the gray/white tissue intensity contrast has not been equally documented. Additionally, although the gray/white tissue intensity contrast may be sensitive to changes in myelin, it is important to bear in mind that they are not *direct* measures of myelination. Prior studies have, in general, employed DTI techniques to study myelin. However, DTI has limitations in identifying the exact nature of myelin changes as the FA may reflect different processes like myelination, axonal swelling, or atrophy, and is also sensitive to confounding effects of fiber crossings³¹⁷. To tackle some of these issues, Palaniyappan and colleagues³¹⁸ suggested combining DTI with myelin volume to study treatment effects and future studies may want to employ this method.

Also, the effect of antipsychotic medication contra symptom fluctuation has to be studied in a well-characterized population before any firm conclusions can be made. Employing multimodal MRI could aid in this pursuit, e.g., by describing structural findings in terms of their relationship with other tissue properties, including diffusion properties. More reliable studies from non-medicated patients may also aid in this process. For future studies, we also suggest focusing on longitudinal designs for investigation of medication effects as such studies has the advantage of within-subject analyses.

6.3.5 Statistical issues

Attrition in longitudinal studies is common and hard to avoid altogether. If the final group no longer reflects the original sample, such attritions could endanger the validity of the study results. In order to check for variables missing at random, we used Little's Missing Completely at Random (MCAR) test, which showed that variables were indeed missing at random - see the statistical sections in Studies 1 and 2. We also checked whether subjects lacking data differed in a significant manner from the ones with a full dataset concerning demography, the severity of symptoms, lifestyle or medication use, determining that there were no significant differences.

The choice of statistical approaches used to minimize the effect of missing variables is equally important and could alter any findings markedly. We used linear mixed-effects models, which “tackles” data with a different number of repeated measurements for each subject³¹⁹. Other advantages of mixed-effects models in studies with repeated measures include: accounting for the correlation of repeated measures observations and any variability in the time between assessments for each subject. Moreover, time-dependent covariates can be used³¹⁹.

Another important aspect of statistical testing is the correction for multiple comparisons. This is necessary to avoid type I errors, i.e., detecting a group difference that is not present (false positive) as increasing the number of tests increases the likelihood of obtaining p-values below the threshold set for statistical significance.

The studies in this doctoral thesis were mostly hypothesis-driven, decreasing, in general, the number of statistical tests performed when investigating specific associations. For Study 3, however, we had three groups and multiple cortical regions, each with a possible link to a lipid; thus, correction for multiple comparisons was prudent. While the most common way of dealing with multiple testing is a Bonferroni-correction where the critical p-value 0.05 is divided by the total number of tests, setting a new threshold for significance, such corrections are also known to be too stringent for many clinical settings. We, therefore, employed a repeated Benjamini-Hochberg procedure, which also takes into consideration the dependency of the measures used (details are described in the Statistical section of Study 3).

6.4 POSSIBLE CLINICAL AND SCIENTIFIC IMPLICATIONS

Studies so far have identified negative symptoms and cognitive dysfunctions as unmet challenges in the treatment of schizophrenia, which should be prioritized, especially as they play a critical role in the functional decline observed in many individuals with schizophrenia. We, therefore, believe that the findings in this thesis are clinically relevant and that they may argue for using changes in serum HDL-C for monitoring treatment response in the first year of antipsychotic drug treatment, mainly as measuring serum lipids could easily be implemented in the daily clinical practice. Moreover, our findings of a specific HDL-C-related link to negative and cognitive symptoms advocates for exploiting specific lipid pathways with overlap to treatment response in developing more effective treatments in the future. The HDL-C association could also indicate a disease mechanism that may be amenable to other intervention by, e.g., increasing HDL-C levels as an add-on treatment for cognitive remediation. Exploring these possibilities in the right setting is highly warranted. Guidance and support in making healthy lifestyle modifications should also be an integral part of the treatment of psychiatric disorders as we found the HDL-C link to clinical improvement being independent of changes in BMI. As roughly one-fourth of the patients show only mild functional impairment after the first-episode of psychosis, identifying factors that may help to understand better outcomes may also improve functioning. Here, research into the early phases of psychotic disorders is particularly

relevant as the different contributing factors that are in play during the transition from normality to pathology will be present, and the danger of misinterpreting research findings due to chronicity, recall bias or the effects of long-term medication is reduced. The studies included in this thesis, further, indicate a need for more research on patients with similar longitudinal symptom courses above and beyond constricts of diagnostic categories.

7. CONCLUSION AND FUTURE PERSPECTIVES

7.1 Conclusion

Prior to the current study, several papers in chronic patients with schizophrenia had already indicated a correlation between clinical improvement and adverse metabolic effects (weight gain and serum TG levels) during antipsychotic drug treatment. The present doctoral thesis is the first to uncover an antipsychotic-related HDL-C link to clinical improvement (negative symptoms and verbal learning) in patients with an FEP, and also supports the notion of an antipsychotic (OLZ)-related effect on cortical intensity contrast and a more specific HDL-C effect on cortical thickness suggestive of increased intracortical myelin. Our findings need to be replicated in future studies, and in particular, the impact of antipsychotic medication use on brain structure alterations needs to be clarified.

7.2 Future perspectives

While our understanding of the relationship between lipids and psychiatric disorders is increasing, there are still many unanswered questions that require further investigation:

- One question is whether the association between serum lipid levels and clinical outcomes during antipsychotic drug treatment is a general feature of all antipsychotics used in the first year of treatment, or whether it is related to specific antipsychotic agents. Additionally, understanding other possible

mediators that may be involved in the relationship between dyslipidemia and psychiatric disorders is also essential, and an RCT study design may aid in this request.

- As studies show that there may be different facets and trajectories within the group of “negative symptoms” with potentially different origin, it may be interesting to investigate the individual symptom components and to examine any relations with changes in serum HDL-C (and other lipids) during antipsychotic drug treatment.
- The question regarding the unique consequence of antipsychotic medications (including the potentially different role of FGAs and SGAs) in the progression of structural abnormalities should also be in focus in future neuroimaging studies. Here a longitudinal study design with multiple time points and a multimodal MRI approach may help in better understanding of the timing and progression as well as the meaning of changes in brain structures; making it possible to infer causality.
- Additional studies, including other antipsychotic agents and more direct measures of intracortical myelin, are also needed before any firm conclusions can be made. Given the complex and capricious clinical features and cognitive impairments associated with psychotic disorders, it seems likely that numerous brain systems are involved to varying extents in different individuals. This could imply that different features of the disorder mirrors underlying disturbances of distinctive brain functions and moreover that these may cross current diagnostic boundaries. These considerations also entail that we could anticipate that novel treatments would target particular symptoms or groups of symptoms sharing common underlying mechanisms and that they will be applicable across diagnostic groups.

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9. APPENDIX

Table A.1 Antipsychotic drug use of each patient at baseline and at 12 months

Antipsychotics at baseline			Antipsychotics at 12 months	
1. antipsychotic agent	2. antipsychotic agent	3. antipsychotic agent	1. antipsychotic agent	2. antipsychotic agent
Amisulpride			Amisulpride	
Aripiprazole			Aripiprazole	
Aripiprazole			Quetiapine	Clorprothixene
Aripiprazole	Olanzapine		Aripiprazole	Quetiapine
Aripiprazole	Risperidone inj.		Quetiapine	
Aripiprazole			Olanzapine	
Aripiprazole	Olanzapine		Olanzapine	Zuclopendithoxol
Aripiprazole				
Aripiprazole			Aripiprazole	
Aripiprazole	Olanzapine		Olanzapine	Risperidone inj.
Aripiprazole	Clorprothixene		Quetiapine	
Aripiprazole				
Aripiprazole	Clorprothixene		Aripiprazole	
Aripiprazole			Aripiprazole	
Aripiprazole	Olanzapine		Aripiprazole	
Aripiprazole			Olanzapine	
Aripiprazole	Olanzapine		Sertindole	
Aripiprazole			Aripiprazole	
Aripiprazole				
Aripiprazole	Olanzapine	Zuclopendithoxol	Sertindole	
Aripiprazole			Aripiprazole	
Aripiprazole			Aripiprazole	
Flupentixol			Zuclopendithoxol	
Olanzapine			Risperidone	
Olanzapine			Olanzapine	
Olanzapine	Aripiprazole		Clozapine	Olanzapine
Olanzapine			Olanzapine	
Olanzapine			Quetiapine	
Olanzapine			Aripiprazole	
Olanzapine			Aripiprazole	
Olanzapine			Olanzapine	
Olanzapine			Quetiapine	Risperidone inj.
Olanzapine			Risperidone inj.	
Olanzapine			Olanzapine	Risperidone
Olanzapine	Risperidone		Olanzapine	
Olanzapine			Risperidone inj.	
Olanzapine			Olanzapine	
Olanzapine			Perhenazine	
Olanzapine			Aripiprazole	
Olanzapine	Clorprothixene		Olanzapine	Clorprothixene
Olanzapine			Olanzapine	
Olanzapine			Perhenazine deconate	
Olanzapine			Ziprasidone	
Olanzapine			Olanzapine	Clorprothixene
Olanzapine			Ziprasidone	
Olanzapine			Olanzapine	
Olanzapine			Olanzapine	
Olanzapine			Olanzapine	
Olanzapine			Olanzapine	
Olanzapine			Aripiprazole	
Olanzapine				
Olanzapine			Olanzapine	
Olanzapine	Chlorpromazine	Levomepromazine	Aripiprazole	Olanzapine
Olanzapine			Aripiprazole	
Olanzapine	Risperidone		Olanzapine	
Olanzapine	Levomepromazine		Aripiprazole	
Olanzapine			Quetiapine	
Olanzapine				
Olanzapine			Olanzapine	
Olanzapine	Risperidone		Aripiprazole	Aripiprazole
Olanzapine			Quetiapine	
Olanzapine			Aripiprazole	
Olanzapine	Paliperidone		Aripiprazole	
Olanzapine			Aripiprazole	Olanzapine

Paliperidone			Paliperidone	
Perhenazine			Aripiprazole	
Perhenazine			Quetiapine	
Perhenazine decanoat			Olanzapine	
Quetiapine	Aripiprazole		Aripiprazole	Quetiapine
Quetiapine	Aripiprazole			
Quetiapine		Clorprothixene	Aripiprazole	Risperidone inj.
Quetiapine	Olanzapine		Risperidone	
Quetiapine	Amisulpride	Olanzapine	Quetiapine	Amisulpride
Quetiapine			Quetiapine	
Quetiapine	Aripiprazole			
Quetiapine	Olanzapine		Quetiapine	
Quetiapine	Olanzapine		Quetiapine	
Quetiapine			Ziprasidone	Aripiprazole
Quetiapine			Quetiapine	
Quetiapine			Quetiapine	
Quetiapine				
Quetiapine	Risperidone	Clorprothixene	Quetiapine	
Quetiapine				
Quetiapine			Quetiapine	Aripiprazole
Quetiapine	Olanzapine		Clozapine	
Risperidone	Risperidone		Quetiapine	
Risperidone			Risperidone inj	
Risperidone			Risperidone	
Risperidone				
Risperidone			Aripiprazole	
Risperidone			Aripiprazole	
Risperidone			Olanzapine	
Risperidone	Levomepromazine		Risperidone	Olanzapine
Risperidone			Aripiprazole	
Risperidone			Clozapine	
Risperidone inj.				
Risperidone inj.			Risperidone	
Ziprasidone			Risperidone inj.	
Ziprasidone	Zuclopenthixol		Ziprasidone	
Ziprasidone			Ziprasidone	Quetiapine
Ziprasidone			Aripiprazole	
Ziprasidone	Chlorpromazine		Aripiprazole	Ziprasidone
Ziprasidone			Ziprasidone	
Ziprasidone			Quetiapine	
Ziprasidone	Olanzapine		Olanzapine	
Ziprasidone			Quetiapine	
Ziprasidone			Aripiprazole	Olanzapine
Ziprasidone			Olanzapine	
Ziprasidone			Aripiprazole	
Ziprasidone			Amisulpride	Ziprasidone
Ziprasidone			Risperidone inj.	
Ziprasidone			Olanzapine	
Ziprasidone			Clorprothixene	
Ziprasidone			Perhenazine	
Ziprasidone			Aripiprazole	
Ziprasidone			Aripiprazole	
Ziprasidone			Quetiapine	
Ziprasidone			Aripiprazole	Quetiapine
Ziprasidone			Aripiprazole	

Table A.2 Co-medication at baseline in the FEP sample

Active substance	Baseline (n)
Antiepilepticum	
Lamotrigine	4
Gabapentin	1
Clonazepam	5
Carbamazepine	1
Antidepressants	
Escitalopram	17
Citalopram	4
Venlafaxine	8
Fluoxetine	3
Mirtazapine	4
Amitriptyline	1
Paroxetine	2
Sertraline	4
Duloxetine	1
Anxiolytics, sedatives and hypnotics	
Zopiclone	5
Oksazepam	2
Alimemazine	2
Diazepam	1
ADHD	
Methylphenidate	1

This table shows the psychotropic drugs used at baseline by the FEP patients.
n= number of patients.

PAPERS 1-3



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Increase in serum HDL level is associated with less negative symptoms after one year of antipsychotic treatment in first-episode psychosis

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ABSTRACT

Background: A potential link between increase in total cholesterol and triglycerides and clinical improvement has been observed during antipsychotic drug treatment in chronic schizophrenia patients, possibly due to drug related effects on lipid biosynthesis. We examined whether changes in serum lipids are associated with alleviation of psychosis symptoms after one year of antipsychotic drug treatment in a cohort of first-episode psychosis (FEP) patients.

Methods: A total of 132 non-affective antipsychotic-treated FEP patients were included through the Norwegian Thematically Organized Psychosis (TOP) project. Data on antipsychotic usage, serum lipids (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (TG)), body mass index (BMI) and clinical state were obtained at baseline and after 12 months. The Positive and Negative Syndrome Scale (PANSS) was used to assess psychotic symptoms. Mixed-effects models were employed to examine the relationship between serum lipids and psychotic symptoms while controlling for potential confounders including BMI.

Results: An increase in HDL during one year of antipsychotic treatment was associated with reduction in PANSS negative subscores ($B = -0.48, p = 0.03$). This relationship was not affected by concurrent change in BMI (adjusted HDL: $B = -0.54, p = 0.02$). No significant associations were found between serum lipids, BMI and PANSS positive subscores.

Conclusion: We found that an increase in HDL level during antipsychotic treatment is associated with improvement in negative symptoms in FEP. These findings warrant further investigation to clarify the interaction between lipid pathways and psychosis.

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1. Introduction

Metabolic disturbances such as obesity and dyslipidemia are common in schizophrenia (Allison et al., 1999; Mitchell et al., 2013; Vancampfort et al., 2013). These metabolic abnormalities may be caused by environmental factors, but can also be intrinsic to the illness itself (Mitchell et al., 2013; Vancampfort et al., 2013). Indeed, dyslipidemia has been observed in antipsychotic-naïve and in first-episode psychosis (FEP) patients (Chen et al., 2013; De Hert et al., 2006; Enez Darcin et al., 2014; Fleischhacker et al., 2013; Kaddurah-Daouk et al., 2012; Misiak et al., 2016; Saari et al., 2004; Thakore, 2004; Verma et al., 2009; Wu et al., 2013; Zhai et al., 2017). In line with these findings, there is also evidence of overlapping genetic markers between disturbed lipid metabolism and schizophrenia (Andreassen et al., 2013). Additional findings of

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white matter abnormalities and reduced myelination in schizophrenia (Bernstein et al., 2015; Davis et al., 2016; Mighdoll et al., 2015) also indicate an involvement of lipids, as cholesterol is crucial for myelin formation and functioning (Dietschy and Turley, 2004; Saher et al., 2005; Verheijen et al., 2003).

The metabolic effects of many antipsychotic drugs further illuminate the possible link between lipid factors and schizophrenia. It is well known that treatment with antipsychotics may lead to weight gain and dyslipidemia (Goncalves et al., 2015; Musil et al., 2015; Young et al., 2015). Weight gain, mainly caused by enhanced appetite and food intake, may indirectly increase lipid levels, but it has also been shown that dyslipidemia can occur independently of weight gain in antipsychotic treated patients (Birkenaes et al., 2008; Lally et al., 2013; Procyshyn et al., 2007). Although antipsychotic-related metabolic changes have been associated with negative health consequences (De Hert et al., 2011; Mitchell et al., 2013; Nasrallah et al., 2015; Newcomer, 2005), there are also several studies that report a positive link between treatment-related weight gain and improvement in psychosis (Bai et al., 2006; Czobor et al., 2002; Gupta et al., 1999; Hermes et al., 2011; Lamberti et al., 1992; Lane et al., 2003; Leadbetter et al., 1992; Meltzer et al., 2003; Sharma et al., 2014). Similarly, treatment-related increases in serum triglycerides (TG) have been associated with improvement in overall psychotic symptoms, and with a reduction in positive symptoms (Atmaca et al., 2003; Lally et al., 2013; Pande et al., 2002). There are also reports of an association between an increase in TG and/or total cholesterol, and improvement in negative symptoms (Chen et al., 2014; Procyshyn et al., 2007) and in cognitive symptoms (Krakowski and Czobor, 2011). Recent advances in lipidomics research, moreover, have linked changes in cell membrane lipid profiles to treatment response, signifying the multifaceted role of lipids in psychosis (Kaddurah-Daouk et al., 2012; Tessier et al., 2016). Nevertheless, the nature of these associations is not fully clarified, as prior studies have mainly involved chronic patients in whom the long-term effect of poor lifestyle and multiple drug exposures may be difficult to disentangle.

The main objective of the present study was to explore the relationship between serum lipids and symptom relief in FEP patients during their first year of antipsychotic treatment. Our main hypothesis was that an increase in serum lipids during antipsychotic treatment would be associated with improvement of psychosis-related symptoms, even after controlling for potential confounders including changes in body mass index (BMI). To test our hypothesis, we used data from a longitudinal sample of FEP patients where data regarding serum lipids, BMI and clinical state (i.e. positive and negative symptoms) at baseline and after 12 months of treatment were obtained.

2. Materials and methods

2.1. Study design

The present study is a prospective longitudinal study with a naturalistic design, with patients recruited at their first treatment for a psychotic disorder from inpatient and outpatient psychiatric units in the catchment areas of the major hospitals in Oslo, Norway, as part of the larger Thematically Organized Psychosis (TOP) study (<http://www.med.uio.no/norment/english/>). The Regional Ethics Committee and The Norwegian Data Inspectorate approved the study.

2.2. Patients

One hundred and thirty-two FEP patients were included in the present study (see Fig. 1). The inclusion criteria followed the general inclusion criteria for the TOP study: (1) age 18 to 65 years, (2) meeting the diagnostic criteria for a broad schizophrenia spectrum psychosis according to Diagnostic and Structural Manual of Mental Disorders, fourth version (DSM-IV, American Psychiatric Association, 2000), (3) no head

trauma, neurological or other medical disorder that could influence CNS functioning, and (4) IQ over 70. The specific inclusion criteria for this longitudinal study was that the patient had not previously received adequate treatment for their psychotic disorder. Adequate treatment was defined as antipsychotic medication in doses over 1 Defined Daily Dosage (DDD) for >12 weeks or shorter if this treatment was followed by symptomatic remission; “first episode psychosis”. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (https://www.whocc.no/ddd/definition_and_general_considera/). In general, the patients were recruited in the early phases of treatment. However, some individuals were too psychotic to give informed consent at an early stage and patients could thus give consent to enter the study up to 52 weeks after start of first treatment (for details see Simonsen et al., 2017). For the purposes of the analyses in the current paper we did not include patients who (1) were not using any antipsychotics at baseline as well as at follow-up, and (2) participants treated with cholesterol-lowering medications (statins and fibrates).

The distribution of diagnoses was as follows: $N = 87$ (66%) with a diagnosis of schizophrenia, $N = 5$ (4%) schizophreniform disorder, $N = 16$ (12%) schizoaffective disorder and $N = 24$ (18%) psychotic disorder not otherwise specified (psychosis NOS).

2.3. Clinical assessments

Sociodemographic history (including age, gender, ethnicity, education), smoking, alcohol consumption, diet, exercise habits, duration of untreated psychosis (DUP), hospitalization, antipsychotic medication, and use of cholesterol-lowering medication were obtained through structured interviews. The ethnicity of patients was categorized as Caucasian or non-Caucasian. All patients were diagnosed with the Structural Clinical Interview for DSM-IV (SCID) (First et al., 1996). Inter-rater reliability was good, with an overall kappa score of 0.77 (95% CI: 0.60–0.94). Psychotic and other related symptoms were assessed using The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), we report the means for a five-factor model (Wallwork et al., 2012). Depression was assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1992). The extent of alcohol use was measured with The Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993). Diet and exercise habits were assessed at inclusion and at 12 months by interviews. The patients were asked to describe their eating habits as healthy, moderately healthy or unhealthy. This variable was then dichotomized into “similar or poorer diet” (including patients who did not change their diet habits from inclusion to 12 months, as well as patients who reported a poorer diet at 12 months) and “better diet” (consisting of patients who reported a beneficial change in diet). Exercise was also initially assessed as light, moderate or hard, and then dichotomized into “similar or reduced exercise” and “increased exercise” at 12 months. Our rationale for dichotomizing diet and exercise was that we were primarily interested in the change in these variables, as they would reflect improvement or decline in lifestyle.

2.4. Use of antipsychotic medication

Information about current and previous use of antipsychotics was obtained through interviews with the patients combined with prescription data from the medical charts. All participants used one or more antipsychotics at least once during the study period (see Supplementary Tables 1–4, for information concerning antipsychotic and non-psychotropic drug use). For the purpose of this study, where our main goal was to investigate if serum lipid changes during antipsychotic drug therapy were related to improvement in psychosis, we defined treatment with any type of antipsychotic agent throughout the study period as continuous antipsychotic use ($n = 100$; 76%). In contrast, treatment

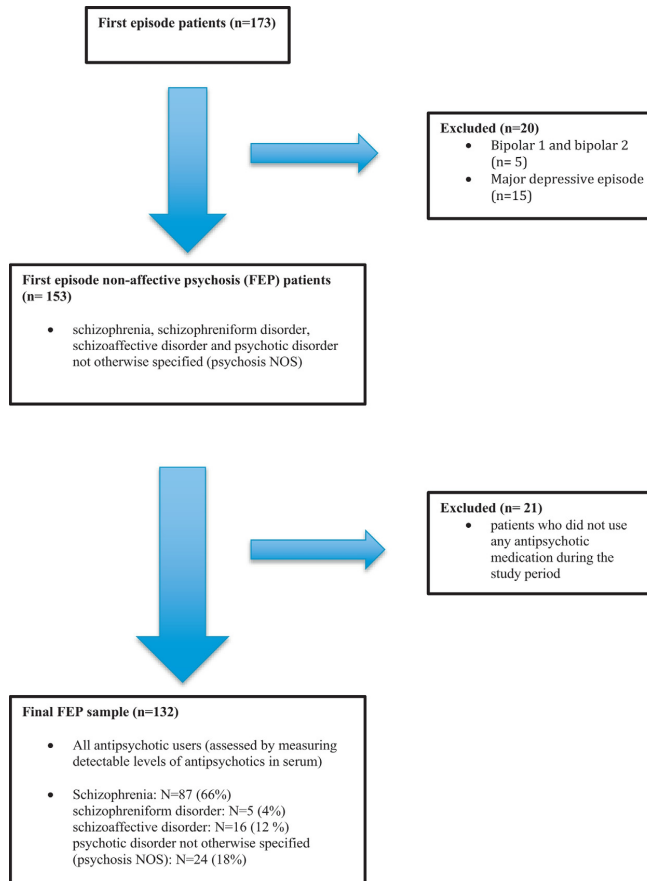


Fig. 1. Participants flow chart.

with any type of antipsychotic agent, either at baseline or at 12 months ($n = 32$; 24%), was defined as intermittent antipsychotic use, see Table 1 for details. Since the number of patients using the same antipsychotic agent as monotherapy at both time points was low (Table 1), we did not have the statistical power to perform subgroup analyses for the different drugs.

Compliance was checked by measuring antipsychotic drug levels in serum samples analyzed by standard therapeutic drug monitoring methods at Diakonhjemmet Hospital, Oslo, Norway (Solberg et al., 2016). Since antipsychotic drug levels give information on the drug treatment at one particular point in time, which in the present study did not necessarily reflect the drug treatment for the whole study period, the drug levels were not included in the main analyses, but this information was used to exclude non-adherent patients.

2.5. Metabolic parameters

2.5.1. Serum lipid measurements

Blood was sampled in the morning after overnight fasting. Cholesterol (total cholesterol, HDL, LDL) and TG were analyzed at the Department of Clinical Chemistry at Oslo University Hospital with standard enzymatic methods from Roche Diagnostics Norge AS, Oslo, Norway. Data on serum lipids are reported in Table 2.

2.5.2. BMI measurement

All participants were weighed on calibrated digital weights under equal conditions and height was measured with standard methods. Body mass index (BMI) was calculated according to the standard formula: $BMI = \text{weight (in kilograms) divided by height (in meters squared)} (kg/m^2)$.

2.6. Statistical analysis

All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA/IBM, New York, USA). For the comparison of demographic and clinical characteristics, chi-squared test and t -tests were used. Paired t -tests were used to examine the change in serum lipid levels, BMI and PANSS positive and negative subscores during the follow-up period. Pearson correlation coefficients were used to examine the correlation between serum lipid levels and BMI. Multivariate regression analyses controlling for age, gender and continuous vs. intermittent antipsychotic use were applied to examine the relationship between metabolic variables and outcome measurements at baseline and after 12 months. Two-sided tests were employed in all analyses, and the significance level was set to $p \leq 0.05$.

Linear mixed effects models were applied to investigate the association between change in PANSS positive and negative subscores and

Table 1
Demographic and treatment characteristics of the FEP sample.

Characteristics	
Age (years), mean (SD)	26.7 (7.6)
Gender (male), n (%)	85 (64.4)
Ethnicity (Caucasian), n (%)	87 (65.9)
Education (years), mean (SD)	12.9 (2.8)
Change in diet ("better diet" ^a), n (%)	20 (15.2)
Change in exercise ("increased exercise" ^b), n (%)	21 (15.9)
Smoking (daily), n (%)	60 (45.5)
Alcohol use (AUDIT), mean (SD)	7.3 (7.6)
DUP (weeks), median (range)	40.0 (1–1040)
Hospitalization (at inclusion), n (%)	30 (22.7)
Antipsychotic treatment	
Continuous antipsychotic use ^c , n (%)	100 (76)
Intermittent antipsychotic use ^d , n (%)	32 (24)
Typical antipsychotics ^e , n (%)	16 (16)
Atypical antipsychotics, n (%)	116 (88)
Monotherapy ^f , n (%)	34 (26)
Polypharmacy ^g , n (%)	41 (31)

SD = standard deviation, n = number of subjects, % = percentage, AUDIT = Alcohol Use Disorder Identification Test, DUP = duration of untreated psychosis.

^a Diet was dichotomized into "similar or poorer diet" (including patients who did not change their diet habits from inclusion to 12 months, as well as patients who reported a poorer diet at 12 months) and "better diet" (consisting of patients who reported a beneficial change in diet).

^b Exercise was dichotomized into "similar or reduced exercise" (including patients who did not change their exercise habits from inclusion to 12 months, as well as patients who reported a reduced exercise at 12 months) and "increased exercise" (consisting of patients who reported increased exercise at 12 months).

^c Continuous antipsychotic use was defined as use of any type of antipsychotic agent throughout the study period.

^d Intermittent antipsychotic use was defined as use of any type of antipsychotic agent, either at baseline or at 12 months.

^e All typical antipsychotic agents were used in combination with atypical agents.

^f Monotherapy with the same antipsychotic agent at baseline and at 12 months, n:

olanzapine 15, aripiprazole 7, quetiapine 4, risperidone (tablet or injection) 3, ziprasidone 3, and paliperidone 1.

^g Polypharmacy was defined as using multiple antipsychotic agents either (or both) at baseline and at 12 months.

change in metabolic parameters (total cholesterol, HDL, LDL, TG and BMI) from baseline to one year follow-up. In this procedure, both PANSS positive and negative subscores were investigated in separate models along with each metabolic parameter (total cholesterol, HDL, LDL, TG and BMI). The PANSS subscores were defined as dependent factors, while time (baseline and 12 months), age, gender, continuous vs. intermittent antipsychotic use, serum lipid levels (total cholesterol, HDL, LDL, TG) and BMI were defined as fixed factors (independent variables). Time was considered a repeated factor with compound covariance. The final model was chosen based on the information criteria (Akaike information criterion). Preliminary analyses were conducted to ensure assumptions of normality, linearity, multicollinearity and

Table 2
Paired *t*-tests examining the change in clinical characteristics from baseline to 12 months.

	n	Baseline mean (SD)	12 months mean (SD)	Δ mean (SD)	t (df)	<i>p</i> -value
Psychotic symptoms						
Total PANSS scores	129	63.2 (13.9)	55.2 (14.7)	−8.1 (14.0)	−6.6 (128)	<0.001
PANSS positive subscores	131	2.6 (1.0)	2.1 (1.0)	−0.5 (1.1)	−5.3 (130)	<0.001
PANSS negative subscores	132	2.2 (1.0)	2.0 (0.9)	−0.2 (0.9)	−2.2 (130)	0.03
Metabolic parameters						
Total cholesterol	99	4.90 (0.97)	4.92 (0.96)	0.02 (0.72)	0.29 (98)	0.77
HDL (mmol/L)	90	1.39 (0.40)	1.32 (0.37)	−0.07 (0.27)	−2.39 (89)	0.02
LDL (mmol/L)	86	2.99 (0.82)	3.08 (1.27)	0.16 (1.06)	1.44 (85)	0.15
Ln TG (mmol/L)	89	0.15 (0.55)	0.20 (0.52)	0.07 (0.55)	1.15 (88)	0.25
BMI (kg/m ²)	112	24.9 (4.3)	26.3 (4.7)	1.4 (2.5)	5.83 (111)	<0.001

n = total number of subjects with both baseline and 12 months data, PANSS = Positive and Negative Syndrome Scale, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, Ln TG = ln of triglycerides, BMI = body mass index, SD = standard deviation, Δ = change from baseline to one year follow-up, t = *t*-test, df = degrees of freedom. *P*-values are obtained from paired *t*-tests.

homoscedasticity. Serum TG values were ln-transformed after inspection of residuals. Due to issues with multicollinearity, we did not enter all the lipids in the same mixed model analysis. There were no problems with linearity or homoscedasticity.

Missing variables were treated pairwise. Preliminary analyses showed that the missing variables were randomly distributed (Little's MCAR test: chi-square = 463.54, df = 440, and *p* = 0.21) and that there were no significant differences in sociodemography, illness-related factors or antipsychotic usage between the patients with complete lipid datasets and the ones with missing lipid data. To further ensure the validity of the results we reran the mixed model analyses including only subjects with full dataset (total cholesterol *n* = 99; HDL *n* = 90; LDL *n* = 86; ln TG *n* = 89; BMI *n* = 112).

3. Results

One hundred and thirty-two FEP patients participated, of whom 85 (64%) were males and 87 (66%) were Caucasians. Mean age was 26.7 (SD = 7.6) years and median DUP 40.0 (range 1–1040) weeks. See Table 1.

3.1. Changes in serum lipid levels and BMI

There was a statistically significant decrease of 0.07 mmol/L (SD = 0.27) in mean HDL from baseline (1.39 mmol/L; SD = 0.38) to 12 months (1.32 mmol/L; SD = 0.37) at the group level (*p* = 0.02); 49 subjects (54%) experienced a decrease and 41 subjects (46%) an increase in their HDL levels (Table 2). There were no significant changes in serum total cholesterol, LDL or ln TG (Table 2). Also, there were no significant differences in the direction of lipid change between continuous vs. intermittent antipsychotic use (data not shown).

Paired sample *t*-test showed that mean BMI increased significantly from 25.0 (SD = 4.2) to 26.3 (SD = 4.7) during the follow-up period (*p* < 0.001) (Table 2). Eighty-three patients (74%) with BMI measurements experienced weight gain. Forty-four (39%) out of these cases experienced a clinically significant increase in BMI, i.e. $\geq 7\%$ of BMI at baseline. Twenty-nine patients (26%) displayed a reduction in BMI, of whom 20 subjects (69%) were using antipsychotic medication during the entire study period. There were no significant differences in direction of weight change between patients with continuous antipsychotic use vs. patients with intermittent use (chi-square (1, *N* = 112) = 1.71, *p* = 0.19).

3.2. Relationship between serum lipids and BMI

Pearson correlation coefficients showed that changes in total cholesterol levels were correlated with changes in HDL (*r* = 0.21, *p* = 0.05), LDL (*r* = 0.64, *p* < 0.001), ln TG (*r* = 0.22, *p* = 0.04) and BMI (*r* =

0.22, $p = 0.04$). Ln TG levels were correlated with changes in HDL ($r = -0.28$, $p = 0.01$) and LDL ($r = 0.33$, $p = 0.002$) levels.

3.3. Relationship between serum lipid levels, BMI and psychotic symptoms

At baseline, multivariate linear regression analyses showed a negative association between HDL level and PANSS negative subscores when controlling for age, gender and continuous vs. intermittent antipsychotic use ($B = -0.67$, $p = 0.02$) (Supplementary Table 5). At 12 months, there were no significant associations between serum lipids, BMI, and PANSS positive and negative subscores (Supplementary Table 5).

The mixed effects model demonstrated a significant association between an increase in HDL and a decrease in PANSS negative subscores after one year ($B = -0.48$, $p = 0.03$) when controlling for age, gender and continuous vs. intermittent antipsychotic use (Table 3). Similar results were found when we analyzed with complete lipid dataset ($B: -0.62$, $p = 0.01$). Furthermore, the association between change in HDL and change in negative symptoms remained significant after controlling for BMI change ($B = -0.54$, $p = 0.02$) (Table 4). No significant associations were found between total cholesterol, LDL, Ln TG, BMI and PANSS positive and negative subscores (Table 3).

3.4. Post hoc analyses examining the negative association between HDL and PANSS negative subscores

Group comparison between patients with an increase in HDL levels ($n = 41$, 46%) versus those with a decrease ($n = 49$, 54%) during the follow-up period displayed no significant differences in sociodemographic or illness-related factors except that the HDL increase group had higher mean PANSS negative subscore at baseline, 2.5 ($SD = 1.1$) vs. 2.0 ($SD = 1.0$) ($p = 0.04$) and a higher mean AUDIT score at 12 months, 8.8 ($SD = 7.0$) vs. 5.1 ($SD = 5.2$) ($p = 0.01$), respectively (Supplementary Table 6).

Post hoc mixed model analyses showed that neither illness (including diagnosis subgroup, DUP, hospitalization, concurrent changes in PANSS positive subscores and CDSS scores) nor lifestyle-related factors (including smoking, alcohol use, changes in diet and changes in exercise) significantly influenced the relationship between HDL and PANSS negative subscores (Supplementary Table 7).

4. Discussion

The main finding of the present one year follow-up study of FEP patients was that increase in HDL levels during one year of antipsychotic treatment was significantly associated with a reduction in negative psychotic symptoms (i.e. PANSS negative subscores), an association that remained significant after controlling for potential confounders, including demographic variables, lifestyle factors, and BMI.

The important role of cholesterol (total, HDL, and LDL) for human health has been known for decades. Patients with schizophrenia have markedly increased prevalence of metabolic abnormalities including

dyslipidemia, and several meta-analyses have demonstrated hypertriglyceridemia and low HDL-cholesterol in chronic schizophrenia (Mitchell et al., 2013; Vancampfort et al., 2013). More recently, such low HDL levels have also been reported in FEP, including antipsychotic drug-naïve patients (Enez Darcin et al., 2014; Fleischhacker et al., 2013; Misiak et al., 2016; Wu et al., 2013; Zhai et al., 2017) and even subjects with prodromal symptoms only, i.e. at high risk of developing psychosis (Cordes et al., 2016). These findings suggest that a suboptimal level of HDL cholesterol serves as an unfavorable lipid marker in early psychosis.

It is, therefore, interesting that we demonstrate a significant association between an increase in HDL level and a reduction in PANSS negative subscores during one year of antipsychotic treatment in FEP patients. Usually, the lipid disturbances in schizophrenia tend to worsen with time, and multi-episode patients with schizophrenia have significantly higher prevalence of abnormally low HDL cholesterol as compared to FEP and antipsychotic naïve patients (Vancampfort et al., 2013). We found on a group level that the mean HDL level decreased following one year of antipsychotic treatment, which is in accordance with the literature on medicated FEP (Correll et al., 2014; Wu et al., 2013). Still, almost half of the FEP patients in our study experienced an increase in HDL level. The reasons for this beneficial change in HDL are uncertain, but they may be related to treatment effects (including antipsychotic drugs) and changes in lifestyle and diet. As the different antipsychotic agents have different effects on serum lipid levels, it would have been interesting to examine the subgroups of antipsychotics (e.g., olanzapine) that have previously been shown to have a high tendency to cause dyslipidemia. However, due to the low number of subjects treated with each of the antipsychotic agent throughout the study period, we could not look specifically at the subgroups of drugs.

Our data do not prove any causal relationship between the increase in HDL and decrease in negative symptoms in FEP patients. An interesting but speculative theory is to consider HDL in serum as an indirect proxy for cholesterol in the brain, where improved supply could play a positive role in myelination. It has previously been indicated that patients with schizophrenia have reduced myelination in the CNS (Bernstein et al., 2015; Davis et al., 2016; Mighdoll et al., 2015), and in vivo MRI and animal studies have demonstrated pro-myelinating effects of antipsychotic drugs (Bartzokis et al., 2012, 2007; Ebdrup et al., 2016; Xu et al., 2010) that in part could be related to their lipid-stimulating effects (Cai et al., 2015; Steen et al., 2017). It is also possible that genetic factors per se could influence lipid metabolism as a risk factor for schizophrenia (Andreassen et al., 2013; Solberg et al., 2016). On the other hand, the observed link between HDL and PANSS negative subscores could represent an indirect effect of successful treatment that reduces the negative symptoms, leading to subsequent changes in lifestyle and diet improving HDL levels. The fact that the patients who experienced an increase in HDL had lower HDL levels at baseline and more pronounced negative symptoms could to some degree support this. Nevertheless, it is worth mentioning that we found a similar link between higher HDL levels and lower negative psychotic symptoms also at baseline. Additionally, the patients who increased in HDL levels

Table 3

Mixed models examining the association between change in metabolic parameters and PANSS positive and negative subscores trajectories from baseline to 12 months.

	PANSS positive subscores			PANSS negative subscores		
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
Total cholesterol	0.10	(-0.05, 0.25)	0.19	0.01	(-0.14, 0.16)	0.90
HDL	0.33	(-0.09, 0.75)	0.13	-0.48	(-0.90, -0.06)	0.03
LDL	0.09	(-0.04, 0.23)	0.17	0.03	(-0.10, 0.16)	0.68
Ln TG	0.07	(-0.18, 0.33)	0.56	0.15	(-0.10, 0.40)	0.23
BMI	-0.01	(-0.04, 0.02)	0.45	-0.01	(-0.04, 0.03)	0.73

PANSS = Positive and Negative Syndrome Scale, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, Ln TG = Ln of triglycerides, BMI = body mass index, CI = confidence interval. Analyzed with mixed effects model and adjusted for covariates age, gender, and antipsychotic use. Antipsychotic use was dichotomized into continuous antipsychotic use (use of any type of antipsychotic agent throughout the study period) vs. intermittent antipsychotic use (use of any type of antipsychotic agent, either at baseline or at 12 months).

Table 4
Mixed models examining the association between change in metabolic parameters and PANSS positive and negative subscores trajectories from baseline to 12 months while controlling for BMI.

	PANSS positive subscores			PANSS negative subscores		
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
Total cholesterol	0.14	(−0.02, 0.29)	0.09	0.02	(−0.14, 0.18)	0.81
HDL	0.36	(−0.09, 0.81)	0.12	−0.54	(−0.98, −0.09)	0.02
LDL	0.10	(−0.04, 0.23)	0.16	0.04	(−0.10, 0.17)	0.61
Ln TG	0.14	(−0.13, 0.40)	0.32	0.18	(−0.08, 0.44)	0.18

PANSS = Positive and Negative Syndrome Scale, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, Ln TG = ln of triglycerides, CI = confidence interval. Analyzed with mixed effects model and adjusted for covariates age, gender, antipsychotic use and body mass index (BMI). Antipsychotic use was dichotomized into continuous antipsychotic use (use of any type of antipsychotic agent throughout the study period) vs. intermittent antipsychotic use (use of any type of antipsychotic agent, either at baseline or at 12 months).

did not differ from those who decreased with respect to sociodemographic, lifestyle- or illness-related factors, except for reporting higher alcohol consumption at 12 months. Still, there was no increase in alcohol use during the follow-up period as these patients had similar levels of alcohol consumption at baseline. In addition, it is unlikely that higher alcohol consumption could explain why these patients improved in negative psychotic symptoms as high alcohol consumption is often related to more psychotic symptoms (Addington et al., 2014).

Prior studies that have investigated the potential relationship between lipid changes and improvement of psychotic symptoms during antipsychotic treatment have predominantly reported an association between increase in serum TG levels and reduction in overall psychotic symptoms and in positive symptoms (Atmaca et al., 2003; Lally et al., 2013; Pande et al., 2002; Procyshyn et al., 2007) leading us to hypothesize that a similar relationship could also be found in our sample of FEP patients. However, we did not observe such a relationship. One possible explanation for this difference may be that the patients in prior studies were often treated with clozapine, a drug reserved for patients with treatment-resistant psychosis and recognized for its dyslipidemic potential (Mitchell et al., 2013). In our sample (with only three clozapine users), TG levels were not significantly altered during the follow-up period. This may have impeded a potential relationship between TG levels and psychotic symptoms.

Many studies have reported an association between treatment-related weight gain and improved clinical outcome in schizophrenia (Bai et al., 2006; Basson et al., 2001; Bustillo et al., 1996; Czobor et al., 2002; Hermes et al., 2011; Meltzer et al., 2003; Yang et al., 2014). We did not observe such a link between increased body weight and reduced psychotic symptoms, despite the fact that two thirds of our patients experienced an increase in BMI. Although BMI and serum lipids may be correlated, we did not find a significant correlation between these two metabolic variables. It should also be noted that these parameters may be partly independent in patients treated with antipsychotic drugs (Birkenaes et al., 2008; Kang and Lee, 2015; Lally et al., 2013; Procyshyn et al., 2007).

The present study has limitations that require consideration. Because of the naturalistic study design there are many confounding factors, which cannot be controlled for. The dynamic nature of treatment for schizophrenia with frequent changes in antipsychotic regimens during the follow-up period is an important limitation. Furthermore, serum lipids were missing for a number of patients, especially at 12 months. We did, however, try to minimize the effect of these missing variables by using mixed effects models. Also, when we repeated the analyses including only subjects with a complete dataset, similar results were found. We did not provide structured assessments of intake of fish oil and dietary seafood, or habitual amount of exercise, factors that may influence both the metabolic parameters and symptom levels. However, we used self-report assessments of changes in diet and exercise habits to partially control for these potential confounders in the mixed model analyses. We also controlled for the effect of smoking, alcohol use and education, which may be regarded as proxies for lifestyle

factors. It is nevertheless possible that other factors not accounted for could have influenced the results. Patients were receiving standard treatment from the University Hospital and followed recent guidelines, thus, the clinical change was not due to different quality of treatment.

In conclusion, we found that an increase in HDL level during antipsychotics treatment was related to improvement in negative symptoms, independent of weight change. To further elaborate the clinical significance of the effects of antipsychotic treatment on lipid metabolism, sufficiently powered longitudinal studies in drug-naïve patients are needed.

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Contributors

PBG analyzed the data and was responsible for design of the study, interpretation of results and drafting of the first version of the manuscript, together with IM and VMS. OAA and ID contributed with data, interpretation of results and writing of the manuscript. CS, TVL, EZH, TI, SHL and RHM contributed with data. SS contributed with interpretation of results. All authors contributed to the writing of the manuscript and have approved the final version.

Conflict of interest

The authors of this paper have no conflict of interests.

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Appendix A. Supplementary data

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Improvement in verbal learning over the first year of antipsychotic treatment is associated with serum HDL levels in a cohort of first episode psychosis patients

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Abstract

To investigate whether changes in serum lipids are associated with cognitive performance in first episode psychosis (FEP) patients during their first year of antipsychotic drug treatment. One hundred and thirty-two antipsychotic-treated FEP patients were included through the TOP study along with 83 age- and gender-matched healthy controls (HC). Information regarding cognitive performance, psychotic symptoms, lifestyle, body mass index, serum lipids [total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, and triglycerides] and antipsychotic treatment was obtained at baseline and after 1 year. The cognitive test battery is comprised of assessments for verbal learning, processing speed, working memory, verbal fluency, and inhibition. Mixed-effects models were used to study the relationship between changes over time in serum lipids and cognitive domains, controlling for potential confounders. There was a significant group by HDL interaction effect for verbal learning ($F = 11.12$, $p = 0.001$), where an increase in HDL levels was associated with improvement in verbal learning in FEP patients but not in HC. Practice effects, lifestyle, and psychotic symptoms did not significantly affect this relationship. Antipsychotic-treated FEP patients who increased in HDL levels during the first year of follow-up exhibited better verbal learning capacity. Further investigations are needed to clarify the underlying mechanisms.

Keywords Schizophrenia · Psychosis · Antipsychotics · Lipids · Cognition · Outcome

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Introduction

More than 70% of patients with schizophrenia are estimated to experience cognitive impairments [1]. For several cognitive domains—including verbal learning and memory, attention, perception, and processing speed—the impairment may be as prominent as two standard deviations below healthy controls [2] indicating a clinically relevant decrease or deficits in cognitive functioning. These deficits can have a more substantial impact than positive psychotic symptoms in determining real-world functional outcome [3, 4], and may be present even after successful reduction in psychotic symptoms [5, 6]. Although considerable efforts have been made to understand the neurobiology of cognitive impairment in psychosis, the background is still mostly undetermined.

Lipids are essential for CNS development and functioning [7–10], including myelination and synapse communication. In schizophrenia and related psychotic disorders, both lipid disturbances as well as brain structural changes have been demonstrated. While several studies in the normal aging population, as well as in other neuropsychiatric disorders [11–17], characterized by compromised brain functioning have indicated a link between serum cholesterol levels, in particular HDL cholesterol, and cognition, few studies have examined the potential relationship between serum lipids and cognition in patients with schizophrenia. In a cross-sectional study, Lancon et al. [18] found low HDL levels (along with hypertriglyceridemia, and abdominal obesity) to be related to impairment in verbal learning and memory. Another cross-sectional study [19] demonstrated that patients with schizophrenia and co-morbid metabolic syndrome exhibited impairments in processing speed, attention/vigilance, working memory and problem solving, compared to those without metabolic syndrome. However, when the authors examined the different components of the metabolic syndrome, they found that the HDL level was positively associated with attention/vigilance. Also, studies in antipsychotic-treated patients have reported a link between serum lipids and cognitive performance. Krakowski and colleagues found that an increase in total cholesterol level and LDL level after a 12-week period of antipsychotic drug treatment was positively associated with improvements in global cognition [20] with verbal memory being the most prominent domain. Still, there are other studies in schizophrenia that have failed to show any associations between serum lipids and cognition [21, 22], and some have even found negative associations between serum lipids and cognitive performance [23].

These discrepancies in prior studies may be due to the potential confounding effects of long-term medication,

age-related neurodegeneration and disease risk-related environmental factors, as most previous studies have been focusing on chronic schizophrenia patients in a cross-sectional study design. Another important limitation is a lack of age- and gender-matched healthy individuals to control for practice effects [24] and naturally occurring variations in serum lipid levels.

Aims of the study

The present longitudinal study of an FEP cohort was undertaken to investigate potential associations between serum lipid levels and cognitive performance in the first year of antipsychotic treatment in a group of FEP patients with limited prior drug exposure, compared to a group of age- and gender-matched healthy controls (HC). We further investigated the possible influence of lifestyle (smoking, alcohol, diet, and exercise), metabolic measures connected to serum lipids (body mass index), improvements in clinical symptomatology secondary to antipsychotic drug treatment, and other illness-related factors (antipsychotic drug treatment, hospitalization, and depressive symptoms) on the relationship between serum lipids and cognition in the patient group.

Methods and materials

Participants

The longitudinal FEP sample, recruited between 2003 and 2013 through the Thematically Organized Psychosis (TOP) study (Oslo, Norway), was the same as used by Gjerde et al. [25]. The inclusion criteria for the TOP study were age between 18 and 65 years, and having a diagnosis within a broad schizophrenia spectrum psychosis according to the Diagnostic and Structural Manual of Mental Disorders, fourth version (DSM-IV, American Psychiatric Association, 2000). Participants were recruited in a stable phase of their disorder. Exclusion criteria were current IQ under 70, the presence of a neurological disorders or a history of head injuries. Additionally, for the longitudinal FEP study, patients who previously had received adequate antipsychotic drug treatment were not recruited [25]. Healthy controls (HC) were randomly selected and recruited from the same geographic catchment area as the patients, using national statistical records (2003–2011). They were matched for age and gender. To ensure a reliable HC sample, subjects were excluded if they or any of their first-degree relatives had a history of a severe psychiatric disorder as indicated by the Primary Care Evaluation of Mental Disorders [26]. The final sample consisted of 132 first episode psychosis (FEP) patients and 83 HC. Participants were tested at baseline

and after 1 year. None of the participants used medication against thyroid problems, diabetes, hypertension or cholesterol-lowering medications (statins or fibrates).

All participants gave written informed consent prior to their inclusion in the study, and the Regional Ethics Committee and The Norwegian Data Inspectorate approved the study.

Clinical assessments

Demographic and clinical data (including antipsychotic drug treatment) were obtained through structured interviews and from hospital medical records. The diagnosis was established by use of the Structural Clinical Interview for DSM-IV (SCID) [27]. Psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) [28] and depressive symptoms with the Calgary Depression Scale for Schizophrenia (CDSS) [29]. Remission was defined as at least 1 week with no score of ≥ 4 on any of the following five PANSS items: P1, P3, P5, P6, or G9. Alcohol use was

measured with the Alcohol Use Disorders Identification Test (AUDIT) [30]. Information on diet and exercise habits for the FEP patients was obtained by self-assessment at baseline and follow-up. Patients were asked to describe their eating habits as healthy, moderately healthy or unhealthy, while exercise was initially assessed as light, moderate or hard. Diet was then dichotomized into “similar or poorer diet” (including patients who did not change their diet habits from inclusion to 12 months, as well as patients who reported a poorer diet at 12 months) and “better diet” (consisting of patients who reported a beneficial change in diet). Exercise was likewise dichotomized into “similar or reduced exercise” and “increased exercise” at 12 months (for more details, see [25]).

Antipsychotic drug treatment in the FEP group

As we did not have sufficient statistical power to create separate subgroups for the different antipsychotic agents (see supplementary Tables 1, 2 and 3 for antipsychotic use), we

Table 1 Demographic, metabolic, and cognitive characteristics of the FEP and HC sample

	FEP (<i>n</i>)	HC (<i>n</i>)	FEP, mean (SD)	HC, mean (SD)	<i>t</i>	<i>p</i> value
Age (years)	132	83	26.7 (7.6)	29.0 (6.8)	− 2.6	0.01
Education (years)	132	83	12.9 (2.8)	14.2 (2.0)	− 4.43	< 0.001
Alcohol use (AUDIT scores)	120	71	7.3 (7.4)	5.9 (3.0)	1.89	0.06
DUP (weeks), median (range)	132		40.0 (1–1040)			
Total PANSS scores	132		63.2 (13.9)			
PANSS-positive subscores	132		2.6 (1.0)			
PANSS-negative subscores	132		2.2 (1.0)			
Depressive symptoms (CDSS scores)	128		6.2 (4.5)			
	FEP (<i>n</i>)	HC (<i>n</i>)	FEP, <i>n</i> (%)	HC, <i>n</i> (%)	χ^2	<i>p</i> value
Gender (male)	132	83	85 (64.4)	80 (59.7)	0.62	0.45
Ethnicity (Caucasian)	132	83	87 (65.9)	132 (98.3)	52.32	< 0.001
Smoking (daily)	132	86	60 (45.5)	17 (19.8)	15.04	< 0.001
Hospitalization at inclusion	132		30 (22.7)			
Change in diet (“better diet”) ^a	132		20 (15.2)			
Change in exercise (“increased exercise”) ^b	129		21 (15.9)			
Continuous antipsychotic drug use ^c	132		100 (76)			
Intermittent antipsychotic drug use ^d	132		32 (24)			
Antipsychotic monotherapy	132		91 (69)			
Antipsychotic polypharmacy	132		41 (31)			

p values are obtained from *T* tests and chi-square test

p values in bold indicate numbers that are significant on the 95% confidence limit

FEP first episode psychosis, HC healthy controls, SD standard deviation, *n* number of subjects, % percentage, AUDIT Alcohol Use Disorder Identification Test, DUP duration of untreated psychosis, PANSS Positive and Negative Syndrome Scale, CDSS Calgary Depression Scale for Schizophrenia

^aDiet was divided into “similar or poorer” and “better” compared to diet habits at baseline

^bExercise was divided into “similar or reduced” and “increased” compared to exercise habits at baseline

^c“Continuous antipsychotic drug use” refers to the continuous use of any antipsychotic agent during the study period

^d“Intermittent antipsychotic drug use” refers to the use of any antipsychotic agent, either at baseline or 12 months

Table 2 Mixed models examining serum lipids, BMI and cognitive performance at baseline in FEP and HC

	FEP, mean (SD)	HC, mean (SD)	Group		Group	
			<i>F</i>	<i>p</i> value	<i>B</i>	SE (<i>B</i>)
Total cholesterol (mmol/L)	4.97 (1.00)	4.59 (0.90)	8.94	0.003	0.39	0.13
HDL (mmol/L)	1.39 (0.40)	1.44 (0.43)	0.08	0.79		
LDL (mmol/L)	2.99 (0.82)	2.59 (0.81)	11.54	0.001	0.38	0.11
Ln TG (mmol/L)	0.81 (0.31)	0.77 (0.26)	0.82	0.37		
BMI (kg/m ²)	24.9 (4.3)	24.1 (3.7)	1.57	0.21		
Verbal learning (total scores)	49.31 (11.80)	59.22 (8.54)	35.25	< 0.001	- 8.82	1.48
Processing speed (total scores)	60.40 (16.82)	79.55 (13.32)	65.19	< 0.001	- 16.77	2.08
Working memory (total scores)	9.21 (2.61)	11.89 (2.40)	48.33	< 0.001	- 2.50	0.36
Verbal fluency (total scores)	35.58 (14.54)	45.39 (9.98)	18.27	< 0.001	- 7.65	1.79
Inhibition (total scores)	66.07 (24.14)	49.52 (10.83)	27.75	< 0.001	15.08	2.86

p values in bold indicate numbers that are significant on the 95% confidence limit

Verbal learning was measured with California Verbal Learning Test, processing speed with Digit Symbol Test, working memory with Letter number span, verbal fluency with Verbal Fluency Test, and inhibition with Color-Word Interference Test. Analyzed with mixed-effects models while controlling for age, gender, education, and group (FEP vs. HC). The HC were defined as the reference group

FEP first episode psychosis, HC healthy controls, SD standard deviation, *F* *F* value, *B* regression coefficient, *SE* standard error of the regression coefficient, HDL high-density lipoprotein cholesterol, LDL low-density lipoprotein cholesterol, Ln TG Ln of triglycerides, BMI body mass index

Table 3 Mixed models examining serum lipid, BMI and cognitive trajectories over 1 year in FEP and HC

	Time		Group × time		Group × time	
	<i>F</i>	<i>p</i> value	<i>F</i>	<i>p</i> value	<i>B</i>	SE (<i>B</i>)
Total cholesterol (mmol/L)	0.005	0.94	0.003	0.96		
HDL (mmol/L)	2.77	0.10	2.24	0.14		
LDL (mmol/L)	0.32	0.57	1.48	0.23		
Ln TG (mmol/L)	0.05	8.39	0.05	0.82		
BMI (kg/m ²)	23.84	< 0.001	6.99	0.01	0.95	0.36
Verbal learning (total scores)	17.60	< 0.001	6.86	0.01	3.54	1.35
Processing speed (total scores)	0.05	0.003	2.27	0.13		
Working memory (total scores)	0.10	0.75	0.10	0.75		
Verbal fluency (total scores)	0.21	0.65	6.38	0.01	- 3.15	1.25
Inhibition (total scores)	0.60	0.02	0.37	0.54		

p values in bold indicate numbers that are significant on the 95% confidence limit

Verbal learning was measured with California Verbal Learning Test, processing speed with Digit Symbol Test, working memory with Letter number span, verbal fluency with Verbal Fluency Test, and inhibition with Color-Word Interference Test. Analyzed with mixed-effects models examining a time × group interaction while controlling for age, gender, education, time, and group (FEP vs. HC). The HC were defined as the reference group

FEP first episode psychosis, HC healthy controls, *F* *f* value, *B* regression coefficient, *SE* standard error of the regression coefficient, HDL high-density lipoprotein cholesterol, LDL low-density lipoprotein cholesterol, Ln TG Ln of triglycerides, BMI body mass index

organized data on antipsychotic medication as “continuous antipsychotic drug use” versus “intermittent antipsychotic drug use” [25]. Continuous use was defined as using any antipsychotic agent at baseline and at 12 months (not necessarily the same agent at both time points), while intermittent use was defined as using any antipsychotic agent at either baseline or at 12 months. In addition, we differentiated between antipsychotic monotherapy (using only one

antipsychotic at the specific time point) and polypharmacy (using two or more antipsychotic agents at the same time point). All patients who used first-generation drugs also used second-generation drugs, and due to insufficient information regarding switches and duration of antipsychotic treatments during the follow-up period, it was not possible to calculate cumulative drug exposure.

Cognitive tests

The cognitive test battery is comprised of five cognitive domains (verbal learning, processing speed, working memory, verbal fluency, and inhibition) based on previous findings related to cognitive dysfunction in FEP patients [31].

Psychologists trained in standardized neuropsychological testing carried out the cognitive assessment. Current IQ was estimated from the Wechsler Adult Intelligence Scale (WASI); subscale similarities and block design. Verbal learning was measured with the California Verbal Learning Test (CVLT-II) [32], verbal learning sub-score. Processing speed was measured with the Digit Symbol Test [33]. Working memory was measured with the Letter number sequencing test [33]. Verbal fluency was measured with the Verbal Fluency Test, phonetic sub-score from the Delis–Kaplan Executive Functioning System (D-KEFS) [34]. Finally, inhibition was measured with the Color-Word Interference Test from the D-KEFS [34], inhibition sub-score. Raw scores were reported for all tests to be able to calibrate the cognitive performance of the FEP patients compared to a representative age- and gender-matched HC group from the same catchment area as the patients. Higher scores indicated better performance on all tests except for the inhibition sub-test where higher scores indicated poorer performance. All participants showed an adequate neuropsychological test effort indicated by two errors or less on the forced recognition trial of the California Verbal Learning Task (CVLT-II) [32].

Serum lipids and BMI

Blood was drawn from the antecubital vein in the morning after overnight fasting at baseline and 12 months, on the same day as the neuropsychological testing took place (time period: 2003–2013). The Department of Clinical Chemistry at Oslo University Hospital, using standard enzymatic methods from Roche Diagnostics Norge AS (Oslo, Norway), analyzed cholesterol (total, HDL, LDL) and triglycerides (TG). All blood samples were sent immediately after collection and analyzed continuously as routine samples. Digital weights were used to weight all the participants and body mass index (BMI) calculated accordingly: $BMI = \text{weight (in kilograms)} / \text{height (in meters squared)} (kg/m^2)$.

Statistical analyses

The data were analyzed with SPSS version 23 (SPSS Inc., Chicago, IL, USA/IBM, New York, USA). The level of statistical significance was preset to $p < 0.05$ (two tailed). For the comparison of demographic characteristics, chi-square tests and t tests were used as appropriate.

For the main analyses, we employed linear mixed models with unstructured covariance matrix to examine longitudinal

changes and between-group effects of lipid measures on cognitive measures. Preliminary analyses were conducted to ensure assumptions of normality, linearity, multicollinearity, and homoscedasticity. Serum TG values were ln-transformed after inspection of residuals. Due to issues with multicollinearity, we did not enter all the lipids in the same mixed model analysis. There were no problems with linearity or homoscedasticity.

In separate mixed models, we first examined any baseline differences in metabolic and cognitive measures controlling for age, gender, and education. Then, we explored the 1-year changes in serum lipids, BMI, and cognitive performance. In the latter longitudinal models, we also included time and a group (FEP and HC) \times time interaction.

Our approach to the interpretation of statistical results obtained from the cognitive models was that a main effect of time would indicate cognitive changes due to drug treatment or other causes (i.e., practice effects). To disambiguate the latter two possibilities, we would compare the cognitive performance of the patient group with that of the HC group. Group \times time interactions that favored steeper improvement in the FEP group would be viewed as an indication of a possible treatment effect, reflecting cognitive enhancement. A main effect for time in the absence of such an interaction could be regarded as representing practice effects.

The mixed models that displayed a significant group \times time interaction were subsequently examined for a potential relationship with serum lipids. The rationale for this was that group-specific changes to cognition might be related to alterations in serum lipids due to antipsychotic drug treatment. In these mixed models, the scores from the specific cognitive tests were defined as dependent variables, while time (baseline and 12 months), age, gender, years of education, group affiliation (FEP or HC), and serum lipids were entered as independent variables. To investigate if there was a group-dependent effect of lipids on cognition, we also included a group \times lipid interaction.

In post hoc analyses, using similar mixed models as in our main analyses, we further examined if any group-specific lipid effects on cognition could be explained by ethnicity, lifestyle-related factors (smoking, alcohol, diet, and exercise), concomitant changes in BMI, be secondary to antipsychotic treatment effects on positive and negative symptoms, remission status at 12 months, or be explained by other illness-related factors (hospitalization and depressive symptoms).

Missing data

Preliminary analyses indicated a random distribution of the missing variables and that there were no significant differences in sociodemographic characteristics or cognitive test scores between the subjects with a complete dataset on

serum lipids compared to the ones with missing data (Little's MCAR test: chi-square = 1912.51, $df=1865$, $p=0.22$). Forty-seven (36%) of the FEP patients lacked cognitive data at follow-up. These FEP patients were included in the main analyses because they had baseline data and a mixed linear model approach using all available information was employed. As a precaution, we also checked the validity of our results by repeating the analyses excluding participants with an incomplete dataset.

Results

For a detailed description of demographic characteristics and group comparison of FEP with HC, see Table 1. In summary, the FEP patients had significantly shorter education, more non-Caucasian ethnicity and a higher percentage of daily smokers, compared to the HC.

Group differences in serum lipids at baseline and after 1 year of follow-up

As described in Table 2, the FEP patients had significantly higher levels of total cholesterol and LDL compared to the HC at baseline, ($F=8.94$, $p=0.003$) and ($F=11.54$, $p=0.001$), respectively. During the follow-up, there were no significant changes in mean levels of serum lipids among the FEP patients when compared to the HC at the group level (Table 3). Still, there were individual differences, and at the individual level the serum lipid changes for the FEP were the following: 47 participants (47%) experienced a decrease and 52 participants (53%) an increase in their total cholesterol levels; 49 participants (54%) experienced a decrease and 41 participants (46%) an increase in their HDL levels; 43 participants (50%) experienced a decrease and 43 participants (50%) an increase in their LDL levels; 40 participants (45%) experienced a decrease and 49 participants (55%) an increase in their TG levels.

Group differences in cognition at baseline and after 1 year of follow-up

The FEP patients demonstrated marked impairments in cognitive functioning across all domains at baseline ($p<0.001$) (Table 2). During the 1-year follow-up, there was a main effect of time ($F=17.60$, $p<0.001$) (indicating significant changes in cognitive performance from baseline to 12 months) as well as a group by time interaction for verbal learning ($F=6.86$, $p=0.01$), with a steeper change in FEP compared to HC ($B=3.54$, $p=0.01$), indicating that practice effects alone cannot explain the relatively higher improvement in patients compared to HC. The mixed model analyses also showed a group by time interaction for verbal

fluency ($F=6.38$, $p=0.01$); here, the FEP group exhibited a deterioration in comparison with the HC group, ($B=-3.15$, $p=0.01$), respectively.

Association between serum lipids and cognition

When examining the two cognitive domains that showed a group by time interaction (verbal learning and verbal fluency) for associations with serum lipid levels, we found that there was a significant group by HDL interaction effect for verbal learning ($F=11.12$, $p=0.001$), where an increase in HDL level was related to improvement in verbal learning among FEP patients compared to the HC ($B=10.32$, $p=0.001$). Verbal fluency, in contrast, did not evidence any significant group by lipid interactions. Follow-up analyses excluding patients with incomplete cognitive datasets produced comparable results (data not shown).

Because the FEP patients, in contrast to HC, included several subjects with their primary education outside Norway, which could influence the cognitive test scores, we also reran the analyses without these patients and obtained similar results as in our main analyses (data not shown).

Post hoc analyses exploring the significant associations found between serum lipids and cognition

The post hoc mixed models controlling for antipsychotic usage (i.e., continuous use vs. intermittent use), and positive and negative symptoms indicated that the group (i.e., FEP)-specific link between HDL and verbal learning remained highly significant ($F=7.45$, $p=0.007$). A significant main effect of positive symptoms ($F=4.67$, $p=0.03$) and negative symptoms ($F=11.77$, $p=0.001$), but not for antipsychotic drug use ($F=1.03$, $p=0.31$), was also exhibited. As the magnitude of the effect is reflected in the standardized regression coefficients, we examined these coefficients to discern whether HDL cholesterol had a stronger impact than negative and positive symptoms on verbal learning. Our results indicated that HDL ($B=3.13$, $p=0.007$) was a stronger predictor for verbal learning than were negative ($B=-2.20$, $p=0.001$) and positive symptoms ($B=-1.76$, $p=0.03$). Likewise, controlling for remission status did not significantly impact the observed link between serum HDL and verbal learning in the FEP group ($B=8.42$, $p=0.002$).

We further investigated the influence of antipsychotic drug treatment (continuous use vs. intermittent use, and antipsychotic monotherapy vs. polypharmacy) on the relationship between HDL levels and verbal learning. The group (FEP)-specific HDL-link remained highly significant, ($F=10.76$, $p=0.001$) and ($F=10.54$, $p=0.001$), whereas the main effect of antipsychotic drug treatment was absent,

inferring limited value to differential treatment effects on the observed link between HDL and verbal learning.

Furthermore, though there was a main effect of BMI on verbal learning ($F=4.88$, $p=0.03$), the group by HDL interaction remained significant ($F=9.86$, $p=0.002$) indicating that the link between HDL and verbal learning was independent of BMI. Of note, ethnicity, hospitalization, depressive symptoms, smoking habits, diet, exercise, and alcohol use demonstrated no attenuation of results for the observed link between HDL and verbal learning (data not shown).

Discussion

The current study of antipsychotic-treated FEP patients showed that during the first year of follow-up, an increase in serum HDL was associated with better verbal learning capacity. This relationship was independent of practice effect (as controlled by a group of age- and gender-matched HC), lifestyle, concurrent changes in BMI, and improvements in clinical symptomatology. Having in mind that cognitive performance is an important predictor of longitudinal clinical and functional outcomes in patients with psychotic disorders, our findings may be of clinical relevance.

Consistent with prior literature [35], the FEP patients performed poorer on all cognitive tests compared to the HC. During the follow-up, there was a group-specific improvement in verbal learning, which subsequent analyses showed was associated with an increase in HDL levels among the FEP patients but not amongst HC. Our findings are in line with Lancon and colleagues [18] finding a positive association between HDL and verbal learning and memory in a cross-sectional sample of chronic schizophrenia patients. The present study is, however, the first to report such an association in a cohort of FEP patients with age- and gender-matched healthy controls.

The observed link between HDL and cognition is also consistent with the mechanisms that relate lipids to the brain while also agreeing with evidence of impaired lipid metabolism (including cholesterol) in psychotic patients [36–40]. Lipids are not only essential for myelination; synaptic growth and regeneration also depend greatly on the availability of brain cholesterol [41, 42]. Depletion of cholesterol in tissue cultures has, for example, been shown to inhibit synaptogenesis and causes neurodegenerative changes [42]. Brain structures such as the hippocampus express high transcript levels of lipid-biosynthesizing enzymes [42], are densely populated by synapses, and play a prominent role in verbal learning and memory [43, 44]. Several studies have found a positive link between performances on verbal learning and hippocampal volumes [45–47], as well as on distinct subfield volumes [48]. More importantly, a growing number of evidence in the normal aging population and patients

with neuropsychiatric disorders, points to high serum HDL levels, in particular, being protective against hippocampal atrophy [49]. This dependency of the hippocampus on intact cholesterol metabolism may at least in parts explain our finding of a distinct link between HDL cholesterol and the hippocampus-based task of verbal learning. While studies are reporting a correlation between different cognitive domains within an individual [50–55], there are several investigators that have emphasized a cognitive architecture best described by relatively independent cognitive domains [2, 56–58], and verbal learning is recognized as one such independent cognitive dimension. In further support of distinguishable cognitive dimensions is the fact that pharmacological interventions, including antipsychotic drug treatment, have been shown to cause changes in specific cognitive domains [59], indicating a pharmacological dissociation of certain groups of cognitive processes.

For decades, the traditional view has been that the cholesterol in the brain is synthesized *de novo*; newer evidence, however, suggests that excessive cholesterol synthesis may be regulated by intricate efflux mechanisms linking central and peripheral cholesterol levels [60–63]. Indeed, serum HDL has been found to be highly correlated with HDL in cerebrospinal fluid [64]. Still, the nature of this relationship, between serum lipids and lipids in the CNS, is not fully elucidated. It is, however, likely that long-term lipid status may have a different impact on brain structure and functioning than the short-term impacts observed in treatment studies [19, 20, 65], and that these changes in brain structure and functioning may be more pronounced in the developmental lifespan [66]. While we included a relatively young FEP population (with a mean age of 25 years), future studies may consider including high-risk patients, as well as having a longer study period with frequent observation points.

We recently demonstrated that an increase in HDL during antipsychotic drug treatment was related to an improvement in negative symptoms in the same FEP cohort [25]. Other studies have shown a relationship between negative symptoms and verbal learning [67]. As we now find HDL levels being associated with specific cognitive domains, it is plausible that improvements in cognitive functioning over time were more related to clinical symptom improvement, reflecting “pseudospecificity” [68]. Additionally, lack of motivation and motor retardation inherent in the negative syndrome could also have disturbed test performance in patients with prominent negative symptoms. We attempted to disentangle these phenomena by controlling for secondary changes in negative (and positive) symptoms during antipsychotic drug treatment, obtaining similar results as in our main analyses. Intriguingly, the standardized regression coefficients revealed that the HDL level was more profoundly related to working memory than positive and negative symptoms were, adding support to the growing literature on the role of lipids

in psychotic disorders. Also, other factors that are known to influence cholesterol metabolism as well as cognitive function such as lifestyle and behavioral factors [69–73] were controlled for in the post hoc analyses, achieving similar results as in our main analyses.

The present study has some additional limitations that need to be addressed. The constitution of the HC group was different from the FEP group since the latter included subjects with their primary education from outside Norway, which could influence cognitive performance especially for verbal tests. We tried to minimize the effect of this limitation by controlling for education in the mixed model analyses. Also, we reran the analyses excluding the patients without a Norwegian education, generating similar results. Information on diet and exercise habits was only available for FEP but not for HC. Additionally, self-assessment about diet and exercise may be problematic as it may be linked to high social desirability; on the other hand, achieving truly reliable data on these parameters may be difficult outside the confinement of an institution. Due to power issues, we were not able to examine specifically and compare different antipsychotic agents and how this may influence our results. Still, our main objective was to examine the effect of serum lipids per se on cognition in FEP patients, and for this particular aim, differentiating the antipsychotic agents might be less prudent. We further recognize that other factors than practice can explain a main effect of time: the controls are healthy, and could in theory be susceptible to a ceiling effect in the amount of change that can be achieved; leading to potential differences in the learning potential in the two groups. While an untreated control group may have been ideal to address this matter, it is not ethically feasible. Finally, as our study is naturalistic in design, temporality cannot be established, and studies with a randomized controlled design, which include treatment targeted explicitly at elevating HDL levels and measurements of change in cognitive performance, are necessary.

In conclusion, the present study of antipsychotic-treated FEP patients showed that during the first year of follow-up, an increase in serum HDL was associated with better cognitive performance. Further research, implementing clinical data with for instance myelin-focused brain imaging techniques, is warranted. As cognitive deficits dramatically impact social and occupational functioning, our findings of a link between HDL and cognition could potentially contribute to the development of new treatment strategies, with functional improvements achieved by increasing HDL levels as an add-on treatment for cognitive remediation that has shown to be effective in patients with psychosis.

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Author contributions PBG analyzed the data and was responsible for design of the study, interpretation of results and drafting of the first version of the manuscript together with IM and VMS. OAA, CS, TVL, TU, and NES contributed with data. All authors contributed to the writing of the manuscript and have approved the final version.

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Compliance with ethical standards

Conflict of interest The authors of this paper have no conflict of interests.

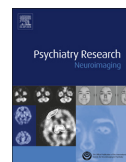
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Association between olanzapine treatment and brain cortical thickness and gray/white matter contrast is moderated by cholesterol in psychotic disorders



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ABSTRACT

Altered cortical brain morphology is observed in psychotic disorders. Despite the importance of lipid homeostasis for healthy brain functioning, knowledge about its role in cortical alterations in psychosis is limited. In a sample of patients with psychotic disorders, we investigated the relationship between treatment with olanzapine (OLZ), and cortical thickness and gray/white matter intensity contrast, and the association between these measures and serum lipid levels. We included 33 OLZ users, 19 unmedicated psychotic patients and 76 healthy controls (HC). Data on serum lipids and cortical measures based on MR brain images processed with FreeSurfer were analyzed with General Linear Models. We found that intensity contrast was similar in OLZ users as compared to HC and that the cortex (frontal, orbitofrontal, medial temporal) was thinner in OLZ users ($p < 0.05$, Bonferroni corrected). An OLZ-specific HDL interaction effect was further found for the pericentral cortical thickness measure ($p < 0.05$, Bonferroni corrected). Additionally, nominally significant findings indicated similar OLZ-specific interaction effects for cortical thickness in several regions, and an OLZ-specific interaction with LDL for occipital lobe contrast ($p < 0.05$, uncorrected). Our findings may suggest a drug-related lipid-effect on brain myelination. Experimental studies and replications in different study samples are needed to clarify these complex relationships further.

1. Introduction

Altered cortical morphology is a replicated brain structural finding in psychotic disorders (Crespo-Facorro et al., 2011; Jung et al., 2011; Narr et al., 2005; Rimol et al., 2012; Schultz et al., 2010; Uranova et al., 2001; Weinberger and Lipska, 1995), and it is widely held that understanding these alterations are key to understanding the pathophysiology of psychosis (Bartzokis, 2012; Lewis and Lieberman, 2000; Murray and Lewis, 1987; Uranova et al., 2001). In schizophrenia, cortical volume has been shown to be reduced primarily in frontal and temporal regions (Hajima et al., 2013; Walterfang et al., 2006). The

reductions are mainly due to cortical thinning, rather than surface area reductions (Rimol et al., 2012). Using structural magnetic resonance imaging (MRI), other properties of the cerebral cortex have been shown to be abnormal in schizophrenia. In a recent study from our group, increased gray/white matter intensity contrast along the cortical surface was observed in primary sensory and motor regions of schizophrenia patients (Jørgensen et al., 2016), known to be highly myelinated areas of the human cerebral cortex (Glasser et al., 2014; Glasser and Van Essen, 2011).

Despite the importance of lipid homeostasis for brain function in health (Orth and Bellosta, 2012; Schmitt et al., 2015), and the mounting

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evidence of altered lipid metabolism in psychotic disorders (Andreassen et al., 2013; De Hert et al., 2006; Fleischhacker et al., 2013; Kaddurah-Daouk et al., 2012; Misiak et al., 2016; Saari et al., 2004; Thakore, 2004; Verma et al., 2009; Wu et al., 2013; Zhai et al., 2017); research on the role of lipid metabolism for cortical thickness or contrast variations observed in psychosis patients is scarce. It is, however, established that impaired lipid metabolism can affect brain myelination (Chrast et al., 2011; Mauch et al., 2001; O'Brien and Sampson, 1965). *In vivo* MR studies as well as post-mortem brain research findings have indicated that abnormal myelination is involved in the pathophysiology of schizophrenia (Davis et al., 2003; Kubicki et al., 2007; Vikhreva et al., 2016). While white matter myelination is the most studied, the cerebral cortex is also myelinated, and cortical myelin is critical for the optimization of brain function (Bartzokis, 2011). *In vivo* MRI and postmortem studies of brains of schizophrenia patients have demonstrated alterations of cortical myelin (Bartzokis, 2012; Bartzokis and Altshuler, 2005; Tishler et al., 2017; Uranova et al., 2011). Hence, it may be hypothesized that altered lipid metabolism can cause alterations of cortical myelination which may be reflected in altered macrostructural properties of the cerebral cortex and detected using MRI. In particular, changes in lipid metabolism are seen during treatment with several of the antipsychotic drugs (Allison et al., 1999; Young et al., 2015), especially olanzapine and clozapine (Newcomer, 2005). Antipsychotic-related increase in lipid levels has furthermore been associated with symptom improvement (Gjerde et al., 2017; Lally et al., 2013; Spivak et al., 1999), and one proposed mechanism is increased myelination (Bartzokis, 2012).

Cortical thickness and cortical gray/white matter intensity contrast are both measures with indirect and partly undetermined relationships with cortical myelin content. For cortical thickness, it is known that the inner layers of the cortex are heavily myelinated (Braitenberg, 1962), and that they constitute a significant fraction of its overall thickness (Rowley et al., 2015). Therefore, increased cortical myelin content is expected to result in increased cortical thickness. The gray/white matter intensity contrast has previously been investigated in normal aging (Salat et al., 2009; Vidal-Pineiro et al., 2016) and illness states including Alzheimer's disease (Salat et al., 2011) and psychiatric disorders (Jørgensen et al., 2016; Kong et al., 2015, 2012). While the biological interpretation of this measure is not fully clarified, it is influenced by genetic variation independent from cortical thickness (Panizzon et al., 2012). The T1 signal itself shows a strong positive relationship with tissue myelin content (Koenig et al., 1991), but given that the gray/white matter contrast is computed as a ratio between values from gray and white matter, increased cortical myelin content is expected to lead to a decrease of the gray/white matter intensity contrast. Therefore, hypotheses with different directionality are needed for these measures.

The present study aimed to determine how treatment with a metabolically potent antipsychotic agent, olanzapine (OLZ), relates to cortical thickness and gray/white matter intensity contrast in patients with non-affective psychotic disorder, and to study the relationship between these cortical measures and serum lipid levels. To distinguish between the effect of illness and antipsychotic treatment on brain structure, we included a group of unmedicated non-affective psychosis patients and a group of healthy control (HC) subjects for comparison. We hypothesized that the OLZ users, in contrast to the unmedicated patients, would be similar to HC in cortical thickness and contrast measures, but show higher cortical thickness and lower gray/white matter contrast compared to unmedicated patients, owing to a putative positive effect of OLZ on cortical myelination. These effects were expected to be widespread, but we also investigated the possibility of region-specific effects. We further hypothesized that serum lipid levels are associated with cortical thickness and contrast measures, with most distinct effects among OLZ users compared to unmedicated patients and HC.

2. Methods

2.1. Study design and sample

For the present cross-sectional study, a total of 52 patients with non-affective psychosis and 76 healthy controls were selected from the ongoing Thematically Organized Psychosis (TOP) study, conducted at the Norwegian Centre for Mental Disorders Research (NORMENT), Oslo, Norway. Inclusion criteria for the main TOP study are a diagnosis of psychotic disorder, age between 18 and 65 years, no history of neurological disorder or severe head injury, and IQ > 70 (for a more detailed description of the TOP study see Engh et al., 2010). The HC were drawn from the Norwegian national population registry and selected from the same catchment area as the patients and excluded if they had current or previous psychiatric illnesses, family history of severe mental disorders, or met criteria for alcohol or substance dependency. There was no age- or gender matching.

Patients were excluded if the time interval between MRI scan and blood sample exceeded 90 days (mean interval = 38.8 days, SD = 28.6). We selected a subsample of patients with non-affective psychotic disorders who were either on stable OLZ monotherapy ($n = 33$) or unmedicated ($n = 19$). Stable monotherapy was defined as using the same daily dose of OLZ (minimum 5 mg) at the time of blood sampling and on the day of MRI. Being unmedicated was defined as the absence of any antipsychotic medication at the time of blood sampling and at the time of MRI scanning. None of participants were using cholesterol-lowering medication (statins or fibrates), or medications against hypertension, diabetes or thyroid disorders.

The distribution of DSM-IV diagnoses in the OLZ group was: schizophrenia, $N = 12$ (36%); schizophreniform disorder, $N = 5$ (15%); schizoaffective, $N = 4$ (12%); and other psychotic disorders (psychosis NOS), $N = 12$ (36%). For the unmedicated group the diagnoses were: schizophrenia, $N = 9$ (47%); schizophreniform disorder $N = 1$ (5%); other psychotic disorder (psychosis NOS) $N = 9$ (48%).

The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study.

2.2. Current and prior medication use in the OLZ group

Information about medication use on the day of MRI scanning was obtained by clinical interview, and supplemented by chart review and information from the clinical assessment. Median OLZ dose was 10 mg (range: 2.5–25 mg) and median duration from the start of OLZ treatment to study time was 3.5 months (range: 0.03 – 132 months). Compliance was assured by measuring antipsychotic drug levels in serum samples.

Of the 33 OLZ users, nine had received previous treatment with other antipsychotic agents; one had received previous treatment with OLZ during two separate time periods while ten had not received any antipsychotic medication before initiating OLZ treatment. Information about previous medication was missing for 13 participants in this group.

2.3. Prior medication use in the unmedicated patient group

Of the 19 unmedicated patients, six were antipsychotic-naïve while ten patients had used antipsychotics previously. Information about previous medication was missing for three participants in this group. Among the ten patients who had received antipsychotic treatment earlier, the average time since last treatment with any antipsychotic medication was 18 months (SD: 16 months, range 3–47 months, data was missing for one patient). Six of these subjects had previously used OLZ (mean dosage 10 mg, SD: 6.1 mg, data missing for one patient). The duration of OLZ treatment was short (< 6 months), except for one patient who had undergone 5 years of OLZ treatment (data missing for two subjects). Average time passed since last

Table 1
Sociodemographic and clinical characteristics among olanzapine-treated (OLZ) and unmedicated patients and healthy controls.

	1. OLZ N = 33	2. Unmedicated N = 19	3. Healthy controls N = 76	p-values	Post-hoc tests
Age (years), mean (SD)	31.0 (11.2)	33.1 (11.1)	31.9 (9.6)	NS	
Gender (male), n (%)	18 (55)	14 (74)	45 (59)	NS	
Ethnicity (Caucasian), n (%)	28 (85)	14 (74)	74 (97)	$\chi^2 (8, N = 128) = 18.09, p = 0.02$	2 vs. 3
Education (years), mean (SD)	13.2 (3.2)	12.2 (2.4)	14.2 (2.4)	$F (2,115) = 3.54, p = 0.03$	2 vs. 3
Handedness (right), n (%)	25 (96)	13 (81)	65 (86)	NS	
Smoking (daily), n (%)	20 (62.5)	8 (47.1)	12 (22)	NS	
Diet, n (%)	H: 23 (71.9) MH: 8 (25.0) UH: 1 (3.1)	H: 10 (58.8) MH: 7 (41.2) UH: 0	NA NA NA	NS	
Exercise, n (%)	L: 21 (70) M: 7 (23.3) F: 2 (6.7)	L: 6 (46.2) M: 5 (38.5) F: 2 (15.4)	NA NA NA	NS	
Alcohol use (AUDIT), mean (SD)	8.0 (8.9)	9.8 (8.4)	NA	NS	
Substance use (DUDIT), mean (SD)	5.7 (10.3)	6.5 (8.1)	NA	NS	
Diagnosis, n (%)	SZ = 12 (36), SF = 5 (15), SA = 4 (12), NOS = 12 (36)	SZ = 9 (47), SF = 1 (5), SA = 0 (0), NOS = 9 (48)	NA	NS	
DUP (weeks), median (range)	16.5 (1–468)	104.0 (1–1040)	NA	$U = 104.5, Z = -2.64, p = 0.01$	1 vs. 2
Duration of illness (years), mean (SD)	2.9 (4.0)	7.6 (7.2)	NA	$t(34) = -2.53, p = 0.02$	
Currently hospitalized, n (%)	6 (18.2)	1 (5.3)	NA	NS	
Previous admissions due to psychosis, mean (SD)	1.3 (1.0)	0.7 (1.1)	NA	NS	
OLZ dosage (mg/day), mean (SD)	11.82 (4.98)	NA	NA	NA	
OLZ treatment duration (months), mean (SD)	19.2(33.3)	NA	NA	NA	
Total PANSS, mean (SD)	54.6 (15.0)	57.1 (10.2)	NA	NS	
Positive PANSS subscores, mean (SD)	11.9 (4.1)	15.3 (4.7)	NA	$t(50) = -2.67, p = 0.01$	1 vs. 2
Negative PANSS subscores, mean (SD)	14.5 (7.4)	11.2 (3.3)	NA	NS	
Global functioning, function (GAF-F), mean (SD)	47.4 (12.1)	47.5 (12.6)	NA	NS	
Global functioning, symptoms (GAF-S), mean (SD)	47.8 (12.2)	44.0 (11.6)	NA	NS	
Total cholesterol (mmol/L), mean (SD)	5.10 (0.10)	5.06 (1.15)	4.99 (0.89)	NS	
HDL (mmol/L), mean (SD)	0.82 (0.18)	0.88 (0.18)	0.91 (0.18)	$F (2,125) = 3.28, p = 0.04$	1 vs. 3
LDL (mmol/L), mean (SD)	3.25 (0.91)	3.14 (0.94)	2.82 (0.72)	$F (2,122) = 3.51, p = 0.03$	1 vs. 3
TG (mmol/L), mean (SD)	0.76 (0.23)	0.70 (0.17)	0.83 (0.33)	NS	
BMI (kg/m ²), mean (SD)	25.4 (3.5)	23.7 (2.1)	24.7 (3.5)	NS	

Groups: 1 = Olanzapine-treated patients (OLZ), 2 = unmedicated patients, 3 = healthy controls. Diet was classified as H = healthy, MH = moderately healthy, and UH = unhealthy. Exercise was classified as L = little, M = moderate, and F = frequent. AUDIT = Alcohol Use Disorder Identification Test, DUDIT = Drug Use Disorder Identification Test, DUP = duration of untreated psychosis, was defined as the number of weeks from the first occurrence of a psychotic symptom above clinical threshold to the first adequate treatment. PANSS = Positive and Negative Syndrome Scale, GAF-F = Global Assessment of Functioning- functions, GAF-S = Global Assessment of Functioning-symptoms, HDL = high-density lipoprotein cholesterol (Ln of HDL values are reported in the table), LDL = low-density lipoprotein cholesterol, TG = triglycerides (Ln of TG values are reported in the table), BMI = body mass index, SZ = schizophrenia, SF = schizophreniform, SA = schizoaffective, NOS = psychosis not otherwise specified, N = number of subjects, NA = not applicable, SD = standard deviation, F = F-test, T = t-test, df = degrees of freedom. P -values are obtained from one-way ANOVA, T -tests, Chi-square test and Mann-Whitney U test. Post-hoc tests (t -tests) were performed for the F -tests that were significant and we only report the significant group differences.

olanzapine treatment was 21 months (SD: 22 months, range 5–53 months, data missing for two patients). For details of the unmedicated group see Table 1.

2.4. Clinical assessment

Trained psychiatrists or clinical psychologists interviewed the patients. Sociodemographic history (age, gender, ethnicity, education level), current smoking, alcohol consumption, substance use, duration of untreated psychosis (DUP), illness duration, global functioning, psychiatric symptoms, previous or current psychiatric hospitalization and antipsychotic medication were recorded from interviews and medical records.

All patients were diagnosed using the Structural Clinical Interview for DSM-IV (SCID) (First et al. 1996). Psychotic symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). DUP was defined as the number of weeks from the first occurrence of a psychotic symptom above clinical threshold to the first adequate treatment (for details see Bratlien et al., 2013). Global functioning was assessed using the Global Assessment of Functioning (GAF) split version (with separate scales for symptoms (GAF-S) and functioning (GAF-F)) (Pedersen et al., 2007). Alcohol and substance use was measured with the Alcohol Use Disorders Identification Test (AUDIT)

(Saunders et al., 1993) and the Drug Use Disorders Identification Test (DUDIT) (Berman et al., 2005). In patients' interviews, information regarding diet (classified as healthy, moderately healthy or unhealthy) and exercise habits (classified as light, moderate or frequent) was obtained, these data were however not available for the HC.

2.5. Serum lipid measurements

Blood was sampled in the morning after overnight fasting. Cholesterols (total, HDL, LDL) and triglycerides (TG) were analyzed at the Department of Clinical Chemistry at Oslo University Hospital with standard enzymatic methods (Roche Diagnostics Norge AS, Oslo, Norway). Sampling was conducted between the years 2004–2011.

2.6. MRI acquisition

Subjects were scanned at Oslo University Hospital, Ullevål, using a Siemens Magnetom Sonata 1.5T system (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard eight-channel head coil. Two sagittal T1-weighted images (MPRAGE) were acquired using the $tf3d1_ns$ pulse sequence, with the following parameters: Echo time = 3.93 ms, repetition time = 2730 ms, inversion time = 1000 ms, flip angle = 7°, field of view = 24 cm, voxel

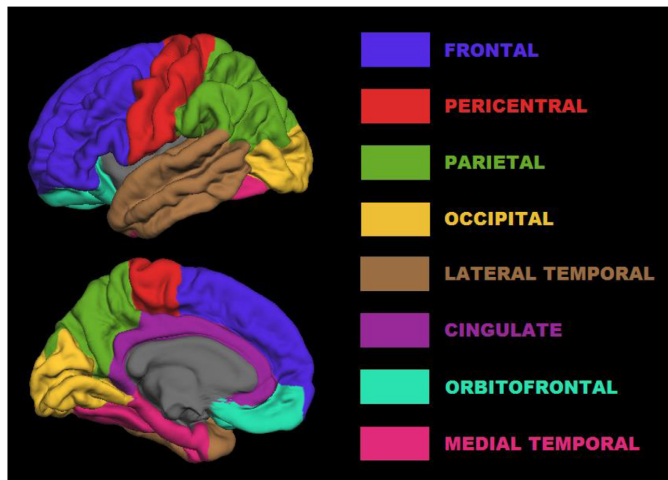


Fig. 1. Overview of the eight lobar regions that were used in the analyses.

size = $1.33 \times 0.94 \times 1$ mm, number of partitions = 160. Acquisition parameters were optimized for increased cortical contrast. A neuroradiologist evaluated all scans for brain pathology.

2.7. MRI processing and calculation of cortical thickness

Three-dimensional models of the cortical surfaces were created using FreeSurfer 5.3.0 (<http://surfer.nmr.mgh.harvard.edu/>). Detailed description of the FreeSurfer processing steps can be found in Fischl (2012). All surfaces were inspected, and manual editing was performed according to standard FreeSurfer quality control procedures. From the reconstructed surfaces, cortical thickness was measured as the shortest distance from the white to the pial surface at each vertex. For the main analyses, we extracted average cortical thickness for each label in the Desikan-Killiany atlas (34 regions) (Desikan et al., 2006) and merged 33 of these labels (all except the insular cortex) into eight bilateral lobar regions, as shown in Fig. 1. Average cortical thickness across the cortical surface was also extracted. Additionally, vertex-wise analyses using the GLM function in FreeSurfer were performed to probe more region-specific effects. Correction for multiple comparisons was applied using FDR set at 5%. We further explored group differences using a more lenient threshold of $p < 0.01$, uncorrected (Supplementary Fig. 1).

2.8. Calculation of cortical contrast

The cortical contrast was defined as the normalized difference between signal intensity values at each side of the gray/white matter boundary. Specifically, intensity values were sampled from the non-uniform intensity normalized volume (nu.mgz) along the reconstructed gray/white matter boundary using `mri_vol2surf`. In GM, an average of intensity values sampled from 0–60% into the cortical ribbon was obtained at each vertex. In the white matter, intensity values sampled from 0–1.5 mm into the subcortical white matter were obtained at each vertex. The percentage difference between gray matter and white matter intensity values was then calculated at each vertex, as the difference between the two divided by their mean $\times 100$ (for details see Jørgensen et al., 2016). Average percentage contrast was then calculated for each of the eight lobar regions described above, and for the whole cortical surface. In our previous study (Jørgensen et al., 2016) we observed low to moderate and region-specific correlations between

cortical thickness and cortical gray/white matter intensity contrast. In the present study, cortical thickness and contrast were also correlated in all regions except for cingulate and pericentral cortex (Supplementary Table 1).

2.9. Statistical analyses

Statistical analyses were performed using SPSS version 23 (SPSS Inc, Chicago, IL, USA / IBM, New York, USA). For comparison of demographic and clinical characteristics, one-way ANOVA, Student's *t*-test, Mann-Whitney *U* test and χ^2 statistics were used. Two-sided tests were used for all analyses, and the significance level was set at $p \leq 0.05$.

For the main analyses, a set of General Linear Models (GLM) was applied covarying for age and sex. Group (OLZ-treated patients, unmedicated patients or HC) was entered as a factor. Cortical intensity contrast and cortical thickness were investigated as dependent variables in separate models along with each metabolic parameter (total cholesterol, HDL, LDL, TG) as the independent variable. OLZ users and unmedicated patients were compared with HC, and with each other. We also tested a group \times lipid interaction with HC as a reference group. Serum HDL and TG were ln-transformed to obtain a normal distribution.

A sequential Bonferroni correction procedure was applied for multiple testing. First, we corrected the *F*-tests, where eight regions of interest gave a corrected *p*-value of $0.05 / 8 = 0.00625$. Bonferroni post-hoc tests were applied subsequently for each test. For the regression analyses with serum lipids, a corrected *p*-value of 0.00625 was used.

Additional post-hoc analyses were performed to investigate potential confounding. Variables that were significantly different between the groups (ethnicity, education, DUP, illness duration and positive symptoms, see Table 1) were treated as potential confounders. By adding these variables to each of the group comparisons described above, using separate models to examine the contribution of each potential confounder, we examined if our variable of interest (*group*) remained significant also in these models. In addition, as previous studies have indicated that BMI change may be related to brain volume change (Jørgensen et al., 2017) and serum HDL levels to negative symptoms (Gjerde et al., 2017), we also controlled for these factors in separate models.

Clinical correlates (i.e. positive and negative symptoms) of our lipid findings were further examined with partial correlations controlling for

age and gender within the OLZ group. Similar partial correlations were used to examine the influence of OLZ dose and duration on serum lipid levels.

Finally, we conducted post-hoc power analyses using the statistical package G*Power (3.1.9.3 for Mac).

3. Results

Demographic and clinical characteristics are shown in Table 1. In summary, the HC group had a higher percentage of Caucasians compared to OLZ users and unmedicated patients, and higher HDL and lower LDL levels compared to OLZ users. Moreover, OLZ users had shorter DUP, shorter duration of illness, and less positive symptoms compared to the unmedicated patients. There were no significant differences in diagnostic distribution, hospitalization status, global functioning, smoking, alcohol use, illicit drug use, diet, exercise, serum lipid values or BMI between the two patient groups.

3.1. Group comparisons of intensity contrast

The OLZ users had similar cortical gray/white matter intensity contrast measures as the HC ($p < 0.05$, Bonferroni corrected) (Table 2). Although the unmedicated patients had higher nominally intensity contrast compared to HC (frontal, cingulate, lateral temporal, and medial temporal regions) ($p < 0.05$, uncorrected), they did not remain significant after correction for multiple comparisons ($p > 0.05$, Bonferroni corrected)

3.2. Group comparisons of cortical thickness

OLZ users had significantly thinner cortices compared to HC in frontal, orbitofrontal, and medial temporal regions ($p < 0.05$, Bonferroni corrected) (Table 2), while there were no significant differences in cortical thickness between unmedicated patients and HC

(Table 2).

3.3. Examining group difference in vertex-wise analyses

In the vertex-wise analyses, no significant group differences were found in cortical thickness or contrast after FDR correction. For completeness, regions showing significant group differences using a threshold of $p < 0.01$ (uncorrected) are shown in the Supplementary Fig. 1.

3.4. Group specific interactions with lipid levels for cortical thickness and intensity contrast

There was a group specific interaction with HDL cholesterol where OLZ treated patients with higher HDL levels had thicker cortices in mean, frontal, orbitofrontal, cingulate, occipital, and pericentral regions ($p < 0.05$, uncorrected). However, only the pericentral region remained significant after correcting for multiple comparisons ($p < 0.05$, Bonferroni corrected) (Supplementary Table 2). No interactions were found between HDL levels and thickness measures among unmedicated patients or HC. Also, there were no significant interactions between group and total cholesterol/TG/LDL levels for cortical thickness.

For the gray/white matter intensity contrast, a group-specific interaction with LDL cholesterol for occipital lobe contrast was observed where higher LDL levels were associated with higher intensity contrast in OLZ users specifically ($p < 0.05$, uncorrected) (Supplementary Table 2). However, this interaction did not remain significant after corrections for multiple comparisons were applied ($p > 0.05$, Bonferroni corrected).

Table 2
Group differences in cortical thickness (mm) and gray/white matter intensity contrast.

	1. OLZ, Estimate (SD)	2. Unmedicated, Estimate (SD)	3. Healthy controls, Estimate (SD)	F-test	Post-hoc tests, 1 vs. 3, 2 vs. 3 and 2 vs. 1
Cortical thickness (mm)					
Mean thickness	2.29 (0.02)	2.36 (0.02)	2.35 (0.01)	$F(2,123) = 4.50, p = 0.01$	
Frontal	2.40 (0.02)	2.48 (0.03)	2.49 (0.01)	$F(2,123) = 5.97, p = 0.003$	1 vs. 3 $p = 0.003$, 2 vs. 3 $p = NS$, 2 vs. 1 $p = NS$
Orbitofrontal	2.40 (0.02)	2.47 (0.03)	2.48 (0.01)	$F(2,123) = 5.60, p = 0.005$	1 vs. 3 $p = 0.004$, 2 vs. 3 $p = NS$, 2 vs. 1 $p = NS$
Cingulate	2.50 (0.02)	2.53 (0.03)	2.53 (0.01)	$F(2,123) = 0.91, p = 0.41$	
Lateral temporal	2.67 (0.02)	2.75 (0.03)	2.75 (0.02)	$F(2,123) = 4.63, p = 0.01$	
Medial temporal	2.64 (0.02)	2.73 (0.03)	2.73 (0.02)	$F(2,123) = 6.08, p = 0.003$	1 vs. 3 $p = 0.003$, 2 vs. 3 $p = NS$, 2 vs. 1 $p = NS$
Parietal	2.10 (0.02)	2.17 (0.03)	2.14 (0.01)	$F(2,123) = 2.46, p = 0.09$	
Occipital	1.86 (0.02)	1.87 (0.02)	1.86 (0.01)	$F(2,123) = 0.12, p = 0.89$	
Pericentral	2.06 (0.02)	2.13 (0.03)	2.10 (0.01)	$F(2,123) = 2.56, p = 0.08$	
Cortical gray/white matter intensity contrast					
Total mean contrast	27.39 (0.24)	28.30 (0.32)	27.68 (0.16)	$F(2,123) = 2.62, p = 0.08$	
Frontal	28.36 (0.28)	29.91 (0.19)	29.63 (0.38)	$F(2,123) = 3.71, p = 0.03$	
Orbitofrontal	29.01 (0.28)	30.15 (0.38)	29.50 (0.19)	$F(2,123) = 2.95, p = 0.06$	
Cingulate	29.58 (0.26)	30.66 (0.35)	29.95 (0.17)	$F(2,123) = 3.07, p = 0.05$	
Lateral temporal	29.31 (0.27)	30.43 (0.36)	29.74 (0.18)	$F(2,123) = 3.12, p = 0.05$	
Medial temporal	28.77 (0.27)	29.92 (0.37)	29.19 (0.18)	$F(2,123) = 3.16, p = 0.05$	
Parietal	27.37 (0.24)	28.13 (0.32)	27.58 (0.16)	$F(2,123) = 1.87, p = 0.16$	
Occipital	24.56 (0.23)	24.97 (0.31)	24.42 (0.15)	$F(2,123) = 1.33, p = 0.27$	
Pericentral	24.28 (0.21)	24.87 (0.28)	24.36 (0.14)	$F(2,123) = 1.59, p = 0.21$	

The uncorrected p -values for group 2 (unmedicated) vs. group 3 (HC) were between 0.07–0.09.

Groups: 1 = Olanzapine-treated patients (OLZ), 2 = unmedicated patients, 3 = healthy controls. NS = not significant, $p = p$ -values. Analyzed with GLM adjusted for age, gender and group. Specific hypothesis testing if OLZ users (1) were more alike HC (3), and if unmedicated patients (2) were different from HC (3). Only the post-hoc tests that remained significant after sequential Bonferroni procedure are reported.

Of note, for the cortical gray/white matter intensity contrast, the uncorrected p -values were significant for group 2 (unmedicated) vs. group 1 (OLZ) comparisons for frontal, cingulate, lateral temporal, and medial temporal regions ($p < 0.05$, uncorrected).

3.5. Post hoc analyses

3.5.1. Examining the influence of demography and illness on the observed group and lipid specific relationships

In general, the group effects found in the main analyses remained significant when controlling for potential confounders, including ethnicity, education, DUP, illness duration, and positive symptoms ($p < 0.05$, uncorrected) (for details see Supplementary Tables 3a and 3b). Moreover, the significant interactions demonstrated in the main analyses (HDL \times group for cortical thicknesses and LDL \times group for intensity contrast), remained significant when controlling for BMI and negative symptoms ($p < 0.05$, uncorrected). Of note, neither BMI nor negative symptoms were significantly related to cortical thickness or contrast (data not shown).

3.5.2. Post hoc analyses examining the clinical relevance of the serum lipid levels

Partial correlations controlling for age and gender, demonstrated no significant correlations between serum HDL (or LDL) levels and severity of positive and negative symptoms (data not shown).

3.5.3. Serum lipid levels in relation to dose and duration of OLZ treatment

Partial correlation analyses controlling for age and gender showed no significant correlations between HDL and LDL levels, and OLZ dose and duration (data not shown).

3.5.4. Post-hoc power analyses

Post-hoc power analyses showed that the statistical power in our study was between 0.5–0.7 for intensity contrast measures, 0.5–0.9 for the thickness measures, and 0.5–0.7 for the interaction term group \times HDL; thus, medium-strong power.

4. Discussion

The main findings of the present study were that the gray/white matter intensity contrast in OLZ users was comparable to the HC, but increased in the unmedicated patients. This is consistent with the hypothesized “normalizing” effect of OLZ treatment on contrast measures. Furthermore, although a general thinning of the cortex was found in OLZ users, a moderating effect of serum HDL cholesterol was also observed; an effect possibly explained by increased access to lipids during antipsychotic drug treatment with implications on lipids related cortical measures.

Coherent with our hypothesis, the cortical gray/white matter intensity contrast was comparable in OLZ users and HC. The unmedicated patients, on the other hand, displayed nominally higher intensity contrasts. While increased gray/white matter contrast in unmedicated patients theoretically could be caused by both lower gray matter intensity values (i.e. lower cortical myelin content) or higher white matter intensity values (or a combination of the two), they overlap with heavily myelinated regions based on MRI-based myelin mapping and post-mortem studies (Glasser et al., 2014; Glasser and Van Essen, 2011). Thus, reduced tissue contrast could reflect higher gray-matter signal intensity, reflecting increased cortical myelin content coherent with our hypothesis (Jørgensen et al., 2016). Still, it is important to acknowledge that the unmedicated group did not consist of solely drug-naïve patients. We can therefore not rule out that prior antipsychotic exposure and illness chronicity could have influenced our findings.

Contrary to our initial hypothesis, we found that the OLZ group had reduced cortical thickness in frontal, orbitofrontal, and medial temporal cortex compared to HC, while the unmedicated patients did not differ significantly from the HC. Indices related to illness severity including symptom load (Ho et al., 2011; Lieberman et al., 2005), hospitalizations (Lieberman et al., 2001) and poorer social functioning (Lieberman et al., 2001) have previously been associated with reduced brain volumes and cortical thinning. In our study, the DUP and illness

duration were longer, and the severity of positive symptoms was greater among the unmedicated patients, who also had a trend towards fewer hospital admissions. Thus, the data did not unequivocally indicate that the OLZ treated patients were a more severely affected group. Our findings converge to some degree with a recently published systematic review examining the relationship between long-term antipsychotic drug treatment (>2 years) and changes in brain structure, reporting that higher drug exposure was associated with parietal volume decrease, and trend-wise with decreases in frontal, temporal, and occipital lobe (Huhtaniska et al., 2017). Our findings further agree with a study published in JAMA Psychiatry (Lesh et al., 2015) demonstrating thinner cortices in antipsychotic treated patients compared to a group of unmedicated patients. Intriguingly, in the latter study, the authors found no evidence of detrimental effects of atypical antipsychotics on cognition or brain activity, underscoring the complexity of the relationship between medications induced effects on brain structures and their clinical relevance.

Our findings further show that in the OLZ group but not in the unmedicated or in the HC group, there was a positive association between serum HDL levels and cortical thickness. To our knowledge, this has not previously been reported. While the cross-sectional design does not allow for inference of causal relationships, there is substantial evidence from *in vivo* MRI and animal studies indicating lipogenic and pro-myelinating effects of atypical antipsychotic drugs (Bartzokis et al., 2012, 2009, 2007; Ebdrup et al., 2016; Erslund et al., 2017; Fernø et al., 2009, 2006, 2005; Steen et al., 2017; Vik-Mo et al., 2008; Vita et al., 2015; Xu et al., 2010; Zhang et al., 2012). Therefore, a potential explanation for the increased cortical thickness in the subgroup of OLZ patients with higher HDL levels may be a cholesterol-dependent effect on myelin. Indeed, HDL in serum may serve as a proxy for cholesterol supply in the brain (Fagan et al., 2000), where improved supply could have a positive effect on myelin. Antipsychotic drugs also upregulate the expression of cholesterol transport proteins (Vik-Mo et al., 2009) and changes in body cholesterol balances have been shown to alter myelin integrity (Dietschy and Turley, 2001). In fact, the specific association between HDL and cortical thickness could perhaps be explained by the fact that HDL can cross the blood-brain barrier (Di Paolo and Kim, 2011; Ferretti and Bacchetti, 2011; Roheim et al., 1979). Increased availability of cholesterol, especially HDL, has further been shown to impact synaptic plasticity and vesicle formation (Koudinov and Koudinova, 2001; Mauch et al., 2001).

A growing number of studies in various neuropsychiatric disorders links higher levels of HDL with less cognitive impairments (Merched et al., 2000; van Exel et al., 2002). Moreover, a recent study of first episode psychosis patients demonstrated that an increase in serum HDL levels during antipsychotic drug treatment was associated with improvement in negative symptoms (Gjerde et al., 2017). Controlling for negative symptoms and education in the present study, no significant changes of the results were found. The specific areas that displayed significant HDL \times group interaction with a thicker cortex in OLZ users (uncorrected) correspond with areas implicated in cognitive deficits, negative symptoms, hallucinations and self-disturbance, which are all core phenomenological features of schizophrenia (Kaufmann et al., 2015; Morch-Johnsen et al., 2015; Shergill et al., 2014).

In the present study, higher levels of LDL were related to higher cortical contrast in OLZ users as compared to the other two groups. However, this interaction did not remain significant after Bonferroni correction. Our findings coincide to some degree with data from a longitudinal study by Szeszko et al. (2014) of first episode psychosis patients treated with atypical antipsychotic drugs (risperidone or aripiprazole) where a significant association was found between increase of LDL levels and reduction in fractional anisotropy as measured by diffusion tensor imaging. Though, a direct effect of LDL on myelin cannot be proven based on the present data, LDL is a risk factor for cardiovascular disease and may indirectly affect thickness through hemodynamic changes (Alosco et al., 2014).

The present study has some limitations that need to be addressed. The naturalistic and cross-sectional study design is a constraint, as causality cannot be determined. Moreover, we did not have enough statistical power to detect small differences in cortical measures. Although we controlled for several potential confounders, including BMI (Jørgensen et al., 2017), we cannot rule out that the medicated and unmedicated groups might differ in other respects as a result of selection by treatment status. Likewise, the HC were screened for mental disorders and cannabis use during the last 3 months; this could have contributed to a more healthy comparison group compared to e.g. the use of unselected population-based control samples. We also lacked data on alcohol, diet, and exercise habits for the HC. Regarding antipsychotic drug treatment, the time interval for OLZ treatment effect on brain structures has not been well clarified. In our sample the duration of OLZ treatment varied (median duration was 3.5 months, range: 0.03–132 months). Longitudinal studies with prolonged monotherapy treatments are needed to address this issue in greater details. Many of the patients in the unmedicated group had prior antipsychotic drug exposure; ideally to clarify the differential effect of illness and antipsychotic drug treatment, investigations in previously drug-naïve patients are preferred. Moreover, while myelin strongly contributes to T1 signal intensity (Koenig et al., 1991), the signal is also influenced by tissue properties including water and iron content, and distinguishing which of these properties contribute to relative differences is not straightforward. To examine potential drug-related pro-myelinating effects directly, cortical myelin mapping using the T1/T2 ratio (Glasser and Van Essen, 2011; Lutti et al., 2014) and field maps during scan acquisitions should be obtained to allow for optimal correction.

To conclude, the cortical gray/white matter intensity contrast was found to be similar among users of the atypical antipsychotic OLZ and HC, suggesting comparable cortical myelin content. Despite the general thinning of the cortex in the OLZ users, there was a moderating effect of HDL on cortical thickness, which may indicate increased cortical myelin among the OLZ users. While the current findings may inform about the neurobiology of antipsychotic drug treatment, experimental studies are needed to determine the mechanisms involved.

Contributors

PBG analyzed the data and was responsible for the design of the study, interpretation of results and drafting of the first version of the manuscript, together with KNJ, IA, and VMS. NES, OAA, and IM contributed with data and writing of the manuscript. All authors have approved the final version.

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Conflict of interest

OAA has received speakers honorarium from Lundbeck. The other authors of this paper have no conflict of interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.10.001.

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