Lipid Disturbances in Adolescents Treated With Second-Generation Antipsychotics:

Clinical Determinants of Plasma Lipid Worsening and New-Onset Hypercholesterolemia

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ABSTRACT

Objective: Lipid disturbances following treatment with second-generation antipsychotics (SGAs) represent a major health concern. A previous study determined that early changes of plasma lipid levels ≥ 5% during the first month of treatment with SGAs predicts further lipid worsening and development of dyslipidemia. This current study aimed to determine the proportion of adolescents with early lipid changes ≥ 5% and who develop dyslipidemia during SGA treatment.

Methods: Data were obtained from a 1-year longitudinal study ongoing since 2007 including 53 adolescent psychiatric (*ICD-10*) patients (median age 16.5 years; interquartile range [IQR], 14.8–17.5 years) whose metabolic parameters were monitored prospectively during treatment. Plasma lipid levels (total, low-density lipoprotein, high-density lipoprotein [HDL-C], and non–high-density lipoprotein cholesterol and fasting triglycerides) were measured at baseline and after 1, 3, and/or 12 months of SGA treatment.

Results: Half (n = 26; 49%) the adolescents had an early increase of total cholesterol levels by 5% or more during the first month of treatment, and one-third (n = 8/24; 33%) developed new-onset hypercholesterolemia during the first year of treatment. Hypercholesterolemia developed more frequently in female patients ($P = .01$) and in patients with an early increase of total cholesterol ≥ 5% ($P = .02$). Finally, patients whose HDL-C levels decreased by ≥ 5% during the first month of treatment had a larger HDL-C worsening after 3 months of treatment as compared with patients with early decrease of HDL-C by < 5% ($P = .02$).

Conclusions: This study underlines the importance of prospectively monitoring metabolic parameters in adolescents after the introduction of SGAs.

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Patients suffering from severe mental illness such as schizophrenia, bipolar disorder, and major depressive disorders have a 10- to 25-year reduced life expectancy compared with individuals from the general population,[1–10] a difference that is mainly attributable to cardiovascular diseases resulting from metabolic syndrome.[11] Multiple risk factors implying complex mechanisms may explain this excessive susceptibility for developing cardiovascular diseases, including psychiatric disease-related factors, an unhealthy lifestyle, poverty, and adverse effects of treatment.[12,13] Thus, although commonly prescribed to reduce psychotic and manic symptoms of schizophrenia and bipolar disorders, the use of psychotropic medications such as antipsychotics (most atypical but also some typical), mood stabilizers (eg, lithium and valproate), and some antidepressants (eg, mirtazapine) can increase the risk of metabolic disorders, including obesity and dyslipidemia.[14,15] Multiple factors have been associated with psychotropic drug-induced metabolic complications, including low baseline body mass index, young age, and no previous exposure to any psychotropic drug, making adolescents particularly susceptible to the development of adverse metabolic effects.[13,16] In addition, some studies, albeit controversial, have suggested that women have a greater vulnerability to psychotropic-drug–induced weight gain than men.[12,17]

Adverse metabolic effects such as weight gain are difficult to manage and can have potential long-term cardiometabolic consequences, especially in young patients.[16,18–20] Other metabolic parameters (eg, lipid profile) can also be worsened in young patients treated with antipsychotics,[19,21–24] which dramatically enhances the risk for long-term cardiovascular morbidity and mortality.[25] Thus, the propensity to develop dyslipidemia (defined as any or all of the following: high total cholesterol [TC], high low-density lipoprotein [LDL] cholesterol [LDL-C], low high-density lipoprotein [HDL] cholesterol [HDL-C], high non-HDL cholesterol

Clinical Points

- Although early changes of the lipid profile during treatment with psychotropic drugs have been demonstrated in adults, this side effect has never been evaluated in adolescent patients.
- Considering the major impact of dyslipidemia on morbidity and mortality, it is critical that health care professionals monitor and control lipid levels in young patients receiving second-generation antipsychotics.

[non-HDL-C], or high triglyceride [TG] levels) in a young patient who receives an antipsychotic medication was estimated to be 2- to 3-fold higher than in a patient who does not receive this type of medication.[26] In addition, this metabolic condition was shown to reach 55% in patients with first-episode schizophrenia who receive antipsychotic treatment.[27] Therefore, regular monitoring for metabolic parameters in patients receiving psychotropic drugs is an important issue. Some programs have proposed monitoring of metabolic parameters during treatment in patients receiving psychotropic drugs known to induce metabolic disturbances, including close monitoring during the first 3 months of treatment.[28,29]

Recent studies recognized that components of the metabolic syndrome may develop early during psychotropic treatment and may initiate a steady process leading to cardiometabolic diseases in the long term.[19,20,30–32] In particular, lipogenic adverse effects may occur very early during treatment and may even precede weight gain.[13,19,33–35] Our research group recently demonstrated the importance of early (ie, after 1 month of treatment) changes of lipid levels to predict worsening of the lipid profile and development of dyslipidemia in the longer term of treatment (≥ 3 months of treatment).[31] In particular, patients whose lipid levels increased by 5% or more during the first month of psychotropic treatment were more prone to have a considerable worsening of their lipid profiles after 3 months of treatment and to develop dyslipidemia as compared with other patients.[31] Interestingly, these early lipid-change predictors were applicable in age-stratified samples, showing an age-independence and suggesting that they were also valid in adolescent patients.[31] However, further characterization of lipid-profile worsening in adolescents could not be assessed due to an insufficient number of patients ≤ 18 years (n = 16). Although some prospective studies observed that some antipsychotics (eg, olanzapine, quetiapine, risperidone) induced significant lipid abnormalities in children and adolescents,[19,36,37] plasma lipid levels were not measured in the early period of treatment (ie, within the first month), which would have been beneficial.

Because of the high morbidity and mortality associated with dyslipidemia, an early detection of adolescent patients at risk for developing lipid disturbances during psychotropic treatment is of major clinical concern. The aim of the present study was to determine the proportion of patients with early lipid change ≥ 5% and to measure the incidence of new-onset dyslipidemia during treatment with psychotropic drugs. Our secondary purpose was to identify demographic and clinical risk factors associated with worsening of the lipid profile.

METHODS

Study Design

A 1-year longitudinal observational study has been ongoing since 2007 in the Department of Psychiatry of Lausanne University Hospital.[38] Patients starting a pharmacologic treatment that is known to have a potential risk to induce metabolic disturbances (ie, an antipsychotic, mood stabilizer, or antidepressant listed in Supplementary Table 1) were included, as described in the flowchart (Supplementary Figure 1). The present study included patients with informed consent from an ongoing pharmacogenetic study (PsyMetab)[39] as described elsewhere. In addition, data of patients in the clinical follow-up (PsyClin) in our department were also analyzed. Due to the noninterventional post hoc analysis study design, no informed consent was requested from the patients who had clinical follow-up. Both studies were approved by the Ethics Committee of the Canton of Vaud (CER-VD).

Diagnoses were based on the *International Classification of Diseases, Tenth Revision* (*ICD-10*): F10–F19, psychoactive substance use; F20–F29, schizophrenia; F30–F39, mood disorders; F40–F48, stress-related disorders; F50–F59, behavioral syndromes; F70–F79, mental retardation; F80–F89, psychological development; and F90–F98, behavioral and emotional disorders. Only adolescent patients (median age of 16.5 years) treated with second-generation antipsychotics (SGAs) and with available lipid levels at least at baseline and at first month (15 to 45 days of treatment; median of 29 days; interquartile range [IQR], 24–32) with no lipid-lowering drug (listed in Supplementary Table 2) were included in the sample used for descriptive statistics of early lipid changes (ie, data 1; n = 53). Of note, 63% of patients were not drug-naïve. Patients whose lipid levels were available at baseline, at first month, and later during treatment (median of 92 days; IQR, 80–101; range, 56–447 days) and who did not meet criteria for dyslipidemia at baseline were included in the second sample, which was used to describe the development of dyslipidemia during psychotropic treatment as a function of lipid changes at first month (ie, data 2; n ≤ 25). The majority of blood samples were drawn in the morning in fasting conditions. Blood samples in non-fasting conditions (ie, within 6 hours following the last meal) were excluded only for TG analysis (not for TC, HDL-C, LDL-C and non-HDL-C).[40,41] As mentioned previously, 16 patients ≤ 18 years old included in the present study had been included in a recent study designed to determine the best early thresholds for predicting further important lipid worsening.[31] However, this number was insufficient to conduct additional analyses specifically

in young patients. The present study design includes a greater number of participants: 37 new patients, for a total of 53.

Quantification of Plasma Lipids

Clinical chemistry assays from plasma samples collected before and after January 2009 were performed at the Unit of Pharmacogenetics and Clinical Psychopharmacology and at the Clinical Laboratory of the Lausanne University Hospital, respectively (both laboratories are ISO 15189 certified), using enzymatic colorimetric assays (Roche Modular P chemistry analyzer, Roche Diagnostics, Basel, Switzerland). Coefficients of variation for these assays were ≤ 1.6%, ≤ 2%, and ≤ 2.8% for TC, TG, and HDL-C measurements, respectively. Low HDL-C level (ie, HDL hypocholesterolemia was defined as < 1 mmol/L), high LDL-C level (ie, LDL hypercholesterolemia was defined as ≥ 3 mmol/L), high TG level (ie, hypertriglyceridemia was defined as ≥ 2 mmol/L), and high total cholesterol level (ie, hypercholesterolemia was defined as ≥ 5 mmol/L), were assessed according to European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines.[42] LDL-C was calculated using the Friedewald formula only when TG levels were lower than 3.5 mmol/L (310 mg/dL).[43,44] Non-HDL-C was calculated from TC minus HDL-C.

Statistical Analyses

To compare distribution of demographic and clinical variables across patient groups, Wilcoxon-Mann-Whitney rank-sum tests and χ^2 tests were conducted for comparison of continuous variables and of categorical variables, respectively. For comparison of metabolic parameters between baseline and after 1 month of treatment, McNemar tests were performed.

Short- and long-term lipid changes. The influence of early lipid changes on long-term lipid changes was estimated by fitting linear mixed effect models on long-term lipid changes adjusting for age, sex, and early weight gain groups (> 4% vs ≤ 4%[20]).

Short-term lipid changes and new-onset dyslipidemia. Kaplan-Meier estimates with log-rank tests were conducted to compare the incidence of new-onset dyslipidemia across patients with or without early lipid change ≥ 5%. For survival multivariate analyses, Cox regression tests were conducted, adjusting for age, sex, psychotropic drug category (olanzapine and quetiapine being associated with the highest risk of dyslipidemia; other drugs conferring a moderate risk[15]), and early weight gain (> 4%[20]), using the survival package of R.

Statistical significance was determined by a P value ≤ 0.05. Statistical analyses were performed using Stata 14 (StataCorp, College Station, Texas) and R environment for statistical computing version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics and Evolution of Lipid Parameters

Table 1 displays the demographic and clinical characteristics of the psychiatric sample. Fifty-three adolescent patients monitored during treatment with SGAs were included. The median age was 16.5 years (IQR, 14.8–17.5 years), and mood disorders (F30–F39) were the most frequent diagnoses (43%). Quetiapine was the most frequently prescribed psychotropic drug (62%), followed by risperidone (23%), olanzapine (13%), and amisulpride (2%). Eight (15%) of the 53 patients received 2 SGAs. Seventeen percent of patients had hypercholesterolemia at baseline, ie, TC ≥ 5 mmol/L (no patient received any lipid-lowering drug). Of note, in a sample from the present study including a higher number of patients (with lipid levels not systematically collected after 1 month of treatment; n = 111), hypercholesterolemia prevalence was similar (ie, 15.3%). In the present sample of 53 patients, 26 (49%), 23 (47%), 19 (42%), 15 (30%), and 24 patients (48%) had early changes of ≥ 5% for TC, LDL-C, TG, HDL-C, and non-HDL-C, respectively, during the first month of SGA treatment. More information is available in Appendix 1.

A sex comparison of demographic and of clinical parameters is shown in Supplementary Table 3. After the first month of SGA treatment, the prevalence of hypercholesterolemia was significantly higher for female patients than for male patients (38% vs 13%; $P = .04$). Similarly, female patients had significantly higher levels of total cholesterol compared with male patients, both before and after 1 month of treatment (4.3 mmol/L vs 3.6 mmol/L, $P = .02$; 4.4 mmol/L vs 3.8 mmol/L, $P = .004$). Finally, quetiapine was more prescribed for female patients than for male patients (76% vs 46%, $P = .02$).

Influence of Short-Term Lipid Changes on Long-Term Lipid Changes

Linear mixed models adjusting for age, sex, early weight gain (ie, > 4% vs ≤ 4%), and SGA category indicated that patients with early decrease (≥ 5%) of HDL-C had significantly higher decrease of HDL-C (16.2%, $P = .02$) after 3 months of treatment as compared with patients without early changes of HDL-C (Supplementary Table 4). In addition, trends of difference for increase of TC and non-HDL-C after 3 months of SGA treatment were also observed between patients with and without early increase of TC and non-HDL-C. Analyses could not be conducted for TG increase due to an insufficient number of observations. Of note, as compared with female patients, male patients had a significantly larger decrease of HDL-C levels (−13%, $P = .04$) and lower increase of TC levels (−15%, $P = .05$) after 3 months of treatment (data not shown).

Influence of Short-Term Lipid Changes on New-Onset Dyslipidemia

Among the 53 young patients monitored during treatment with SGAs, 24 had available data for survival analyses, which were used to characterize the development of new-onset dyslipidemia from 3 months of treatment (IQR, 80–101 days; range, 56–447 days) (Supplementary Figure 1). Demographic and clinical characteristics of patients whose baseline lipid levels were within the normal

Table 1. Demographic Parameters of Patients[a] With or Without Early Modifications of Plasma Lipid Levels

Characteristic	All	TC			LDL-C			TG			HDL-C			non-HDL-C		
		<5%	≥5%	P[b]	<5%	≥5%	P[b]	<5%	≥5%	P[b]	>−5%	≤−5%	P[b]	<5%	≥5%	P[b]
Number of patients	53	27	26		26	23		26[a]	19[a]		35	15		26	24	
Age, median (IQR), y	16.5 (14.8–17.5)	15.6 (14.5–17.0)	16.9 (15.7–17.7)	**.02**	15.6 (14.6–17.4)	16.9 (16.2–17.8)	.05	16.8 (15.5–17.6)	16.6 (14.6–17.5)	.6	16.6 (15.5–17.1)	15.8 (14.1–17.8)	.86	15.8 (14.7–17.4)	16.9 (15.3–17.7)	.12
Male, n (%)	24 (44.3)	12 (44.4)	12 (46.2)	.9	13 (50.0)	11 (47.8)	.88	10 (38.5)	12 (63.2)	.1	16 (45.7)	8 (53.3)	.62	13 (50)	11 (45.8)	.77
Smoking, n (%)	20 (37.0)	11 (40.7)	9 (34.6)	.28	11 (42.3)	8 (34.8)	.48	11 (42.3)	7 (36.8)	.65	12 (34.3)	8 (53.3)	.25	10 (38.5)	10 (41.7)	.13
ICD-10 diagnosis, n (%)																
Psychoactive substance use (F10–F19)	2 (3.8)	1 (3.7)	1 (3.9)	.98	1 (3.9)	1 (4.4)	.93	2 (7.7)	0	.22	1 (2.9)	1 (6.7)	.53	1 (3.9)	1 (4.2)	.95
Schizophrenia (F20–F29)	7 (13.2)	4 (14.8)	3 (11.5)	.73	4 (15.4)	2 (8.7)	.48	3 (11.5)	3 (15.8)	.68	4 (11.4)	2 (13.3)	.85	4 (15.4)	2 (8.3)	.44
Mood disorders (F30–F39)	23 (43.4)	12 (44.4)	11 (42.3)	.88	11 (42.3)	11 (47.8)	.7	12 (46.2)	9 (47.4)	.94	16 (45.7)	6 (40.0)	.71	12 (46.2)	10 (41.7)	.75
Stress-related disorders (F40–F48)	7 (13.2)	2 (7.4)	5 (19.2)	.2	3 (11.5)	3 (13.0)	.87	3 (11.5)	3 (15.8)	.68	4 (11.4)	3 (20.0)	.42	2 (7.7)	5 (20.8)	.18
Behavioral syndromes (F50–F59)	2 (3.8)	1 (3.7)	1 (3.9)	.98	1 (3.9)	1 (4.4)	.93	2 (7.7)	0	.22	2 (5.7)	0	.35	1 (3.9)	1 (4.2)	.95
Mental retardation (F70–F79)	1 (1.9)	0	1 (3.9)	.3	0	1 (4.4)	.28	0	0		1 (2.9)	0	.51	0	1 (4.2)	.29
Psychological development disorders (F80–F89)	2 (3.8)	1 (3.7)	1 (3.9)	.98	0	2 (8.7)	.13	0	2 (10.5)	.09	0	2 (13.3)	**.03**	0	2 (8.3)	.13
Behavioral and emotional disorders (F90–F98)	6 (11.3)	3 (11.1)	3 (11.5)	.96	4 (15.4)	1 (4.4)	.2	1 (3.9)	2 (10.5)	.38	5 (14.3)	0	.12	3 (11.5)	2 (8.3)	.71
Not available	3 (5.7)	3 (11.1)	0	.08	2 (7.7)	1 (4.4)	.63	3 (11.5)	0	.13	2 (5.7)	1 (6.7)	.9	3 (11.5)	0	.09
Medication, n (%)																
Amisulpride	1 (1.9)	1 (3.7)	0	.32	1 (3.9)	0	.34	1 (3.9)	0	.39	0	1 (6.7)	.12	1 (3.9)	0	.33
Olanzapine	7 (13.2)	1 (3.7)	6 (23.1)	**.04**	2 (7.7)	4 (17.4)	.3	1 (3.9)	4 (21.0)	.07	5 (14.3)	1 (6.7)	.45	1 (3.9)	5 (20.8)	.07
Quetiapine	33 (62.3)	18 (66.7)	15 (57.7)	.5	18 (69.2)	13 (56.5)	.36	17 (65.4)	12 (63.2)	.88	23 (65.7)	9 (60.0)	.7	18 (69.2)	14 (58.3)	.42
Risperidone	12 (22.6)	7 (25.9)	5 (19.2)	.56	5 (19.2)	6 (26.1)	.57	7 (26.9)	3 (15.8)	.38	7 (20.0)	4 (26.7)	.6	6 (23.1)	5 (20.8)	.85
Polymedication[c]	8 (15.1)	6 (22.2)	2 (7.7)	.14	5 (19.2)	1 (4.4)	.11	2 (6.9)	4 (21.0)	.19	3 (8.6)	4 (26.7)	.09	5 (19.2)	2 (8.3)	.27
Psychiatric illness duration, median (IQR), y	2.5 (1.5–5.3)	3.2 (2.0–5.1)	2.2 (1.2–10.0)	.7	2.2 (1.8–3.5)	2.2 (1.2–8.9)	.9	2.0 (1.1–4.7)	2.2 (1.5–3.7)	.71	2.0 (1.2–3.3)	6.3 (2.9–10.3)	.052	2.2 (2.0–3.3)	1.9 (0.9–8.9)	.8
Early weight gain[d] (>4%), n (%)																
1st month	21 (40.4)	7 (25.9)	14 (56.0)	**.03**	6 (23.1)	12 (54.6)	**.03**	9 (34.6)	8 (44.4)	.51	16 (47.1)	3 (20.0)	.07	8 (30.8)	11 (47.8)	.3
Laboratory values	median (IQR)	P[e]	median (IQR)	median (IQR)	P[b]	median (IQR)	median (IQR)	P[b]	median (IQR)	median (IQR)	P[b]	median (IQR)	median (IQR)	P[b]	median (IQR)	median (IQR)	P[b]
Total cholesterol, mmol/L																
Baseline	4.1 (3.4–4.4)		4.3 (3.7–4.5)	3.6 (3.2–4.4)	**.04**	4.1 (3.5–5)	3.6 (3.2–4.4)	.22	4.2 (3.5–4.4)	3.4 (3.2–4.4)	.38	3.7 (3.2–4.3)	4.3 (3.6–5.2)	.09	4.2 (3.6–4.5)	3.6 (3.2–4.4)	.2
1st month	4.1 (3.8–5)	.29	4 (3.4–4.4)	4.4 (3.8–5.2)	.15	4 (3.4–4.4)	4.3 (3.8–5.2)	**.05**	4.2 (3.8–5)	3.9 (3.6–4.4)	.19	4.1 (3.8–5)	4 (3.4–4.6)	.69	4 (3.4–4.4)	4.4 (3.8–5.3)	**.04**
LDL cholesterol, mmol/L																
Baseline	2.2 (1.8–2.6)		2.4 (2.0–2.7)	1.8 (1.6–2.4)	**.01**	2.3 (1.9–2.7)	1.9 (1.6–2.6)	.08	2.3 (1.8–2.6)	1.9 (1.6–2.9)	.63	2.2 (1.7–2.5)	2.4 (1.9–3.0)	.12	2.3 (1.9–2.6)	1.8 (1.6–2.8)	**.04**
1st month	2.3 (1.8–2.8)	.54	2.2 (1.8–2.6)	2.4 (1.8–3.3)	.4	2.1 (1.8–2.4)	2.6 (2.0–3.3)	.06	2.3 (2.0–3.0)	2.1 (1.7–2.5)	.32	2.3 (1.9–2.8)	2.1 (1.7–2.9)	.63	2.2 (1.8–2.5)	2.4 (1.9–3.5)	.12
Triglyceride, mmol/L																
Baseline	1 (0.7–1.2)		1.1 (0.6–1.3)	1 (0.7–1.2)	.67	1.1 (0.7–1.2)	1 (0.7–1.2)	.74	1.1 (0.8–1.3)	0.9 (0.6–1.2)	.17	1 (0.7–1.2)	1.1 (0.8–1.2)	.85	1.2 (0.7–1.3)	0.9 (0.7–1.1)	.17
1st month	0.9 (0.7–1.4)	.48	1 (0.6–1.4)	1 (0.7–1.4)	.8	1.1 (0.7–1.4)	0.9 (0.7–1.2)	.68	0.9 (0.6–1)	1.4 (0.8–1.6)	**.007**	0.9 (0.4–1.4)	1.1 (0.8–1.6)	.12	1 (0.7–1.4)	0.9 (0.7–1.4)	.98
HDL cholesterol, mmol/L																
Baseline	1.2 (1-1.5)		1.2 (1.1–1.7)	1.2 (1-1.4)	.52	1.2 (1-1.6)	1.2 (1-1.5)	.86	1.2 (1-1.5)	1.2 (1.1–1.4)	.98	1.2 (1-1.5)	1.2 (1.1–1.8)	.35	1.2 (1-1.6)	1.3 (1.1–1.5)	.4
1st month	1.3 (1-1.6)	.66	1.2 (1-1.5)	1.4 (1.1–1.6)	.32	1.2 (1-1.4)	1.4 (1.1–1.6)	.11	1.4 (1.1–1.7)	1.2 (1-1.4)	.054	1.4 (1.1–1.6)	1.1 (0.9–1.2)	**.004**	1.1 (1-1.5)	1.4 (1.2–1.6)	.07

(continued)

Table 1 (continued).

Characteristic	All		TC			LDL-C			TG			HDL-C			non-HDL-C		
	n/total (%)	*P*[e]	<5%, n/total (%)	≥5%, n/total (%)	*P*[b]	<5%, n/total (%)	≥5%, n/total (%)	*P*[b]	<5%, n/total (%)	≥5%, n/total (%)	*P*[b]	>−5%, n/total (%)	≤−5%, n/total (%)	*P*[b]	<5%, n/total (%)	≥5%, n/total (%)	*P*[b]
Hypercholesterolemia (≥ 5 mmol/L)																	
Baseline	9/53 (17.0)		7/27 (25.9)	2/26 (7.7)	.07	7/26 (26.9)	2/23 (8.7)	.1	4/26 (15.4)	4/19 (21.0)	.62	4/35 (11.4)	5/15 (33.3)	.07	6/26 (23.1)	3/24 (12.5)	.33
1st month	14/53 (26.4)	.27	3/27 (11.1)	11/26 (42.3)	**.01**	3/26 (11.5)	9/23 (39.1)	**.03**	8/26 (30.8)	2/19 (10.5)	.11	10/35 (28.6)	2/15 (13.3)	.27	2/26 (7.7)	10/24 (41.7)	**.005**
LDL hypercholesterolemia (≥ 3 mmol/L)																	
Baseline	7/49 (14.3)		5/26 (19.2)	2/23 (8.7)	.29	5/26 (19.2)	2/23 (8.7)	.29	2/26 (7.7)	4/19 (21.0)	.19	3/35 (8.6)	4/14 (28.6)	.07	4/26 (15.4)	3/23 (13.0)	.82
1st month	10/49 (20.4)	.45	3/26 (11.5)	7/23 (30.4)	.1	3/26 (11.5)	7/23 (30.4)	.1	6/26 (23.1)	3/19 (15.8)	.55	7/35 (20.0)	3/14 (21.4)	.88	2/26 (7.7)	8/23 (34.8)	**.02**
Hypertriglyceridemia (≥ 2 mmol/L)																	
Baseline	1/48 (2.1)		0	1/22 (4.6)	.27	0	1/23 (4.4)	.3	1/26 (3.9)	0	.39	1/33 (3.0)	0	.51	0	1/23 (4.4)	.3
1st month	4/48 (8.3)	.5	1/25 (4.0)	3/23 (13.0)	.26	1/25 (4.0)	2/22 (9.1)	.48	1/26 (3.9)	2/19 (10.5)	.38	1/34 (2.9)	3/14 (21.4)	**.04**	1/25 (4.0)	3/23 (13.0)	.26
HDL hypocholesterolemia (≤ 1 mmol/L)																	
Baseline	13/50 (26.0)		6/26 (23.1)	7/24 (29.2)	.62	7/26 (26.9)	6/23 (26.1)	.95	8/26 (30.8)	4/19 (21.1)	.47	10/35 (28.6)	3/15 (20.0)	.53	8/26 (30.8)	5/24 (20.8)	.42
1st month	13/50 (26.0)	1	7/27 (25.9)	6/24 (25.0)	.94	8/26 (30.8)	4/23 (17.4)	.28	4/26 (15.4)	6/19 (31.6)	.2	6/35 (17.1)	7/15 (46.7)	**.03**	9/26 (34.6)	4/24 (16.7)	.15

[a]Only patients with no lipid-lowering medications and who had available lipid levels at baseline and after 1 month of treatment were included in analyses. Of note, only blood samples in fasting conditions were included for TG analyses.
[b]*P* values were calculated using rank-sum tests for continuous variables and χ^2 tests for categorical variables. Values in bold are significant.
[c]Eight patients received an additional antipsychotic, which may induce metabolic disturbances. More precisely, aripiprazole was coprescribed once with amisulpride and once with risperidone, while amisulpride, aripiprazole, olanzapine, and risperidone were coprescribed with quetiapine in 1, 1, 1, and 3 patients, respectively.
[d]Weight data were missing in the TC ≥ 5%, LDL ≥ 5%, HDL-C > −5%, and non-HDL-C ≥ 5% groups.
[e]*P* values were calculated using McNemar tests to compare metabolic parameters between baseline and first month of treatment. Values in bold are significant.
Abbreviations: HDL-C = high-density lipoprotein cholesterol, *ICD-10 = International Classification of Diseases, Tenth Revision*, IQR = interquartile range, LDL-C = low-density lipoprotein cholesterol, non-HDL-C = non–high-density lipoprotein cholesterol, TC = total cholesterol, TG = triglycerides.

range are indicated in Supplementary Table 5. The proportion of patients who met criteria for dyslipidemia at or after 3 months of SGA treatment ranged from 8% to 33%, (ie, 8% [2/24], 8% [2/25], 9% [2/21], 13% [3/24], and 33% [8/24] for LDL-C, non-HDL-C, HDL-C, TG, and TC, respectively). Of note, analyses conducted in a higher number of patients (n = 79) whose lipid levels at first month were not readily available (and whose baseline lipid levels were within the normal range) showed similar findings, ie, dyslipidemia incidences of 23%, 11%, 5%, 7%, and 6% for TC, LDL-C, TG, HDL-C, and non-HDL-C, respectively.

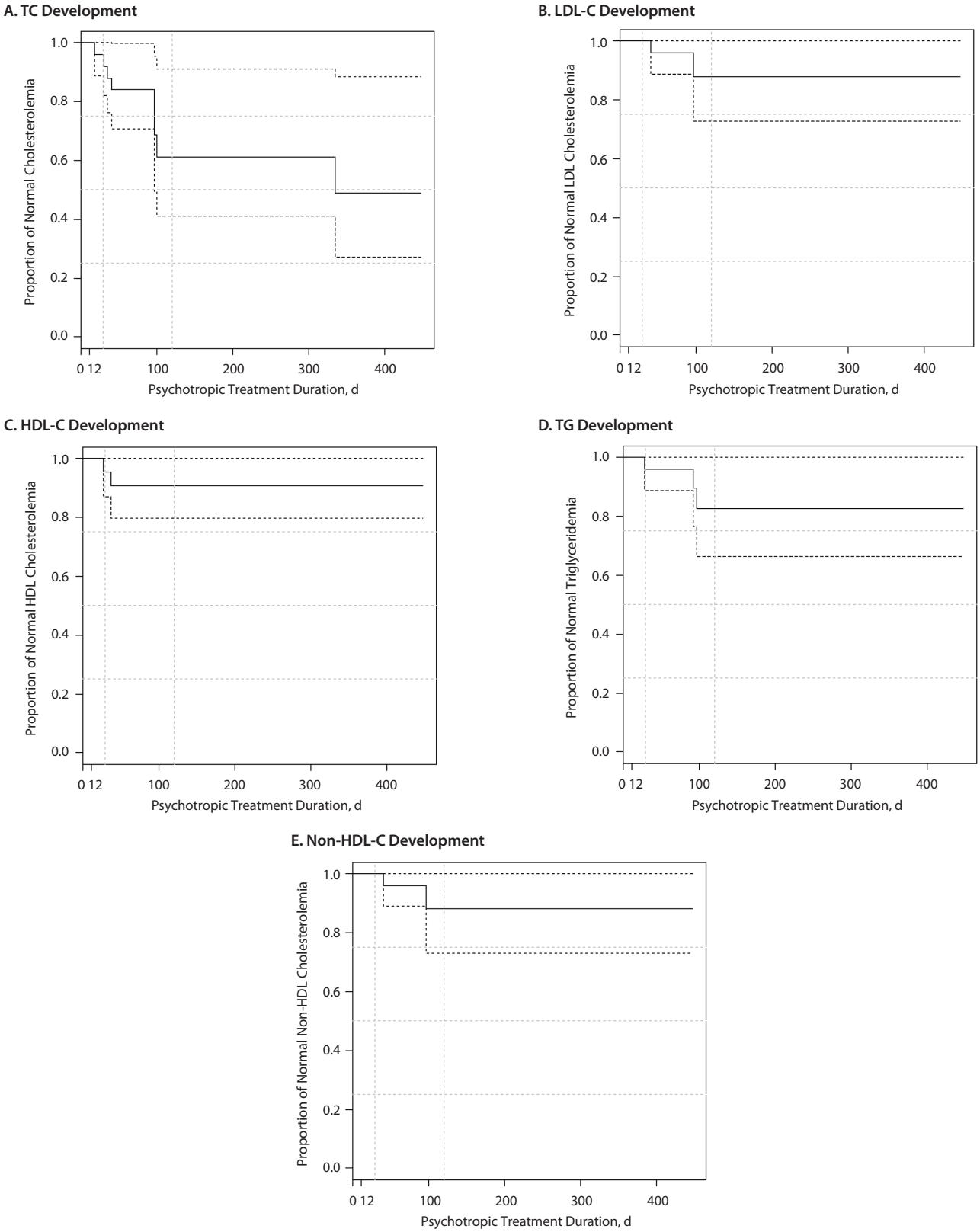
Baseline TC and LDL-C levels were significantly higher in patients who developed dyslipidemia as compared with those who did not ($P \leq .02$). In addition, patients developing TC hypercholesterolemia were more likely to be female ($P = .009$). Finally, although age range was narrow in the present psychiatric sample, patients developing TC hypercholesterolemia were significantly older as compared with those who did not ($P = .05$). Of note, a trend was also observed for higher age to be associated with an increased risk of LDL and non-HDL hypercholesterolemia ($P = .06$).

Development of new-onset dyslipidemia during treatment with SGAs is displayed in Figure 1. As the incidence of dyslipidemia for LDL-C, TG, HDL-C, and non-HDL-C was insufficient to perform multivariate analyses, Cox regression was conducted only on TC. Table 2 shows that female patients were significantly more prone to develop a TC hypercholesterolemia compared with male patients ($P = .01$). In addition, patients whose TC levels increased by ≥ 5% during the first month of treatment had a greater susceptibility to develop TC hypercholesterolemia as compared with others ($P = .02$). Although large confidence intervals were observed due to a small sample size, survival rate curves were significantly divided over time, depending on sex, and a trend of difference was observed for early thresholds of TC increase (Supplementary Figure 2).

DISCUSSION

In the present sample of adolescent patients receiving SGAs, a worrisome hypercholesterolemia prevalence of 17% for total cholesterol was observed at baseline, which is comparable to baseline results from a retrospective study including first-episode patients aged 23.6 years (SD = 5 years).[27] A Spanish pediatric study observed a higher

Figure 1. Patient Survival Curves for New-Onset Dyslipidemia by Unadjusted Kaplan-Meier Curves[a]



[a]Dotted lines indicate the 95% CI of the survival curve.
Abbreviations: HDL-C = high-density lipoprotein hypocholesterolemia, LDL-C = low-density lipoprotein hypercholesterolemia, non-HDL-C = non–high-density lipoprotein hypercholesterolemia, TC = total cholesterol hypercholesterolemia, TG = hypertriglyceridemia.

Table 2. Risk Factors for TC (n = 24) During the First Year of Psychotropic Treatment[a]

	Estimate (SE)	*P* Value
Age		NS
Sex	−4.40 (1.78)	.01
Early lipid increase[b]	4.38 (1.82)	.02
Psychotropic medication[c]		NS
Early weight gain[d]		NS

[a]Results were obtained by fitting a Cox regression controlling for age, sex, current psychotropic drug, and early weight gain > 4% group. Cox regressions could not be performed on low-density lipoprotein hypercholesterolemia, hypertriglyceridemia, and high-density lipoprotein hypocholesterolemia due to an insufficient number of new cases.
[b]Early lipid change groups constructed according to 5% thresholds (≥ 5% vs < 5% of total cholesterol increase for new-onset dyslipidemia TC model).
[c]Risperidone (n = 4) vs quetiapine (n = 14) vs olanzapine (n = 6).
[d]Early weight gain groups were constructed according to the 4% threshold after 1 month of treatment (> 4% vs ≤ 4%) (see Vandenberghe et al[20]).
Abbreviations: NS = not significant, SE = standard error, TC = total cholesterol hypercholesterolemia.

proportion (26%) of hypercholesterolemia at baseline,[36] possibly attributable to a less stringent criterion used to define hypercholesterolemia (ie, ≥170 mg/dL, corresponding to 4.4 mmol/L). In adult patients treated in our department, a much higher prevalence of baseline hypercholesterolemia was observed (38%),[31] which can be explained by a longer duration of illness and of lifetime exposure to psychotropic treatment.

In the present study, almost half the adolescents had early lipid changes of ≥ 5% (ie, 49%, 47%, 42%, 30%, and 48% for TC, LDL-C, TG, HDL-C, and non-HDL-C, respectively), which is comparable with the proportions previously observed in adults (43%, 43%, 57%, 42%, and 47%, respectively).[31] Adolescent patients whose lipid levels changed by ≥ 5% during the first month appeared to have higher changes of lipid levels and a greater tendency to develop hypercholesterolemia during the course of a long-term treatment, as compared with patients whose early lipid levels changed by < 5%. In accordance with a previous study conducted in our department, which included mainly adult patients,[31] the risk of developing hypercholesterolemia was significantly greater for female patients than for male patients. These findings are also consistent with results from a retrospective adolescent cohort[24] and with other studies, albeit controversial, suggesting that women have a greater vulnerability to develop psychotropic-drug–induced metabolic disturbances than men.[12,17,45]

In the present study, young female patients had higher levels of total cholesterol than young male patients, in agreement with results from a recent study on adolescent psychiatric inpatients.[20] Multivariate analyses showed that young female patients and patients with early increase in TC were more likely to develop new-onset hypercholesterolemia as compared with others. On the other hand, previous analyses in a sample including a higher number of patients (aged 13–89 years) showed that male patients were more prone than female patients to develop HDL hypocholesterolemia during treatment with psychotropic drugs.[31] These contrasting results suggest that further studies considering a higher number of adolescents should be performed to determine whether the present sex difference is replicated.

Considering the consequences of dyslipidemia on cardiovascular comorbidities, these worrisome findings should raise concerns about the critical necessity of developing clinical strategies to monitor and control lipid levels in young patients receiving psychotropic treatments that induce metabolic side effects. According to studies conducted between 2000 and 2011 in 5 countries, only 22% of patients initiating a SGA had a lipid profile screen.[46] Even though local and national guideline implementations helped to significantly increase the screening rate (up to 37%), rates of testing remain insufficient.[46] Because we did not have access to information on the total cohort of adolescent patients starting a psychotropic medication in our department, we could not calculate screening rate. However, we observed that among 77 adolescents with available parameters collected in the context of metabolic follow-up (eg, weight), only 60 (ie, 78%) received a blood sample test at baseline. These observations are in accordance with another study[47] showing an insufficient percentage of metabolic follow-up in adolescent patients being prescribed psychotropic medications that induce metabolic side effects. Finally, in the present study, 13% of the patients received olanzapine, a drug without indication in Switzerland in children and adolescents, which is known to induce substantial adverse metabolic effects.[48,49] Thus, putting more effort into the dissemination of knowledge and enforcement of guidelines would tentatively help to increase the rates of metabolic follow-up and improve the quality of life and longevity of young patients.[50]

The findings of the present study need to be considered with some limitations. First, although the median age was low, the majority of patients were not drug naïve, and the observed increase in lipid levels may have resulted from past treatments. However, the naturalistic setting of the present study strengthens the clinical validity of the present findings. Second, information on environmental changes, such as physical exercise or diet habits throughout the treatment, which could have influenced the evolution of lipid levels, were not available and, therefore, not taken into account. Third, a considerable drop-out rate was observed during the prospective study, which reduced the number of available observations after 3 months of treatment and was possibly attributable to psychiatry-related factors, such as treatment switching, poor medication adherence, or refusal of patients participate in follow-up. In addition, medication adherence was not guaranteed, which could lead to the inclusion of some false negatives (for example, patients who did not develop adverse lipid effects because they did not take the drug). However, exclusion of such patients might have led to even worse lipid outcomes. Finally, in the present study, patients received no other psychotropic drugs (ie, first-generation antipsychotics, mood stabilizers, or antidepressants) than SGAs. Future studies that include adolescents receiving drugs other than SGAs should also

be performed to evaluate their impact on the worsening of the lipid profile.

In conclusion, this study underlines the importance of metabolic monitoring following the introduction of SGAs in young patients who are particularly susceptible to adverse metabolic effects. Further research should focus on finding effective interventions to prevent such adverse effects. In cases of metabolic disturbance, if clinically possible, the causative SGA should be replaced after a careful evaluation of the risk-benefit ratio of a drug switch. Considering the major impact of dyslipidemia and its important consequences on morbidity and mortality, it is critical that health care professionals are aware of the risks associated with the prescription of SGAs.

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Author contributions: Dr Eap had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design was provided by Dr Eap. Drs Delacrétaz, Vandenberghe, Glatard, Dubath, Gholam-Rezaee, Holzer, Ambresin, Conus, and Eap and Mr Levierwere involved in data acquisition. Statistical analysis and interpretation were provided by Dr Delacrétaz. Drafting of the manuscript was provided by Dr Delacrétaz. Critical revision of the manuscript for important intellectual content was provided by all authors. Drs Eap and Conus obtained funding for the study. Administrative, technical, or material support was provided by Drs Conus and Eap. All authors gave their approval for the present article.

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REFERENCES

1. Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. *Psychiatr Serv*. 2009;60(2):147–156.
2. Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Curr Opin Psychiatry*. 2012;25(2):83–88.
3. Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009;374(9690):620–627.
4. Miller C, Bauer MS. Excess mortality in bipolar disorders. *Curr Psychiatry Rep*. 2014;16(11):499.
5. Ringen PA, Engh JA, Birkenaes AB, et al. Increased mortality in schizophrenia due to cardiovascular disease—a non-systematic review of epidemiology, possible causes, and interventions. *Front Psychiatry*. 2014;5:137.
6. Crump C, Sundquist K, Winkleby MA, et al. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. *JAMA Psychiatry*. 2013;70(9):931–939.
7. Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophr Res*. 2011;131(1–3):101–104.
8. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World Psychiatry*. 2014;13(2):153–160.
9. Hjorthøj C, Stürup AE, McGrath JJ, et al. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry*. 2017;4(4):295–301.
10. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72(4):334–341.
11. Khan A, Faucett J, Morrison S, et al. Comparative mortality risk in adult patients with schizophrenia, depression, bipolar disorder, anxiety disorders, and attention-deficit/hyperactivity disorder participating in psychopharmacology clinical trials. *JAMA Psychiatry*. 2013;70(10):1091–1099.
12. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends Mol Med*. 2011;17(2):97–107.
13. De Hert M, Detraux J, van Winkel R, et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2011;8(2):114–126.
14. Correll CU, Detraux J, De Lepeleire J, et al. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry*. 2015;14(2):119–136.
15. Diaz FJ, Perez-Iglesias R, Mata I, et al. Using structural equations to test for a direct effect of some antipsychotics on triglyceride levels in drug-naïve first-episode psychosis patients. *Schizophr Res*. 2011;131(1-3):82–89.
16. Krill RA, Kumra S. Metabolic consequences of second-generation antipsychotics in youth: appropriate monitoring and clinical management. *Adolesc Health Med Ther*. 2014;5:171–182.
17. Coccurello R, Moles A. Potential mechanisms of atypical antipsychotic-induced metabolic derangement: clues for understanding obesity and novel drug design. *Pharmacol Ther*. 2010;127(3):210–251.
18. Pisano S, Catone G, Veltri S, et al. Update on the safety of second generation antipsychotics in youths: a call for collaboration among paediatricians and child psychiatrists. *Ital J Pediatr*. 2016;42(1):51.
19. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765–1773.
20. Vandenberghe F, Najar-Giroud A, Holzer L, et al. Second-generation antipsychotics in adolescent psychiatric patients: metabolic effects and impact of an early weight change to predict longer term weight gain. *J Child Adolesc Psychopharmacol*. 2018;28(4):258–265.
21. Tohen M, Kryzhanovskaya L, Carlson G, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *Am J Psychiatry*. 2007;164(10):1547–1556.
22. Patel NC, Hariparsad M, Matias-Akthar M, et al. Body mass indexes and lipid profiles in hospitalized children and adolescents exposed to atypical antipsychotics. *J Child Adolesc Psychopharmacol*. 2007;17(3):303–311.
23. Laita P, Cifuentes A, Doll A, et al. Antipsychotic-related abnormal involuntary movements and metabolic and endocrine side effects in children and adolescents. *J Child Adolesc Psychopharmacol*. 2007;17(4):487–502.
24. McIntyre RS, Jerrell JM. Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents. *Arch Pediatr Adolesc Med*. 2008;162(10):929–935.
25. Reeves GM, Keeton C, Correll CU, et al. Improving metabolic parameters of antipsychotic child treatment (IMPACT) study: rationale, design, and methods. *Child Adolesc Psychiatry Ment Health*. 2013;7(1):31.
26. Enger C, Jones ME, Kryzhanovskaya L, et al. Risk of developing diabetes and dyslipidemia among adolescents with bipolar disorder or schizophrenia. *Int J Adolesc Med Health*. 2013;25(1):3–11.
27. Correll CU, Robinson DG, Schooler NR, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry*. 2014;71(12):1350–1363.
28. Manu P, Dima L, Shulman M, et al. Weight gain and obesity in schizophrenia: epidemiology, pathobiology, and management. *Acta Psychiatr Scand*. 2015;132(2):97–108.
29. Cooper SJ, Reynolds GP, Barnes T, et al; With expert co-authors (in alphabetical order). BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol*. 2016;30(8):717–748.
30. Vandenberghe F, Gholam-Rezaee M, Saigí-Morgui N, et al. Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment. *J Clin Psychiatry*. 2015;76(11):e1417–e1423.
31. Delacrétaz A, Vandenberghe F, Gholam-Rezaee M, et al. Early changes of blood lipid levels during psychotropic drug treatment as predictors of long-term lipid changes and of new onset dyslipidemia. *J Clin Lipidol*. 2018;12(1):219–229.
32. Srihari VH, Phutane VH, Ozkan B, et al. Cardiovascular mortality in schizophrenia: defining a critical period for prevention. *Schizophr Res*. 2013;146(1–3):64–68.
33. Cai HL, Tan QY, Jiang P, et al. A potential mechanism underlying atypical antipsychotics-induced lipid disturbances. *Transl Psychiatry*. 2015;5(10):e661.
34. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in

patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry*. 2003;160(2):290–296.
35. Zhang S, Lan G. Prospective 8-week trial on the effect of olanzapine, quetiapine, and aripiprazole on blood glucose and lipids among individuals with first-onset schizophrenia. *Shanghai Jingshen Yixue*. 2014;26(6):339–346.
36. Arango C, Giráldez M, Merchán-Naranjo J, et al. Second-generation antipsychotic use in children and adolescents: a six-month prospective cohort study in drug-naïve patients. *J Am Acad Child Adolesc Psychiatry*. 2014;53(11):1179–1190, 1190.e1–1190.e4.
37. O'Donoghue B, Schäfer MR, Becker J, et al. Metabolic changes in first-episode early-onset schizophrenia with second-generation antipsychotics. *Early Interv Psychiatry*. 2014;8(3):276–280.
38. Choong E, Solida A, Lechaire C, et al. Follow-up of the metabolic syndrome induced by atypical antipsychotics: recommendations and pharmacogenetics perspectives. *Rev Med Suisse*. 2008;4(171):1994–1996, 1998–1999.
39. Choong E, Quteineh L, Cardinaux JR, et al; ODEX team. Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and the general adult population. *JAMA Psychiatry*. 2013;70(10):1011–1019.
40. Doran B, Guo Y, Xu J, et al. Prognostic value of fasting versus nonfasting low-density lipoprotein cholesterol levels on long-term mortality: insight from the National Health and Nutrition Examination Survey III (NHANES-III). *Circulation*. 2014;130(7):546–553.
41. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet*. 2014;384(9943):626–635.
42. Mancia G, Fagard R, Narkiewicz K, et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31(7):1281–1357.
43. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143–3421.
44. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499–502.
45. Seeman MV. Secondary effects of antipsychotics: women at greater risk than men. *Schizophr Bull*. 2009;35(5):937–948.
46. Mitchell AJ, Delaffon V, Vancampfort D, et al. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. *Psychol Med*. 2012;42(1):125–147.
47. Rettew DC, Greenblatt J, Kamon J, et al. Antipsychotic medication prescribing in children enrolled in Medicaid. *Pediatrics*. 2015;135(4):658–665.
48. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962.
49. Schulz C, Haight RJ. Safety of olanzapine use in adolescents. *Expert Opin Drug Saf*. 2013;12(5):777–782.
50. Mangurian C, Giwa F, Shumway M, et al. Primary care providers' views on metabolic monitoring of outpatients taking antipsychotic medication. *Psychiatr Serv*. 2013;64(6):597–599.

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Supplementary Material

Article Title: Lipid Disturbances in Adolescents Treated With Second-Generation Antipsychotics: Clinical Determinants of Plasma Lipid Worsening and of New-Onset Hypercholesterolemia

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Appendix 1

METHODS

Study design

Clinical data were either collected during hospitalization or in outpatient centers during a medical examination based on the department guideline for the metabolic follow-up of psychotropic drugs performed on a routine basis. Follow-up was restarted from baseline if a treatment was stopped for more than 2 weeks, if a psychotropic drug was replaced by another, or if a second psychotropic drug was added. If two or more follow-ups were available for one patient, only the longest one was included in the analysis.

RESULTS

Some demographic differences were observed between patients whose lipid levels change was <5% or ≥5% (Table 1). In particular, patients whose total cholesterol increase was ≥5% were slightly older ($p = 0.02$), were more likely to receive olanzapine (23% versus 4%; $p = 0.04$), had significantly lower levels of total cholesterol at baseline (3.6 mmol/l versus 4.3 mmol/l; $p = 0.04$), and were more likely to have early weight gain >4% (56% versus 26%; $p = 0.03$) as compared to others. Of note, within the different diagnoses, the prevalence of patients with or without early lipid worsening was similar. In addition, comparing metabolic parameters across the nine different diagnoses did not reveal any significant difference. An increased number of patients in the under-represented diagnosis categories (e.g. those with a number of patients <10) should provide an increased power and would help to perform a more accurate comparison. Finally, patients receiving two SGAs concomitantly were distributed similarly across groups of early lipid levels change (Table 1).

Supplementary Table 1. Drugs included in the metabolic follow-up recommendation

ANTIPSYCHOTICS		ANTIDEPRESSANTS		MOOD STABILIZERS
Atypical (second-generation)	**Typical (first-generation)**	**Tricyclic**	**Other**	
Amisulpride Aripiprazole Asenapine Clozapine Lurasidone Olanzapine Paliperidone Quetiapine Risperidone Sertindole	Chlorprothixene Flupentixol Haloperidol Levomepromazine Pipamperone Promazine Sulpiride Tiapride Zuclopenthixol	Amitriptyline Clomipramine Doxepine Imipramine Nortriptyline Opipramol Trimipramine	Mirtazapine	Carbamazepine Lithium Valproate

According to international recommendations, a metabolic follow-up is ongoing since 2007 in the Department of Psychiatry at the Lausanne University Hospital [1], in which inpatients and outpatients are prospectively monitored when starting a pharmacological treatment known to have a potential risk to induce metabolic disturbances (i.e. drugs listed above). The list is based on psychotropic drugs available in Switzerland).

Supplementary Table 2. Lipid-lowering drugs considered to characterize dyslipidemia

Lipid-lowering drugs
Atorvastatin
Ezetimibe
Fenofibrate
Fluvastatin
Pravastatin
Rosuvastatin
Simvastatin

The list was extracted from [2]. This list only provides lipid-lowering drugs prescribed in the present longitudinal observational study.

Supplementary Table 3. Gender comparison of demographic and clinical parameters in patients without lipid-lowering comedication

Demographic	Men	Women	p-value
Number of patients	24	29	
Age, median (IQR), y	16.1 (14.8-17.5)	16.9 (14.8-17.4)	0.49
Smoking, n(%)	9 (37.5)	11 (37.9)	0.46
Diagnosis, n(%)			
Psychoactive substance use (F10-F19)	1 (4.2)	1 (3.5)	0.89
Schizophrenia (F20-F29)	3 (12.5)	4 (13.8)	0.89
Mood disorders (F30-F39)	9 (37.5)	14 (48.3)	0.43
Stress related disorders (F40-F48)	3 (12.5)	4 (13.8)	0.89
Behavioral syndromes (F50-F59)	0	2 (6.9)	0.19
Mental retardation (F70-F79)	0	1 (3.5)	0.36
Psychological development (F80-F89)	2 (8.3)	0	0.11
Behavioral and emotional disorders (F90-F98)	4 (16.7)	2 (6.9)	0.26
Not available	2 (8.3)	1 (3.5)	0.44
Medication, n(%)			
Amisulpride	1 (4.2)	0	0.27
Olanzapine	4 (16.7)	3 (10.3)	0.5
Quetiapine	11 (45.8)	22 (75.9)	**0.02**
Risperidone	8 (33.3)	4 (13.8)	0.09
Polymedication, n(%) [a]	4 (16.7)	4 (13.8)	0.77
Psychiatric illness duration, median (IQR), y	3.3 (2.0-8.3)	2.2 (1.2-4.7)	0.29
Early weight gain (>4%), n(%)			
1st month	9 (39.1)	12 (41.4)	0.87
Total cholesterol, median (IQR), mmol/l			
Baseline	3.6 (3.2-4.3)	4.3 (3.7-4.6)	**0.02**
1st month	3.8 (3.3-4.2)	4.4 (4-5.2)	**0.004**
LDL cholesterol, median (IQR), mmol/l			
Baseline	2.0 (1.6-2.5)	2.4 (1.9-2.7)	0.09
1st month	2 (1.7-2.6)	2.4 (2.0-2.9)	0.1
Triglyceride, median (IQR), mmol/l			
Baseline	1 (0.6-1.2)	1 (0.7-1.2)	0.56
1st month	1 (0.8-1.4)	1 (0.7-1.4)	0.84
HDL cholesterol, median (IQR), mmol/l			
Baseline	1.2 (1-1.4)	1.2 (1.1-1.5)	0.42

1st month	1.1 (1-1.5)	1.4 (1.1-1.7)	0.08
Hypercholesterolemia (≥ 5 mmol/l), n/total (%)			
Baseline	3/24 (12.5)	6/29 (20.7)	0.43
1st month	3/24 (12.5)	11/29 (37.9)	**0.04**
LDL hypercholesterolemia (≥ 3 mmol/l), n/total (%)			
Baseline	3/24 (12.5)	4/25 (16.0)	0.73
1st month	4/24 (16.6)	6/25 (24.0)	0.52
Hypertriglyceridemia (≥ 2 mmol/l), n/total (%)			
Baseline	0	1/26 (3.9)	0.35
1st month	1/24 (4.2)	3/24 (12.5)	0.3
HDL hypocholesterolemia (≤ 1 mmol/l), n/total (%)			
Baseline	9/24 (37.5)	4/26 (15.4)	0.08
1st month	9/24 (37.5)	4/26 (15.4)	0.08

Only patients without any lipid-lowering medication were included. P-values were calculated using rank-sum tests for continuous variables and Chi2 tests for categorical variables. Values in bold are significant.

[a]: Eight patients received an additional antipsychotic which may induce metabolic disturbances. More precisely, aripiprazole was co-prescribed once with amisulpride and once with risperidone, while amisulpride, aripiprazole, olanzapine and risperidone were co-prescribed with quetiapine in one, one, one and three patients, respectively).

Abbreviations: HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

Supplementary Table 4. Linear regressions fitted on lipid trait changes (%) over time

n	Difference of TC change (%) between <5% and ≥5% groups (95%CI)	p-value	n	Difference of LDL-C change (%) between <5% and ≥5% groups (95%CI)	p-value	n	Difference of HDL-C change (%) between <5% and ≥5% groups (95%CI)	p-value	n	Difference of non-HDL-C change (%) between <5% and ≥5% groups (95%CI)	p-value
29	11.5% (-2.2% - 25.2%)	0.10	26	17.8% (-9.2% - 44.9%)	0.19	27	-16.2% (-30.0% - (-) 2.4%)	**0.02**	27	17.6% (-2.1% - 37.3%)	0.08

Results were obtained by fitting linear regressions controlling for age, gender, early weight gain group (i.e. >4% versus ≤4%) and psychotropic treatment categories (i.e. olanzapine, clozapine, mirtazapine and quetiapine versus other drugs). P-values in bold are significant. Analyses on triglyceride could not be performed due to a too low number of observations. Abbreviations: HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

Supplementary Table 5. Demographic parameters and comparisons between patients with and without new-onset dyslipidemia during the first year of psychotropic treatment

	Patients without NODTC (n=16)	Patients with NODTC (n=8)	p-value	Patients without NODLDL (n=22)	Patients with NODLDL (n=2)	p-value	Patients without NODTG (n=21)	Patients with NODTG (n=3)	p-value	Patients without NODHDL (n=19)	Patients with NODHDL (n=2)	p-value	Patients without NODnonHDL (n=23)	Patients with NODnonHDL (n=2)	p-value
Age, median (IQR), y	15.6 (14.3-16.6)	17 (16.4-17.6)	**0.05**	16 (14.6-17)	18 (18-18)	0.06	16.4 (15.5-17.4)	17.1 (15.6-17.9)	0.36	16.3 (15.5-17.4)	15.8 (14.1-17.5)	0.81	15.8 (14.6-17.0)	17.7 (17.6-17.8)	0.06
Men, n(%)	11 (68.8)	1 (12.5)	**0.009**	11 (50.0)	1 (50.0)	1	12 (57.1)	1 (33.3)	0.44	9 (47.4)	1 (50.0)	0.94	12 (52.2)	1 (50.0)	0.95
Smoking, n(%)	7 (43.8)	2 (25.0)	0.59	9 (40.9)	1 (50.0)	0.85	9 (42.9)	1 (33.3)	0.67	5 (26.3)	2 (100)	0.11	9 (39.1)	1 (50.0)	0.85
Diagnosis, n(%)															
Psychotic disorders	2 (12.5)	2 (25.0)	0.44	3 (13.6)	0	0.58	4 (19.1)	0	0.41	3 (15.8)	1 (50.0)	0.24	3 (13.0)	0	0.59
Bipolar disorders	2 (12.5)	0	0.3	3 (13.6)	0	0.58	3 (14.3)	1 (33.3)	0.24	3 (15.8)	0	0.74	4 (17.4)	0	0.76
Depressive disorders	7 (43.8)	1 (12.5)	0.13	9 (40.9)	0	0.25	8 (38.1)	2 (66.7)	0.35	8 (42.1)	0	0.24	9 (39.1)	0	0.27
Other	4 (25.0)	3 (37.5)	0.53	5 (22.7)	1 (50.0)	0.39	5 (23.8)	0	0.34	4 (21.1)	0	0.47	5 (21.7)	1 (50.0)	0.37
Not available	1 (6.3)	2 (25.0)	0.19	2 (9.1)	1 (50.0)	0.09	1 (4.8)	0	0.7	1 (5.3)	1 (50.0)	**0.04**	2 (8.7)	1 (50.0)	0.09
Medication, n(%)															
Olanzapine	4 (25.0)	2 (25.0)	1	5 (22.7)	0	0.45	3 (14.3)	1 (33.3)	0.41	4 (21.0)	0	0.47	5 (21.7)	0	0.46
Quetiapine	10 (52.5)	4 (50.0)	0.56	14 (63.6)	1 (50.0)	0.7	13 (61.9)	2 (66.7)	0.9	10 (52.6)	2 (100)	0.2	14 (60.9)	1 (50.0)	0.76
Risperidone	2 (12.5)	2 (25.0)	0.44	3 (13.6)	1 (50.0)	0.19	5 (23.8)	0	0.34	5 (26.3)	0	0.41	4 (17.4)	1 (50.0)	0.27
Early weight gain (>4%), n(%)	8 (50.0)	3 (37.5)	0.56	9 (40.9)	1 (50.0)	0.8	7 (33.3)	1 (33.3)	1	5 (26.3)	1 (50.0)	0.48	9 (39.1)	1 (50.0)	0.76
Psychiatric illness duration, median (IQR) *years*	2.5 (1-7)	6 (1-10)	0.56	3 (1-5)	NA		3 (1.5-5)	6 (1-11)	0.71	2.5 (1-4)	4 (4-4)	0.42	3 (1-5)	NA	
Baseline lipid levels [a], median (IQR), *mmol/l*	3.5 (3.2-4)	4.4 (4.3-4.4)	**0.002**	2.2 (1.6-2.3)	2.8 (2.7-2.9)	**0.02**	1 (0.6-1.3)	1 (0.9-1.7)	0.33	1.4 (1.2-1.8)	1.2 (1.2-1.2)	0.27	2.5 (2.1-2.9)	3.2 (3.1-3.3)	0.07

Only patients with no dyslipidemia at baseline are included. P-values were calculated using rank-sum tests (for continuous variables) and chi^2 tests (for categorical variables) between groups. Values in bold are significant.

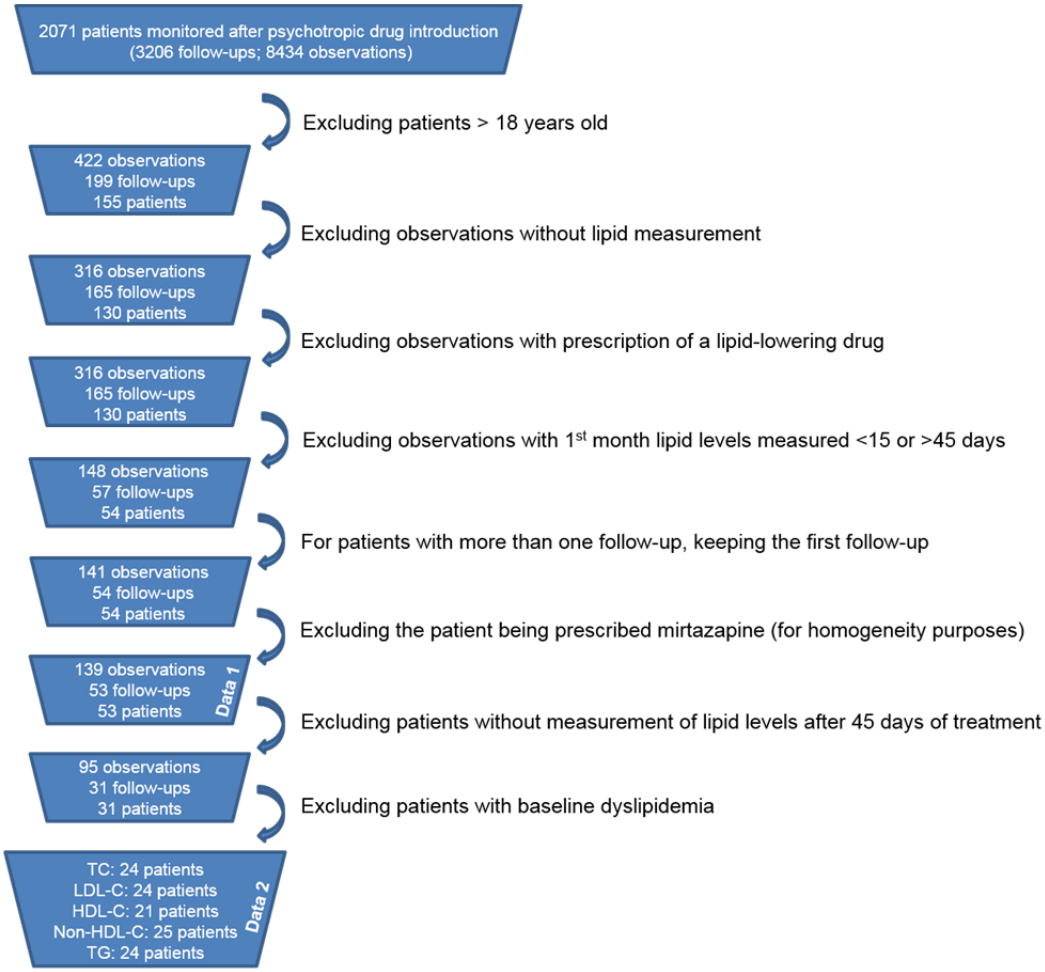
[a] Levels of TC for NODTC groups, LDL-C for NODLDL groups, TG for NODTG groups, HDL-C for NODHDL groups and non-HDL-C for NODnonHDL groups.

Abbreviations: NA: not available; NODHDL: new-onset HDL hypocholesterolemia, defined by plasma levels of HDL cholesterol ≤1 mmol/l (39 mg/dL)*; NODLDL: new-onset LDL hypercholesterolemia, defined by plasma levels of LDL cholesterol ≥3 mmol/l (116 mg/dL)*; NODnonHDL: new-onset nonHDL hypercholesterolemia, defined by plasma levels of non-

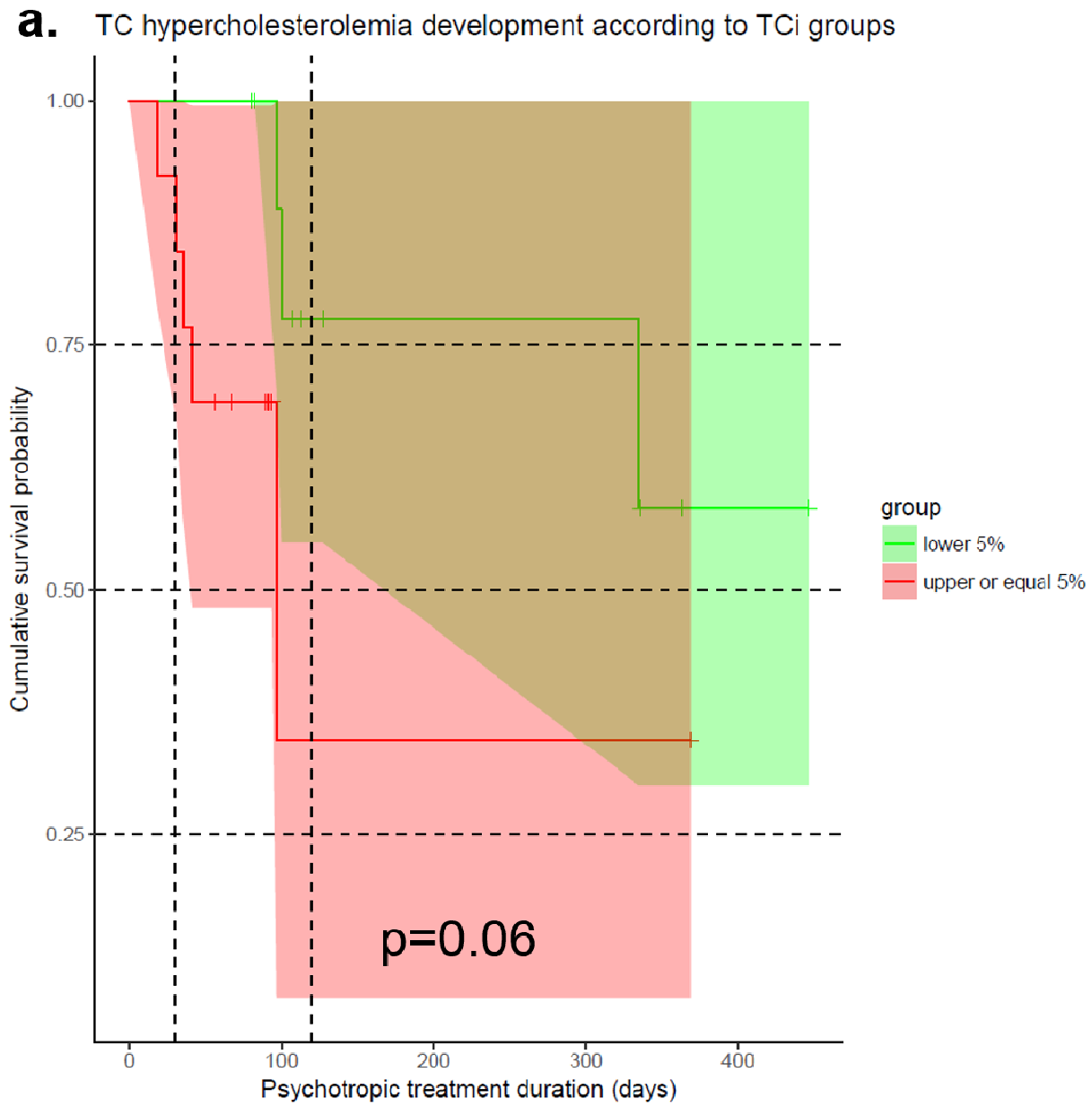
HDL cholesterol ≥4 mmol/l (154 mg/dL)*; NODTC: new-onset hypercholesterolemia, defined by plasma levels of total cholesterol ≥5 mmol/l (193 mg/dL)*; NODTG: new-onset hypertriglyceridemia, defined by plasma levels of triglycerides ≥2 mmol/l (177 mg/dL)*.

*None of the patients were prescribed lipid lowering agents.

Supplementary Figure 1. Flowchart of Patient Selection[a]

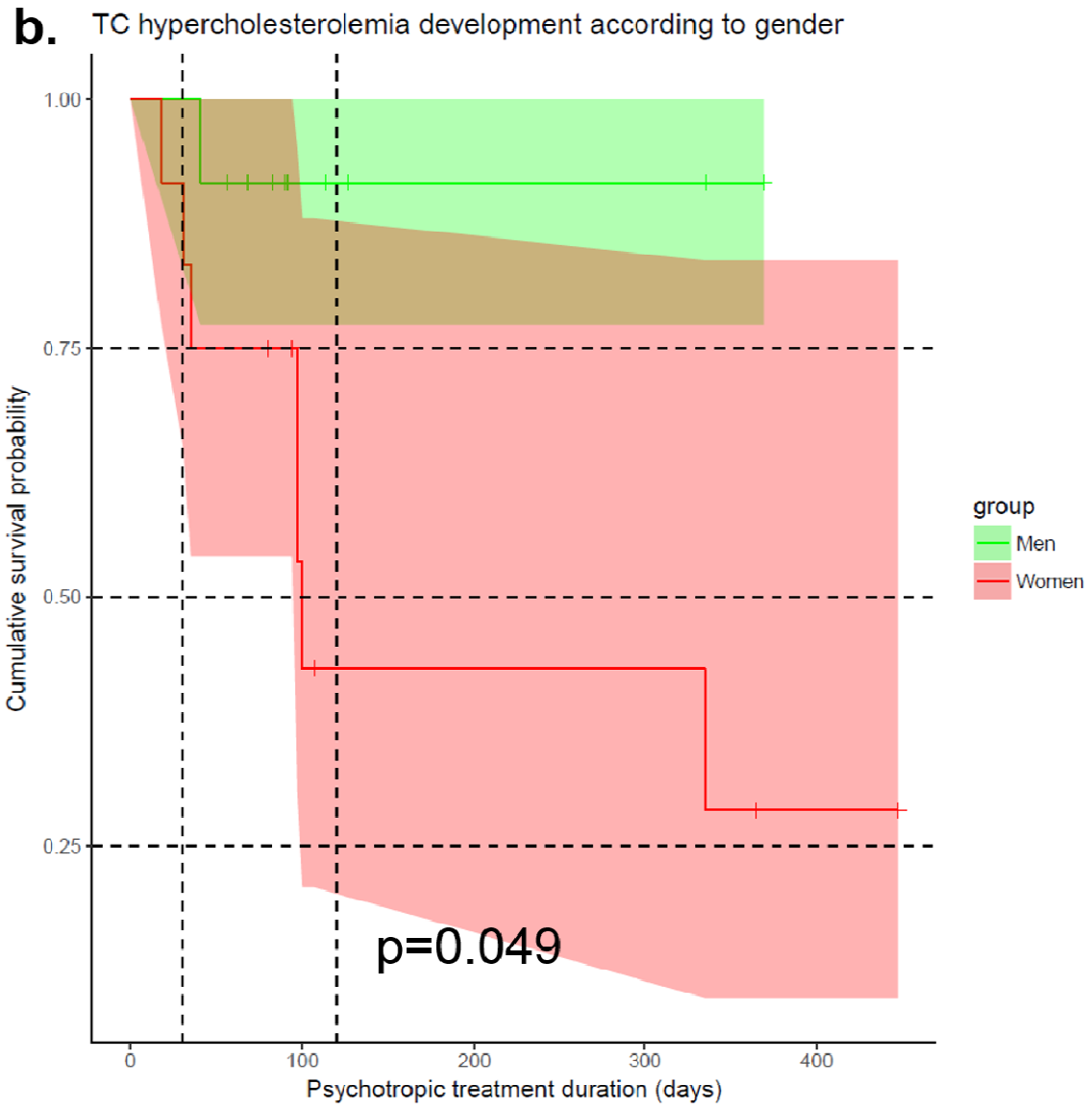


[a]Data 1 were used for the determination of patients who developed an early increase in blood lipid levels.
Data 2 were used for the determination of risk factors associated with the development of new-onset dyslipidemia.



Supplementary Figure 2. Survival curves for total cholesterol (TC) hypercholesterolemia by Kaplan-Meier curves according to clinical parameters

a. Patient survival curves for NODTC (new onset TC hypercholesterolemia) according to TCi (i.e. early 5% TC increase) threshold (n=24). Kaplan-Meier p-value=0.06; Cox p-value=0.02.



S2 Figure. Survival curves for total cholesterol (TC) hypercholesterolemia by Kaplan-Meier curves according to clinical parameters

b. Patient survival curves for NODTC (new onset TC hypercholesterolemia) according to gender (n=24). Kaplan-Meier p-value=0.049; Cox p-value=0.01.

REFERENCES

1. Choong E, Solida A, Lechaire C, Conus P, Eap CB. Follow-up of the metabolic syndrome induced by atypical antipsychotics: recommendations and pharmacogenetics perspectives. *Revue medicale suisse.* 2008;4:1994-1999.

2. Compendium Suisse des Medicaments. Vol 2016. Bern, Switzerland: Institut Suisse des produits thérapeutiques; 2014.