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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.

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-naive 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

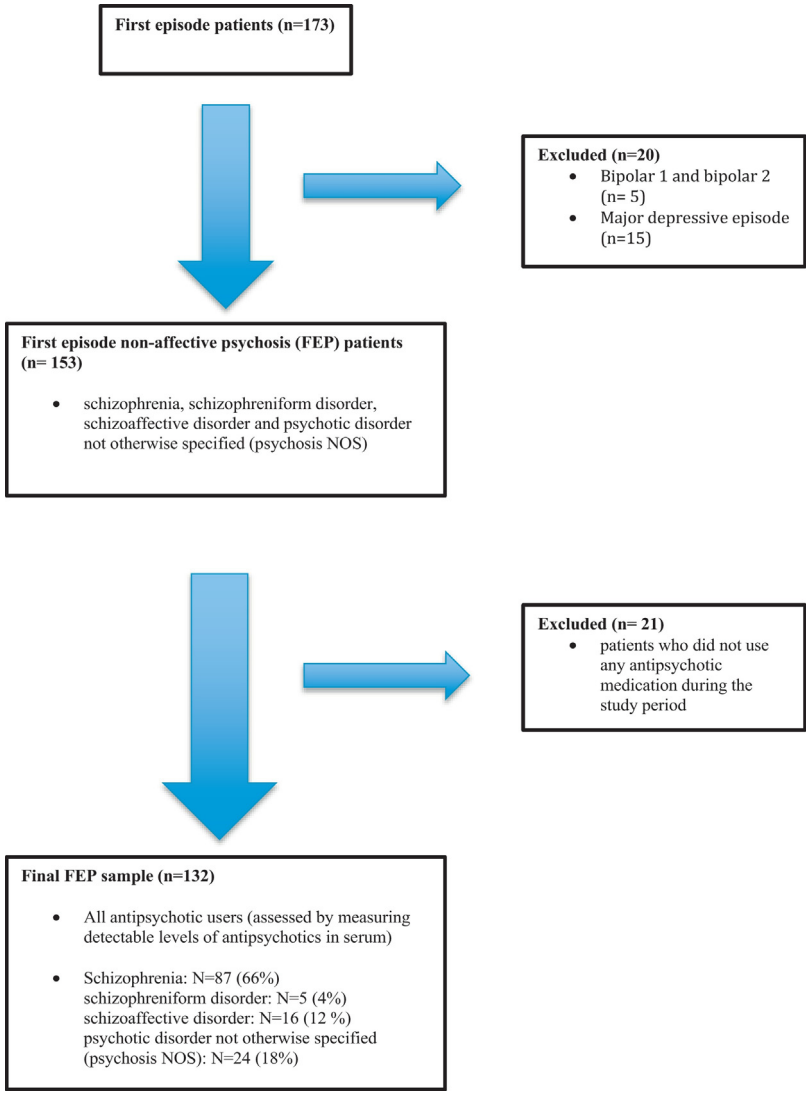

Fig. 1. Participants flow chart.

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 = 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, ziprasidon 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 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. ≥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 =

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

	n	Baseline	12 months	Δ	t (df)	*p*-value
		mean (SD)	mean (SD)	mean (SD)		
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/m2)	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.

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2017.10.042.

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