Lipid alterations in adolescents with early-onset psychosis may be independent of antipsychotic medication

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A R T I C L E  I N F O
Article history:
Received 6 March 2019
Accepted 22 November 2019
Available online 30 November 2019

Keywords:
Dyslipidemia
Cholesterol
Triglycerides
Insulin resistance
Negative symptoms

A B S T R A C T

Background: Dyslipidemia and insulin resistance (HOMA-IR) are cardiovascular risk factors prevalent in patients with psychosis. Whether these factors are intrinsic or affected by lifestyle or antipsychotic medication (AP) is unclear. Therefore, we investigated lipid profiles, HOMA-IR, and psychotic phenotypes in patients aged 12–18 years with early-onset psychosis (EOP) with and without AP exposure.

Method: We measured fasting total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), insulin, and glucose in patients with EOP (n = 39) and healthy controls (HC) (n = 66). Diet information was not available. Negative symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). We used univariate analysis of variance to compare TC/HDL-C ratios and TG and HOMA-IR values, controlling for body mass index (BMI) and AP exposure. We assessed the explained variance of having EOP using multiple regression analysis.

Results: Patients with and without AP exposure had significantly higher TC/HDL-C (p = 0.003, p = 0.029) and TG values (p < 0.001, p = 0.021) than HC. Significantly increased HOMA-IR scores were found only in AP-exposed patients (p = 0.037). EOP significantly increased the explained variance for TC/HDL-C and TG, but not for HOMA-IR. Patients with a PANSS negative score > 21 had significantly higher levels of TG than those with low scores (p = 0.032).

Conclusion: Our results suggest that lipid alterations predate AP treatment in adolescents with EOP. Higher levels of negative symptoms and AP further increase metabolic risk. The preliminary findings propose that subclinical dyslipidemia may be intrinsic to EOP.

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1. Introduction

Persons with severe mental disorders have an estimated reduction in their life expectancy of 15 years compared with the general population (Hjorthøj et al., 2017). Dyslipidemia and insulin resistance (IR) are cardiovascular disease (CVD) risk factors prevalent in persons with psychosis (Horsdal et al., 2017; Misiak et al., 2017; Pillinger et al., 2017b), who show a 78% higher risk for developing CVD, and an 85% higher mortality rate from CVD compared with the general population (Correll et al., 2017). The accumulation of CVD risk factors in persons with psychosis has traditionally been attributed mainly to unhealthy lifestyles (Jakobsen et al., 2018; Storch Jakobsen et al., 2018) and metabolic adversities from antipsychotic medication (AP) (De Hert et al., 2011). However, other factors might also play roles.

Psychosis is a heterogeneous disease entity (Jablensky, 2006) in which altered lipid biosynthesis is one of several candidate pathophysiological mechanisms. Abnormal responses to a niacin skin flush test, indicative of alterations in lipid metabolism, are found in 30% of patients with schizophrenia (SCZ) and are also more prevalent in their healthy relatives (Messamore, 2017; Yao et al., 2016). Overlap between genetic polymorphisms associated with both SCZ and lipid metabolism has been demonstrated, implicating the involvement of lipid biology in the pathophysiology of SCZ (Andreassen et al., 2013). Alterations in fatty acid and cell membrane lipid compositions have been described in blood, erythrocyte membranes, and post-mortem brains from...
patients with SCZ (Bentsen et al., 2012; Ghosh et al., 2017; Taha et al., 2013; Yang et al., 2017). Previous studies have described positive associations between AP treatment response, cognition, and elevations in serum lipids (Gjerde et al., 2017; Krakowski and Czobor, 2011; Lally et al., 2013; Procyslyn et al., 2007; Solberg et al., 2016). This seems to indicate that altered lipid metabolism might be closely associated with psychotic disorders such as SCZ.

As a key metabolic hormone, insulin regulates cellular energy metabolism (Saltiel and Kahn, 2001), and IR can alter lipid metabolism leading to the development of atherogenic dyslipidemia (Ormazabal et al., 2018). Increased risks of prediabetes and type 2 diabetes have been described in adults with AP-naive first episode psychosis (FEP) (Greenhalgh et al., 2017; Perry et al., 2016; Pillinger et al., 2017a).

Different expression of psychotic symptoms is suggested to represent heterogeneity in the underlying etiology (Martuuzzi et al., 2019). Phenotypes characterized by high levels of negative symptoms or a long duration of untreated psychosis (DUP) are associated with poorer functional outcomes (Fervaha et al., 2014; Friis et al., 2016). Therefore, patients with higher levels of negative symptoms or a longer DUP could have psychotic disorders with different pathophysiological underpinnings. We hypothesized that they would feature more lipid biological alterations, as higher serum triglycerides (TG) and total cholesterol (TC) levels at baseline have been associated with poorer function and more severe psychotic symptoms at a 5-year follow-up (Solberg et al., 2016).

Disentangling preexisting CVD risks from treatment effects in patients with psychosis is challenged by confounders and diverse/differing study populations. The latter is illustrated by the finding of progressive increases in the prevalence rates of hyperglycemia, diabetes, and low serum levels of high density lipoprotein cholesterol (HDL—C) in study populations grouped according to adult FEP, unmedicated, and medicated patients not in their first episode (Mitchell et al., 2013). Furthermore, nearly all studies on FEP have been conducted on adults with a mean age of ≥25 years. We know that age itself influences lipid and lipoprotein levels, as demonstrated by population-based reference values (Balder et al., 2017; Jolliffe and Janssen, 2006). Finally, most studies use a broad definition of FEP, either not defined (Misiak et al., 2017) or with a duration of illness of ≤5 years from onset (Pillinger et al., 2017b).

Although patients with early-onset psychosis (EOP) defined as the onset of psychosis <18 years tend to be somatically healthy, in their FEP, within a limited age range, and to have short or no exposure to AP and few CVD risk factors related to lifestyle, studies are lacking on lipid alterations and IR in adolescents with EOP. We hypothesized that adolescents with EOP exhibit intrinsic metabolic alterations in atherogenic direction. Therefore, we investigated (i) whether patients with EOP have atherogenic alterations in metabolic measures (i.e. increased serum levels of TC, low-density lipoprotein cholesterol (LDL-C), TG, increased TC/HDL-C ratio and HOMA-IR, and decreased levels of HDL—C), independent of exposure to AP, (ii) how much of the variance in metabolic measures is explained by having psychosis, after controlling for body mass index (BMI), sex, and exposure to AP, and (iii) whether alterations in metabolic measures are more pronounced in patients with a more severe clinical presentation, by using the levels of negative symptoms, DUP, and diagnosis.

2. Materials and methods

2.1. Study design

All participants were part of the ongoing longitudinal case-controlled Thematically-Organized-Psychosis Study for Youth (Youth-TOP), at the University of Oslo and Oslo University Hospital, part of the TOP research group, Norwegian Centre for Mental Disorder Research, Norway. Here we used only baseline data. Patients with an established or suspected diagnosis of psychosis were recruited from child and adolescent psychiatric in- and outpatient units at hospitals in Oslo and Akershus counties, Norway. They were initially assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and from a review of their medical records. Those with a clear history of psychosis and/or reaching thresholds of current psychotic symptoms were diagnosed further. Inclusion criteria were: (1) meeting the American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria of either SCZ spectrum disorder (SCZ, schizoaffective disorder, schizoaffective disorder); having an affective psychotic disorder (bipolar spectrum disorder, major depressive disorder with psychosis) or other psychotic disorders (psychosis not otherwise specified [NOS], delusional and brief psychotic disorders); (2) aged 12–18 years; (3) being able to provide written consent; and (4) being able to communicate in Norwegian.

Exclusion criteria were: (1) an intelligence quotient (IQ) <70; (2) previous moderate/severe head injury; (3) a diagnosis of substance-induced psychotic disorder; or (4) having organic psychosis. Healthy controls (HC) aged 12–18 years were recruited from the same catchment area as the patients, randomly drawn from the national population registry (www.ssb.no), and invited by letter to participate. HC subjects were excluded if they: (1) currently met criteria for, or previously had received treatment for, any Axis I diagnosis; (2) an IQ <70; (3) a history of organic brain disease; or (4) previous moderate/severe head injury.

Participation was based on informed consent and conducted in accordance with the Helsinki Declaration, version 2008 (sixth revision). For those aged <16 years, consent was provided by parents or guardians. This study was approved by the Regional Ethics Committee (South-East) for Medical and Health Research Ethics (2009/691) and the Norwegian Data Protection Authority (2003/2052).

2.2. Participants

We included patients (n = 39) and HC (n = 66), enrolled between January 2013 and October 2017, with fasting serum lipid, insulin, and glucose values available. None of the participants used antidiabetic or lipid-modifying medications, and all were somatically healthy, with no comorbid substance abuse or dependence. 81% of the HC and 87% of the patients did not report any family history of CVD, lipid abnormalities, diabetes mellitus or obesity (BMI ≥ 30) in 1st degree relatives, with no significant differences ($\chi^2 = 0.64, p$-value = 0.423) (See Supplementary Table 5). The distributions of diagnoses were: SCZ spectrum (n = 20); affective psychosis (n = 4); and psychosis NOS (n = 15). At inclusion, all patients were under treatment for a psychotic disorder, with a duration of illness of 0.07–6.35 years (median 1.1 years).

2.3. Clinical variables

All participants were interviewed with the Norwegian version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Kaufman et al., 1997), performed by trained staff-clinicians (medical doctors or psychologists). Each diagnosis was established in a consensus meeting with a child- and adolescent-psychiatrist on the basis of DSM-IV criteria and all available clinical information. All staff-clinicians attended regular training and supervision by experienced clinical researchers in the psychosis field.

Global functioning was measured by Children’s Global Assessment scale (Shaffer et al., 1983). BMI was calculated using a standard formula as weight divided by height squared (kg/m$^2$). Data were obtained from body weight measured on calibrated digital balances and height was measured manually; both measurements were conducted under equal conditions. Imputations were made for four patients and three HC with missing height values. In such cases, approximate height for age for adolescents was based on the 50th percentile from the Norwegian reference height/age chart (Juliusson et al., 2013).
Clinical and sociodemographic data (DUP, ethnicity, mother’s educational level, physical activity and family history of either CVD, diabetes mellitus, obesity (defined as BMI ≥ 30) or hypertension) were obtained through clinical interviews with participants or parents, whereas medication data were retrieved from medical records. DUP was defined as the time interval in weeks with persistent symptoms qualifying for a score of ≥4 on any of the PANSS items—P1, delusions; P3, hallucinatory behavior; P5, grandiosity; P6, suspiciousness; or G9, unusual thought content—until the subject received adequate treatment for psychosis. HC were assessed using the same psychometric tools as the patients, except for the PANSS.

2.4. Subgroups based on exposure to antipsychotics and symptom severity

Each patient’s previous and current types and doses of AP were converted to a chlorpromazine (CPZ)-equivalent dose according to Andreasen et al. (2010). Each type and dose were converted to CPZ years using the formula [(CPZ in mg) × (time on dosage measured in years)], and summed to provide a cumulative lifetime measure (CPZ years). Patients were divided into AP-naïve and AP-exposed groups. The two groups differed significantly in BMI, but not in self-reported physical activity. Furthermore, physical activity was not significantly correlated with BMI (r = 0.02, p = 0.898).

We identified a subgroup of patients with a more severe psychotic disorder by using three variables: level of negative symptoms, DUP, and diagnosis. PANSS negative symptom sum scores showed a bimodal distribution, with only four patients having scores of 15–20. A sum score of 21 corresponds to an average negative item score of 3, defining a clearly pathological. Therefore, we dichotomized the variables so that 19 patients with PANSS negative sum scores ≥21 were grouped as Severe Negative, and 19 patients with PANSS negative sum scores <21 as Mild Negative. DUP was dichotomized into short and long DUP groups with a cutoff of 26 weeks, as a DUP >26 weeks has proven to be a predictor of poor long-term outcome (Friis et al., 2016). Twenty-four patients had a short DUP and 15 a long DUP. Diagnoses were dichotomized according to the SCZ spectrum. Twenty-two patients were assigned a diagnosis in the SCZ spectrum and 19 were not. The three variables were strongly interrelated as most of the patients in the Severe Negative group had a short DUP and a diagnosis outside the SCZ spectrum and 19 were not. The three variables were strongly interrelated as most of the patients in the Severe Negative group had a short DUP and a diagnosis outside the SCZ spectrum and 19 were not. The three variables were strongly interrelated as most of the patients in the Severe Negative group had a short DUP and a diagnosis outside the SCZ spectrum (negative symptoms and DUP $\chi^2$ = 14.05; p < 0.0002, negative symptoms and SCZ spectrum $\chi^2$ = 21.63; p < 0.0001). Imputation was done for one patient who had a missing PANSS negative score. This patient had a diagnosis of affective psychosis and a DUP of 1 week, and was therefore categorized as Mild Negative, increasing this group size to 20. Because of the strong interrelationships, we used only one of the variables for analytical purposes. We chose to use the negative symptom classification, as we considered the negative symptoms to be the variable with the most promising properties related to biological subtyping (Jones et al., 2016; Owen, 2014).

2.5. Biochemical variables

Venous blood samples were drawn from subjects in the morning, after an overnight fast. Serum was separated by centrifugation (1500g, 15 min) within 2 h. Fasting serum TC, HDL—C, LDL-C and TG levels were measured and analyzed according to standard enzymatic colorimetric methods (Roche Diagnostics Norge AS, Oslo, Norway), and glucose was measured using the hexokinase/glucose-6-phosphate dehydrogenase enzymatic method (Roche Diagnostics Norge AS), all at the Department of Clinical Biochemistry, Oslo University Hospital. Interassay coefficients of variation were <3.5–4% for TC, HDL—C, and TG. The cholesterol (TC and HDL—C) and TG were chosen for analyses because they represent different constituents of the lipid fraction in the blood. The TC/HDL-C ratio was chosen as an established predictor of CVD risk, with a higher predictive value than individual lipoproteins, and valid also in the presence of high TG levels (Millan et al., 2009). Insulin was measured at the Hormone Laboratory, Department of Medical Biochemistry, Oslo University Hospital, by radioimmunoassay, and after mid-November 2015 with a Modular E170-method, both with interassay coefficients of variation <4%. For comparisons, an equation for conversion was provided by the laboratory. Because HOMA-IR contains more information in one outcome variable than glucose and insulin individually, we used this index in analyses. The homeostasis model assessment of insulin resistance (HOMA-IR) was estimated using the HOMA calculator version 2.2.3, provided by Oxford University (https://www.dtu.ox.ac.uk/homacalculator/). We intended to measure HbA1c in all participants, but too many had missing values. However, the results of the available HbA1c values were in accordance with the HOMA-IR results.

2.6. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics (version 25; IBM Corp., Armonk, NY, USA). All analyses were two-tailed with the significance level set at p < 0.05. Data normality was assessed with the Kolmogorov–Smirnov test. Data are presented as means, medians, or percentages as appropriate. Independent Student’s t-tests, Mann–Whitney nonparametric U tests, or Chi-squared tests were used for comparing demographic variables between groups, according to the type and distribution of the variable. Univariate analysis of variance with pairwise comparison was used to compare lipid levels and HOMA-IR values between HC and patient subgroups, while controlling for BMI and total AP exposure. Hierarchical multiple linear regression analysis was used to assess the unique contribution to explained variance by having psychosis on the three dependent variables (TC/HDL-C, TG, HOMA-IR) after having controlled for BMI, sex, and cumulative exposure to AP. Preliminary analyses were conducted to check for assumptions of normality, linearity and homoscedasticity. Tests for assumption of collinearity indicated that multicollinearity was not a concern (BMI, VIF = 1.169; Sex, VIF = 1.029; lnCPZyears, VIF = 1.815; EOP, VIF = 1.690). Because of its skewed distribution, CPZ years were log normal (ln)-transformed to ln (CPZ years + 1). We performed four separate analyses for each dependent variable. Independent variables were entered one by one, with BMI at step 1, sex at step 2, lnCPZ years at step 3, and having psychosis at step 4. P-values were not corrected for multiple testing, as the hypotheses were pre-specified and not data-driven. However, this should be kept in mind in interpretation of the statistical significance.

3. Results

3.1. Clinical characteristics, lipids, and IR between patients and HC

As shown in Table 1, patients had significantly higher BMI, and significantly increased unadjusted levels of TC, low-density lipoprotein cholesterol (LDL-C), TG, TC/HDL-C ratios, and HOMA-IR values relative to HC.

3.1.1. AP-naïve and AP-exposed vs. HC

The AP-naïve patients had similar BMI values to HC, while the AP-exposed ones had significantly increased BMI (Supplementary Table 1). As shown in Fig. 1, both AP-naïve and AP-exposed patients had increased TC/HDL-C ratios and TG after correction for BMI, compared with controls. HOMA-IR was significantly increased in the AP-exposed group only. In omnibus tests there were significant between-subject effects for unadjusted levels of TC/HDL-C, TG and HOMA-IR (see Supplementary Table 3). Post hoc comparisons of observed means showed significant difference in unadjusted level of TG (p = 0.042), but borderline significant differences in unadjusted levels of TC/HDL-C (p = 0.059) and non-significant differences in HOMA-IR (p = 0.703) between AP-naïve and HC (see Supplementary Table 3).
### Table 1

Overall demographics, clinical scores, and unadjusted absolute values of lipids and HOMA-IR for patients and HC.

<table>
<thead>
<tr>
<th></th>
<th>HC (n = 66)</th>
<th>Patients (n = 39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>15.8 (1.5)</td>
<td>16.3 (1.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Female sex</td>
<td>34 (52)</td>
<td>26 (67)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Caucasian ethnicity</td>
<td>59 (89)</td>
<td>33 (85)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mother’s education (years)</td>
<td>15.4 (2.3)</td>
<td>14.8 (2.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>C-GAS score</td>
<td>91 (6)</td>
<td>43 (10)</td>
<td>&lt;0.001d</td>
</tr>
<tr>
<td>DUP in weeks</td>
<td>16 (1–226)</td>
<td>16.1 (4.9)</td>
<td></td>
</tr>
<tr>
<td>PANSS positive</td>
<td>16.1 (4.9)</td>
<td>18.6 (7.9)</td>
<td></td>
</tr>
<tr>
<td>PANSS negative</td>
<td>20.9 (3.0)</td>
<td>23.0 (5.3)</td>
<td>0.028</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.9 (3.0)</td>
<td>23.0 (5.3)</td>
<td></td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>3.9 (0.7)</td>
<td>4.4 (0.8)</td>
<td>-0.001</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.6 (0.4)</td>
<td>1.4 (0.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>2.2 (0.7)</td>
<td>2.7 (0.8)</td>
<td>-0.001</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>0.6 (0.3)</td>
<td>1.0 (0.6)</td>
<td>-0.001</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>2.6 (0.7)</td>
<td>3.3 (1.0)</td>
<td>-0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.3 (0.6)</td>
<td>1.7 (0.8)</td>
<td>-0.001</td>
</tr>
</tbody>
</table>

Diagnosis:
- SCZ spectrum: 20
- Affective psychosis: 4
- Psychosis NOS: 15

Medication:
- Aripiprazole: 12
- Risperidone: 4
- Quetiapine: 6
- Olanzapine: 3
- Clozapine: 1
- Naïve: 13
- CPZ: 154.1 (175.8)
- CPZ years: 7.7 (14.2)

Key: HC, healthy controls; SD, standard deviation; CGAS, Children’s Global Assessment Scale; DUP, duration of untreated psychosis; PANS, Positive and Negative Symptom Scale; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HOMA-IR, homeostatic model assessment of insulin resistance; SCZ spectrum, schizophrenia spectrum; Affective psychosis, Affective psychosis; Psychosis NOS, Psychosis not otherwise specified; Naïve, no lifetime exposure to antipsychotic medication CPZ, chlorpromazine equivalents; CPZ years, lifetime exposure in chlorpromazine equivalents.

### 3.1.2. Explained variance of patient status

As shown in Table 2, having psychosis gave a significant unique contribution of 5% to the explained variance in both TC/HDL-C and TG levels, after adjusting for BMI, sex, and total exposure to AP.

### 3.1.3. Mild negative and severe negative groups vs. HC

Compared with the Mild Negative group, the Severe Negative group had significantly longer DUP and decreased C-GAS scores, but no differences in BMI or total AP exposure (Supplementary Table 2). Compared with HC, patients in the Severe Negative group showed significantly increased adjusted levels of TC/HDL-C and TG, but no difference in HOMA-IR, whereas the Mild Negative group did not differ significantly in adjusted levels of TC/HDL-C, TG or HOMA-IR after correction for BMI and AP exposure (see Fig. 2). The levels of TG were significantly different between the Severe Negative and Mild Negative patient groups after correction for BMI and AP exposure (Fig. 2). In omnibus tests there were significant between-subject effects for unadjusted levels of TC/HDL-C, TG and HOMA-IR (see Supplementary Table 4). Post hoc comparisons of observed means showed significant differences in unadjusted levels of TC/HDL-C and TG in both the Mild Negative and the Severe Negative group relative to HC, whereas levels of unadjusted HOMA-IR were significantly different from HC in the Mild Negative group only (see Supplementary Table 4).

### 4. Discussion

The main findings here were that atherogenic lipid profile alterations were found in patients with EOP even prior to initiating AP, and that having psychosis accounted for an additional 5% of the explained variance for both the TC/HDL-C ratio and TG levels after controlling for BMI, sex, and total exposure to AP. In addition, we found a positive association between negative symptom severity and TG levels after controlling for BMI.

In accordance with our findings, Jensen et al. (2017) reported increased TC and LDL-C with indifferent HDL-C levels in a study of broadly-defined adolescent FEP. However, those lipid profiles contrast with the finding of reduced TC in adult FEP (Misiak et al., 2017), which might indicate that the hypercholesterolemia described in adult patients with chronic disease is secondary to lifestyle and AP exposure. In addition, the hypertriglyceridemia found in broadly-defined adult FEP is suggested to result from intrinsic glucose dysregulation (Pillinger et al., 2017b). We found increased TC/HDL-C ratios and TG levels in the absence of HOMA-IR alterations in young AP-naïve patients with EOP, a finding that seems to contradict this hypothesis. The contradictory findings between adolescent EOP and adult FEP could also represent age-related stage-specific abnormalities in lipid biology. Altered plasma lipidome signatures at age 11 years compared with HC, prior to the development of a psychosis disorder, have been reported from the Avon Longitudinal Study of Parents and Children cohort. A different signature was found when the same subjects were reassessed at age 18 years, suggesting ongoing alterations in phospholipid metabolism and inflammatory abnormalities in psychotic disorders as they develop (O’Gorman et al., 2017). In addition, adjunctive omega-3 dietary supplements have been suggested to have stage-specific effects, with more positive effects observed in the treatment in earlier stages, and progressively diminishing efficacy in later stages of patients with SCZ (Chen et al., 2015).

The lipid alterations we found here did not exceed clinical cutoff limits according to child and adolescent reference charts (Yip et al., 2006), but more patients than HC had lipid levels above the 50th percentile. These findings are important with regard to increased CVD risk in adulthood, as exposure to increased blood lipid levels at a young age leads to the earlier progression of arterial atherosclerotic lesions (Nordestgaard et al., 2013). Several studies have documented an association between dyslipidemia and metabolic dysregulation in childhood and adolescence, and development of early atherosclerosis and an
increased risk of CVD in adulthood (Berenson et al., 1998; Franco et al., 2009; Mahoney et al., 1996; Nelson and Bremer, 2010). In addition, new clinical and genetic insights suggest that elevated levels of TG-rich lipoproteins in plasma have an individual role in the atherosclerotic process and promote systemic low-grade inflammation via apolipoprotein C-III (Crosby et al., 2014; Jørgensen et al., 2014). Thus, our findings in adolescents with EOP suggest that atherogenic processes start early in the development of psychotic disorders, and that these might contribute to the increased CVD mortality in patients with severe mental disorders.

We found no HOMA-IR difference between AP-naïve patients and HC, but significantly increased scores in the AP-exposed subjects, who also had significantly higher BMI values. It has been demonstrated that children and adolescents are vulnerable to metabolic side effects from AP, with weight gain starting early after the initiation of treatment (Arango et al., 2014; Ronssley et al., 2015). A recent meta-analysis reported an increased risk of developing IR and type 2 diabetes after exposure to second-generation AP in adolescents (Galling et al., 2016), possibly an even higher risk than adults with SCZ spectrum disorders during an acute episode of psychosis (Messamore, 2012; Smesny et al., 2003). Additionally, there are indications that high levels of negative symptoms might reflect differences in pathophysiological underpinnings, as they are associated with impaired brain white matter integrity, decreased brain connectivity, reduced treatment-responses, and poorer functional outcomes in adults (Aleman et al., 2017; Buckley and Stahl, 2007; Galderisi et al., 2014; Mucci et al., 2017; Reckless et al., 2015). Reduced niacin sensitivity, indicative of alterations in lipid metabolism, is also associated with higher negative symptom levels and greater functional impairment (Messamore, 2012; Smesny et al., 2003). Additionally, there are indications that high levels of negative symptoms are associated with low polyunsaturated fatty acid levels in adults with SCZ spectrum disorders during an acute episode of psychosis (Bentsen et al., 2012). As such, patients with EOP and a high negative symptom load could represent a phenotype featuring more lipid metabolism alterations.

The strengths of this study were that it covered a very well-characterized group of adolescent patients with a rare diagnosis of EOP, of whom the vast majority were in their first episode. All participants were from the same catchment area, with similar ethnic distribution and duration of mothers’ education. In addition, the sample comprised more female patients than male. Because of the study design, we cannot rule out the possibility that more boys than girls declined participation or were considered too ill to participate. This may imply a disproportionate lower inclusion of more severely ill boys. However, sex-dependent sub-analyses suggest that the uneven sex distribution may have contributed to an underestimation of the differences in levels of HDL between patients and controls (data not shown). Thus, if we had been able to include more boys, probably more severely ill, we expect this would increase the differences in lipid levels between patients and HC. Accordingly there is little reason to believe that the skewed gender distribution have inflated the differences between patients and controls. Third, dietary effects could not be ruled out because dietary intake was not assessed. However, systematic diet differences between the participants seem unlikely, as ethnicity, catchment area, and mothers’ education level, which are proxies for socioeconomic position that have been known to influence dietary patterns, were similar (Camara et al., 2015; Hidaka et al., 2016). Lastly,
we did not correct for physical activity. However, it is unlikely that this would significantly affect the results in this young sample.

5. Conclusions
We found that having psychosis added to the explained variance for TC/HDL-C and TG after correction for confounders, and our results suggested that lipid alterations predate the use of AP in adolescents with EOP. High levels of negative symptoms and exposure to AP medication were associated with more pronounced alterations in lipid levels. These preliminary results suggest that such metabolic alterations might be intrinsic to the disease in a subset of patients with psychosis, which further underscores the need for prioritization of physical health improvements in these patients.

Author contributions
Design of the UTOP study: AMM and IA. Data collection: KWR, VL, RES, and CJ Drafting the article: KWR, SF, and AMM. Data analysis and interpretation: KWR, SF, and OAA. Critical revision of the article and final approval of the version to be published was given by all authors.

Conflict of interest
SF has received an honorarium as a data consultant for RAND Corporation for a project sponsored by the Janssen-Cilag pharmaceutical company. OAA has received a speaker’s honorarium from Lundbeck. During the past 5 years, KBH and SMU have received research grants or honoraria from Mills A5, Tine SA, and Olympic Seafood, and KBB also from Argen, Sanofi, and Pronova, none of which are related to the content of this manuscript. The authors declare no other conflicts of interest.

Funding
This work was supported by the Research Council of Norway, grant numbers 223273, 217300, and 250358; the Southern and Eastern Norway Regional Health Authority, grant numbers 2016-118 and 2017-097; and the Kristian Gerhard Jebsen Foundation.

Acknowledgements
We thank the participants and parents for their contributions, as well as the clinicians involved in the inclusion of patients and healthy controls. Statistical assistance provided by statistician Ole Klingsøyr was greatly appreciated. We give special thanks to Thonny Olafsdottir for her help with data collection, and to Line Gundersen and Eivind Bakken at our laboratory.

Appendix A. Supplementary data
Supplementary data to this article can be found at https://doi.org/10.1016/j.schres.2019.11.039.

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