Title: Early changes of blood lipid levels during psychotropic drug treatment as predictors of long-term lipid changes and of new onset dyslipidemia - SUPPLEMENTARY DATA

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SUPPLEMENTARY DATA

1. METHODS

1.1 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 [1]. 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, as described in the flowchart (**S1 Figure**). Adherence was monitored by therapeutic drug monitoring and only patients for whom adherence was ascertained at each time point were included in analyses for the discovery sample (more information in paragraph 1.3). Diagnoses were based on the International Classification of Diseases 10th (ICD-10): F00-F09: organic disorders; F20.0-F24.9 and F28-F29: psychotic disorders; F25.0-F25.9; schizoaffective disorders; F30.0-F31.9: bipolar disorders; F32.0-F33.9: depression. Anxiety, personality disorders and mental retardation were classified in "other" disorders.

1.2 Blood samples and lipid levels

The majority of blood samples were drawn in the morning in fasting conditions. Non-fasting blood samples (i.e. within six hours following last meal) were excluded only for triglyceride (TG) analysis (not for total (TC), HDL- (HDL-C), LDL- (LDL-C) and non_HDL- (non-HDL-C) cholesterol) [2, 3]. 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). LDL-C was calculated using the Friedewald formula only if TG levels were lower than 4.6 mmol/l (407 mg/dL) [4]. Non-HDL-C was calculated from TC minus HDL-C. The definition of different categories for elevated blood lipid levels varies slightly between different guidelines and recommendations [4-6]. Low HDL-C, high LDL-C, high TG and high TC levels were defined by HDL hypocholesterolemia (<1 mmol/l; 39 mg/dL), LDL hypercholesterolemia (≥3 mmol/l; 116 mg/dL), hypertriglyceridemia (≥2 mmol/l; 177 mg/dL) and hypercholesterolemia (≥ 5 mmol/l; 193 mg/dL), respectively, and/or by the prescription of a lipid-lowering agent (S1 Table), according to European Society of Hypertension and of the European Society of Cardiology (ESH/ESC) guidelines [5]. In order to take into account the large variability of baseline lipid values, relative thresholds expressed in percentage of change were used.

1.3 Quantification of drug concentration

Plasma drug concentrations were quantified at one, three and twelve months in trough conditions (i.e. in the morning before the next drug intake). Liquid chromatography/mass spectrometry methods were used for measuring plasma levels of medications considered in the present study, i.e. aripiprazole, amisulpride, clozapine, haloperidol, mirtazapine, olanzapine, risperidone, OH-risperidone (paliperidone) or quetiapine as previously described [7-9] and/or validated according to the ISO 17025 / 15189 criteria under which the laboratory is accreditated (Eap et al., unpublished data, available on request). Valproate was measured by fluorescence polarization immunoassay (Cobas integra 400 plus Roche ®, Roche Diagnostic, Rotkreuz, Switzerland) and lithium by ion selective electrode (EasyLyte Na/K/Cl/Li, Medica ®, Chatel St-Denis, Switzerland). All methods are used on a routine basis for therapeutic drug monitoring (TDM) in patients.

The accuracy profiles (total error) were included in the acceptance limits of ±30% for biological samples on the entire investigated range, in accordance with the latest international recommendations [10]. Patients were considered non compliant when drug plasma concentrations were lower than 10% of the lower value of the recommended therapeutic range [11]. For risperidone, the sum of plasma concentrations of risperidone and of its active metabolite OH-risperidone was used. Only patients with adherence ascertained at each time point were included in analyses (discovery sample). Thus, patients were included in the present study only if their drug plasma levels were above the arbitrary threshold at 10% of the minimal value of the therapeutic range [11] (i.e. 10 ng/ml, 15 ng/ml, 35 ng/ml, 0.1 ng/ml, 0.05 mmol/l, 3 ng/ml, 2 ng/ml, 10 ng/ml, 2 ng/ml, 2 ng/ml and 5 mg/L for amisulpride, aripiprazole, clozapine, haloperidol, lithium, mirtazapine, olanzapine, quetiapine, risperidone plus OH-risperidone, OH-risperidone (paliperidone) and valproate, respectively). This threshold was chosen to indicate a suspicion of compliance issue and/or a rapid metabolism and/or pharmacokinetics drug interaction and/or low dose prescription (e.g. prescription of 50 mg/day of quetiapine). Less stringent criteria were used to define the replication sample, in which patients were included when at least one observation with adherence ascertained, but with other observations without adherence assessment (i.e. no plasma available for TDM). Of note, patients with at least one observation of non-adherence as defined above were not included in the present study.

1.4 Statistical analyses

1.4.1 Short-term lipid changes as predictors of long-term lipid changes in the discovery sample

Early lipid changes below 5% were not examined because small changes could represent normal fluctuations in lipid concentrations rather than clinically meaningful changes [12]. Indeed, a study investigating the within-person variation in TC and HDL-C plasma levels observed that for a median of 4 days between blood draws, the geometric mean of the within-person standard deviation was 0.13 mmol/l (5 mg/dL) for TC and 0.04 mmol/l (1.5 mg/dL) for HDL-C (coefficient of variation ~3% for both lipid levels) [12].

1.4.2 Confirmatory analyses in discovery and replication samples

The fitted linear mixed effect model had a random effect at the subject level. To be more robust in inferences, a bootstrap analysis was used to evaluate the uncertainty of estimated parameters (evaluated uncertainties are more conservative, but more reliable if there are violations from model assumptions, as normality assumption of residuals). Results were based on 10000 bootstrap replicates at the subject level (subjects were considered to be independently recruited) and increasing the number of bootstraps did not influence substantially the uncertainty of estimated parameters. Results of linear mixed models were tested for replication in an independent replication sample. The replication sample included patients with less strict criteria of drug-adherence, i.e. patients with at least one observation with adherence ascertained, without any observations of non-adherence, but with one or several observations without adherence measurement.

1.4.3 Short-term lipid changes and new onset dyslipidemia

Logistic mixed regression models and Cox regression tests were fitted adjusting for baseline age, baseline body mass index (BMI), gender, smoking status, psychotropic drug category (i.e. olanzapine, clozapine and valproate being associated with the

highest risk of dyslipidemia, mirtazapine, lithium, risperidone, quetiapine conferring an intermediate risk, and aripiprazole, amisulpride and haloperidol being at lower risk [13, 14]) and early weight gain (≥5%) groups. More specifically, TC≥5% was compared to TC<5% patient group on hypercholesterolemia development, LDL-C≥5% was compared to LDL-C <5% patient group on LDL hypercholesterolemia development, TG≥5% was compared to TG<5% patient group on hypertriglyceridemia development, and HDL-C ≤-5% was compared to HDL-C >-5% patient group on HDL hypocholesterolemia development.

Further analyses were conducted using combined predictors integrating multiple early thresholds (i.e. for TC, LDL-C, TG and HDL-C) to predict outcomes integrating multiple dyslipidemia phenotypes (i.e. for TC, LDL-C, TG and HDL-C). Because non-HDL-C integrates both TC and HDL-C, this paramater was not considered in these analyses. Predictors were defined as the number of exceeded early thresholds (EET), ranging from 0 to 4. Outcomes were defined as the number of new onset dyslipidemia after 3 months of treatment, ranging from 0 to 4. Especially, several groups (0 versus 1 or more EET(s); 0 or 1 versus 2 or more EETs; 0, 1 or 2 versus 3 or more EETs; 0,1,2 or 3 versus 4 EETs) were compared to determine the impact of each additional EET on the subsequent risk of developing long-term dyslipidemia. Of note, non adjusted Chi-squared and Fisher exact tests were conducted to confirm results obtained using multivariate analyses.

2. RESULTS

2.1 Demographics and evolution of metabolic parameters

S2 Table displays demographic and clinical characteristics of the psychiatric discovery sample used for the determination of best early thresholds for TC, LDL-C and TG increase and for HDL-C decrease. Median age was 33 years (IQR 23-50), which is younger than in our previous study on early weight increase as predictor on long term weight gain [15], probably explained by the exclusion of patients receiving lipid lowering comedication(s). Psychotic disorders (F20.0-F24.9 and F28-F29) were the most frequent diagnosis (38%), and quetiapine was the most frequently prescribed psychotropic drug (29%). Blood lipid levels and the prevalence of dyslipidemia significantly increased during psychotropic treatment (**S2 Table**). Of note, no data on cardiovascular and/or kidney diseases was available in the present study.

2.2 Short-term lipid changes as predictors of long-term lipid changes in a discovery cohort

Of note, patients with TCi≥5%, LDLi≥5% or HDLd≥5% after the first month of treatment but who did not exceed TCi≥30%, LDLi≥40% or HDLd≥20% after 3 months (i.e. false positives), had still higher TCi, LDLi and HDLd compared to patients with TCi<5%, LDLi<5% or HDLd<5% after the first month of treatment (TCi of 11% vs -4%, p<0.0001; LDLi of 9% vs -8%, p<0.0001; HDLd of 0% vs 8%, p=0.0004). However, patients with TGi≥5% after one month who did not reach TGi≥45% after three months did not differ significantly from patients with TGi<5% (TGi of 0% vs -13%; p=0.13). This lack of significance may probably be explained by an insufficient number of observations due to the exclusion of patients in non-fasting conditions.

2.3 Distribution of demographic and clinical variables according to risk-groups based on early lipid thresholds

Table 1 displays demographic and clinical characteristics of the psychiatric discovery sample according to the early thresholds of blood lipid changes. The characteristics of the one hundred and eighty one patients already described in **S2 Table** are repeated in the first column. A higher proportion of patients suffering from psychotic disorders was observed in patients with early TCi≥5% and LDLi≥5% compared to others (i.e. TCi<5% and LDLi<5%, respectively). Additionally, a lower proportion of patients with LDLi≥5% received aripiprazole (6% versus 19%; p=0.02) and a higher proportion of patients with HDLd ≥5% received valproate (10% versus 1%; p=0.008). Beside, a higher proportion of patients with early weight gain (WG)≥5% was observed in patients with early TCi≥5% (p=0.001), underlining a possible synchrony in the worsening of these two metabolic phenotypes.

For the five lipid phenotypes, at baseline, patients whose early lipid increase outreached 5% had a significantly lower proportion of dyslipidemia as compared to others. Conversely, after the first month of treatment, the proportion of dyslipidemia was significantly higher in patients whose early lipid increase outreached 5% compared to others, underlining a higher propensity of developing dyslipidemia in patients whose early lipid levels outreached 5% compared to others (**Table 1**).

2.4 Confirmation of early lipid changes as predictors of long-term lipid trait changes

Some clinical variables were significantly associated with lipid changes after 3 months of treatment (**S5 Table**). Thus, men had a significantly lower increase of TC levels and a significantly higher decrease of HDL-C levels. In addition, HDL-C levels were significantly decreasing with increasing age and in patients with early WG≥5% (data not

shown). Finally, men had a significantly lower increase of non-HDL-C levels as compared to women (data not shown). In the replication sample, none of the covariates was associated with lipid profile worsening, except age and baseline BMI which were significantly associated with decreased HDL-C.

Notably, early lipid increase thresholds were also significant in age-stratified, gender-stratified and lipid level-stratified subgroups (data not shown). However, medication-stratified analyses could not be conducted because of the low final number of patients in each drug group, even when grouping medication into drug classes.

2.5 Influence of early lipid thresholds on new onset dyslipidemia

An important proportion of patients developed new onset dyslipidemia (NOD) during the first year of psychotropic treatment (**S7 Table**). Most NOD classifications were based on exceeded clinical thresholds and not on new prescriptions of lipid-lowering comedications (only one case). This is in agreement with the reported undertreatment of dyslipidemia in psychiatric patients [16]. Patients developing NOD had significantly higher baseline lipid levels compared to patients who did not develop NOD ($p \leq 0.004$), making them closer to dyslipidemia thresholds, reminding that most included patients were not drug naïve when starting the current psychotropic treatment. The incidence of NOD was significantly higher in patients whose early lipid change outreached 5% compared to others (**S8 Table**).

In addition, the medication group was significantly associated with the incidence of new onset hypercholesterolemia for LDL-C and non-HDL-C ($p=0.01$ and 0.05, respectively). Moreover, men had significantly higher risk of new onset HDL-C and new onset hypertriglyceridemia compared to women ($p=0.007$ and $p=0.04$, respectively) and patients with early weight gain had a higher incidence of new onset hypertriglyceridemia

and of new onset hypercholesterolemia compared to others (p=0.0004 and 0.05, respectively) (**S2 Figure**).

2.6 Influence of the number of early lipid thresholds on new onset dyslipidemia

When restricting analyses to patients without dyslipidemia in any of the four lipid traits at baseline (n=84), 12 patients did not reach any of the four lipid trait thresholds during the first month of treatment, 12 had one EET, 25 had two EETs, 24 had three EETs and 11 had four EETs. EET(s) number was significantly associated with the risk of developing at least one dyslipidemia during psychotropic treatment in whichever of the four lipid traits (**S9 Table**). These results were supported by non-adjusted analyses (Fisher tests) and interestingly, in contrast to results including each lipid trait separately, none of the covariates was associated with the risk of developing dyslipidemia during psychotropic treatment, suggesting that this risk is age- sex- baseline BMI- smoking- psychotropic drug- and weight gain-independent and/or that the early lipid profile worsening captures the main dyslipidemia risk variance.

S1 Table. Lipid-lowering drugs considered as characterizing dyslipidemia

Lipid-lowering drugs
Atorvastatin
Ezetimibe
Fenofibrate
Fluvastatin
Pravastatin
Rosuvastatin
Simvastatin

The list was extracted from [17]. This list only provides lipid-lowering drugs prescribed in the present psychiatric sample.

S2 Table. Demographic parameters and evolution of lipid profile during psychotropic treatment in patients without lipid-lowering comedication

Demographics		**n=181**
Age, median (IQR), y		33 (23-50)
Men, n(%)		96 (53)
Diagnosis, n(%)		
	Psychotic disorders	69 (38.1)
	Schizoaffective disorders	13 (7.2)
	Bipolar disorders	28 (15.5)
	Depressive disorders	26 (14.4)
	Organic disorders	3 (1.7)
	Other	14 (7.7)
	Not available	28 (15.5)
Medication, n(%)		
	Amisulpride	19 (10.5)
	Aripiprazole	23 (12.7)
	Clozapine	13 (7.2)
	Haloperidol	1 (0.6)
	Lithium	13 (7.2)
	Mirtazapine	5 (2.8)
	Olanzapine	33 (18.2)
	Quetiapine	53 (29.3)
	Risperidone	13 (7.2)
	Valproate	8 (4.4)

Variable evolution	**Baseline**	**1 month**	**p-value[1]**	**3 months**	**p-value[2]**	**12 months**	**p-value[3]**
Smoking, n(%)	82 (45.3)	90 (50.0)	0.06	78 (52.0)	0.21	32 (52.5)	0.62
Overweight prevalence (BMI ≥ 25 kg/m2), n(%)	53 (32.1)	58 (35.4)	0.53	56 (41.8)	0.08	27 (46.6)	**0.05**
Obesity prevalence (BMI ≥ 30 kg/m^2), n(%)	19 (11.5)	18 (11.0)	0.88	13 (9.7)	0.61	12 (20.7)	0.08
Total cholesterol, median (IQR) *mmol/l*	4.7 (4-5.4)	4.7 (4.1-5.6)	0.12	4.9 (4.2-5.7)	**0.03**	5.1 (4.2-6.0)	**0.02**
Prevalence of hypercholesterolemia (≥ 5 mmol/l), n/total (%)	68/181 (37.6)	78/181 (43.1)	0.28	79/163 (48.5)	**0.04**	45/84 (53.6)	**0.01**
LDL-C, median (IQR) *mmol/l*	2.6 (2-3.2)	2.7 (2.2-3.3)	0.08	2.8 (2.2-3.4)	0.07	2.9 (2.3-3.6)	**0.03**
Prevalence of LDL hypercholesterolemia (≥ 3 mmol/l), n/total (%)	52/162 (32.1)	61/162 (37.7)	0.29	56/136 (41.2)	0.1	33/69 (47.8)	**0.02**
HDL-C, median (IQR) *mmol/l*	1.3 (1.1-1.7)	1.3 (1.1-1.6)	0.29	1.3 (1.1-1.6)	0.47	1.3 (1-1.6)	0.08
Prevalence of HDL hypocholesterolemia (≤ 1 mmol/l), n/total (%)	30/173 (17.3)	36/173 (20.8)	0.41	28/153 (18.3)	0.82	25/80 (31.3)	**0.01**
Fasting TG, median (IQR) *mmol/l*	1.1 (0.8-1.4)	1.1 (0.9-1.6)	0.25	1.2 (0.8-1.6)	0.4	1.2 (0.9-1.7)	0.12
Prevalence of hypertriglyceridemia (≥ 2 mmol/l), n/total (%)	11/95 (11.6)	15/95 (15.8)	0.4	14/85 (16.5)	0.34	9/37 (24.3)	0.07
Non-HDL-C, median (IQR) *mmol/l*	3.1 (2.6-4)	3.4 (2.8-4.1)	**0.05**	3.4 (2.9-4.3)	**0.02**	3.6 (2.9-4.6)	**0.002**
Prevalence of dyslipidemia, n/total (%)[4]	81/162 (50.0)	91/162 (56.2)	0.26	76/136 (55.9)	0.31	47/69 (68.1)	**0.01**

[1] p-values were calculated using ranksum tests (for continuous variables) and chi^2 tests (for categorical variables) between baseline versus 1 month of treatment. Values in bold are significant.
[2] p-values were calculated using ranksum tests (for continuous variables) and chi^2 tests (for categorical variables) between baseline versus 3 months of treatment. Values in bold are significant.
[3] p-values were calculated using ranksum tests (for continuous variables) and chi^2 tests (for categorical variables) between baseline versus 12 months of treatment. Values in bold are significant.
[4] Dyslipidemia was defined as an elevated TC level (≥ 5 mmol/l (193 mg/dL)), LDL-C level (≥ 3 mmol/l (116 mg/dL)) and/or a low HDL-C level (≤ 1 mmol/l (39 mg/dL)). In order to keep a sufficient number of observations, TG level was not considered in this variable.

S3 Table. Receiver operating parameters for early lipid changes after one month to predict lipid changes after 3 months of psychotropic treatment

TC increase after 1st month (≥,%)	TC increase after 3rd month (≥,%)	PPV	NPV	Sensitivity	Specificity	AUC	Number of positives after 1st month	Number of positives after 3rd month	Number of observations
5	10	69.7	84.38	75.41	80.2	77.8	76	61	162
5	15	57.58	87.5	76	75	75.5	76	50	162
5	20	50	94.79	86.84	73.39	80.11	76	38	162
5	25	40.91	96.88	90	70.45	80.23	76	30	162
5	**30**	**33.33**	**97.92**	**91.67**	**68.12**	**79.89**	**76**	**24**	**162**
5	35	24.24	97.92	88.89	65.28	77.08	76	18	162
10	10	75	80	63.93	87.13	75.53	61	61	162
10	15	61.54	83.64	64	82.14	73.07	61	50	162
10	20	53.85	90.91	73.68	80.65	77.16	61	38	162
10	25	44.23	93.64	76.67	78.03	77.35	61	30	162
10	30	38.46	96.36	83.33	76.81	80.07	61	24	162
10	35	26.92	96.36	77.78	73.61	75.69	61	18	162
15	15	68.29	81.82	56	88.39	72.2	49	50	162
15	20	60.98	89.26	65.79	87.1	76.44	49	38	162
15	25	51.22	92.56	70	84.85	77.42	49	30	162
15	30	43.9	95.04	75	83.33	79.17	49	24	162
15	35	31.71	95.87	72.22	80.56	76.39	49	18	162
20	20	75	87.31	55.26	94.35	74.81	33	38	162
20	25	67.86	91.79	63.33	93.18	78.26	33	30	162
20	30	60.71	94.78	70.83	92.03	81.43	33	24	162
20	35	46.43	96.27	72.22	89.58	80.9	33	18	162
25	25	71.43	89.36	50	95.45	72.73	25	30	162
25	30	66.67	92.91	58.33	94.93	76.63	25	24	162
25	35	47.62	94.33	55.56	92.36	73.96	25	18	162

LDL increase after 1st month (≥,%)	LDL increase after 3rd month (≥,%)	PPV	NPV	Sensitivity	Specificity	AUC	Number of positives after 1st month	Number of positives after 3rd month	Number of observations
5	5	81.13	78.75	71.67	86.3	78.98	68	67	149
5	10	64.15	82.5	70.83	77.65	74.24	68	52	149
5	15	60.38	87.5	76.19	76.92	76.56	68	46	149
5	20	54.72	90	78.38	75	76.69	68	41	149
5	25	52.83	91.25	80	74.49	77.24	68	37	149
5	30	52.83	95	87.5	75.25	81.37	68	33	149
5	35	47.17	96.25	89.29	73.33	81.31	68	29	149
5	**40**	**41.51**	**97.5**	**91.67**	**71.56**	**81.61**	**68**	**24**	**149**
5	45	37.74	97.5	90.91	70.27	80.59	68	22	149
5	50	30.19	97.5	88.89	67.83	78.36	68	18	149
5	55	24.53	97.5	86.67	66.1	76.38	68	15	149
10	10	67.35	82.14	68.75	81.18	74.96	62	52	149
10	15	63.27	86.9	73.81	80.22	77.01	62	46	149
10	20	57.14	89.29	75.68	78.12	76.9	62	41	149
10	25	55.1	90.48	77.14	77.55	77.35	62	37	149
10	30	55.1	94.05	84.38	78.22	81.3	62	33	149
10	35	48.98	95.24	85.71	76.19	80.95	62	29	149
10	40	42.86	96.43	87.5	74.31	80.91	62	24	149
10	45	38.78	96.43	86.36	72.97	79.67	62	22	149
10	50	30.61	96.43	83.33	70.43	76.88	62	18	149
10	55	24.49	96.43	80	68.64	74.32	62	15	149
15	15	62.22	84.09	66.67	81.32	73.99	57	46	149
15	20	57.78	87.5	70.27	80.21	75.24	57	41	149
15	25	57.78	89.77	74.29	80.61	77.45	57	37	149
15	30	57.78	93.18	81.25	81.19	81.22	57	33	149
15	35	51.11	94.32	82.14	79.05	80.6	57	29	149
15	40	44.44	95.45	83.33	77.06	80.2	57	24	149
15	45	40	95.45	81.82	75.68	78.75	57	22	149
15	50	33.33	96.59	83.33	73.91	78.62	57	18	149
15	55	26.67	96.59	80	72.03	76.02	57	15	149
20	20	65.71	85.71	62.16	87.5	74.83	47	41	149
20	25	65.71	87.76	65.71	87.76	76.73	47	37	149
20	30	65.71	90.82	71.88	88.12	80	47	33	149
20	35	57.14	91.84	71.43	85.71	78.57	47	29	149
20	40	48.57	92.86	70.83	83.49	77.16	47	24	149
20	45	45.71	93.88	72.73	82.88	77.81	47	22	149
20	50	40	95.92	77.78	81.74	79.76	47	18	149
20	55	31.43	95.92	73.33	79.66	76.5	47	15	149
25	25	74.07	85.85	57.14	92.86	75	36	37	149
25	30	74.07	88.68	62.5	93.07	77.78	36	33	149
25	35	66.67	90.57	64.29	91.43	77.86	36	29	149
25	40	59.26	92.45	66.67	89.91	78.29	36	24	149
25	45	55.56	93.4	68.18	89.19	78.69	36	22	149
25	50	48.15	95.28	72.22	87.83	80.02	36	18	149
25	55	37.04	95.28	66.67	85.59	76.13	36	15	149

TG increase after 1st month (≥,%)	TG increase after 3rd month (≥,%)	PPV	NPV	Sensitivity	Specificity	AUC	Number of positives after 1st month	Number of positives after 3rd month	Number of observations
5	10	58.33	75.68	75.68	58.33	67	54	37	87
5	15	54.17	81.08	78.79	57.69	68.24	54	33	87
5	20	45.83	81.08	75.86	53.57	64.72	54	29	87
5	25	45.83	81.08	75.86	53.57	64.72	54	29	87
5	30	45.83	83.78	78.57	54.39	66.48	54	28	87
5	35	31.25	86.49	75	49.23	62.12	54	20	87
5	40	31.25	97.3	93.75	52.17	72.96	54	16	87
5	**45**	**31.25**	**100**	**100**	**52.86**	**76.43**	**54**	**15**	**87**
5	50	31.25	100	100	52.86	76.43	54	15	87
10	10	57.78	72.5	70.27	60.42	65.34	51	37	87
10	15	53.33	77.5	72.73	59.62	66.17	51	33	87
10	20	44.44	77.5	68.97	55.36	62.16	51	29	87
10	25	44.44	77.5	68.97	55.36	62.16	51	29	87
10	30	44.44	80	71.43	56.14	63.78	51	28	87
10	35	28.89	82.5	65	50.77	57.88	51	20	87
10	40	28.89	92.5	81.25	53.62	67.44	51	16	87
10	45	28.89	95	86.67	54.29	70.48	51	15	87
10	50	28.89	95	86.67	54.29	70.48	51	15	87
15	15	63.89	79.59	69.7	75	72.35	40	33	87
15	20	52.78	79.59	65.52	69.64	67.58	40	29	87
15	25	52.78	79.59	65.52	69.64	67.58	40	29	87
15	30	52.78	81.63	67.86	70.18	69.02	40	28	87
15	35	36.11	85.71	65	64.62	64.81	40	20	87
15	40	36.11	93.88	81.25	66.67	73.96	40	16	87
15	45	36.11	95.92	86.67	67.14	76.9	40	15	87
15	50	36.11	95.92	86.67	67.14	76.9	40	15	87
20	20	50	76.47	58.62	69.64	64.13	37	29	87
20	25	50	76.47	58.62	69.64	64.13	37	29	87
20	30	50	78.43	60.71	70.18	65.44	37	28	87
20	35	32.35	82.35	55	64.62	59.81	37	20	87
20	40	32.35	90.2	68.75	66.67	67.71	37	16	87
20	45	32.35	92.16	73.33	67.14	70.24	37	15	87
20	50	32.35	92.16	73.33	67.14	70.24	37	15	87
25	25	51.52	76.92	58.62	71.43	65.02	36	29	87
25	30	51.52	78.85	60.71	71.93	66.32	36	28	87
25	35	33.33	82.69	55	66.15	60.58	36	20	87
25	40	33.33	90.38	68.75	68.12	68.43	36	16	87
25	45	33.33	92.31	73.33	68.57	70.95	36	15	87
25	50	33.33	92.31	73.33	68.57	70.95	36	15	87
30	30	51.61	77.78	57.14	73.68	65.41	34	28	87
30	35	35.48	83.33	55	69.23	62.12	34	20	87
30	40	35.48	90.74	68.75	71.01	69.88	34	16	87
30	45	35.48	92.59	73.33	71.43	72.38	34	15	87
30	50	35.48	92.59	73.33	71.43	72.38	34	15	87
35	35	47.83	85.48	55	81.54	68.27	26	20	87
35	40	47.83	91.94	68.75	82.61	75.68	26	16	87
35	45	47.83	93.55	73.33	82.86	78.1	26	15	87
35	50	47.83	93.55	73.33	82.86	78.1	26	15	87

HDL decrease after 1st month (≥,%)	HDL decrease after 3rd month (≥,%)	PPV	NPV	Sensitivity	Specificity	AUC	Number of positives after 1st month	Number of positives after 3rd month	Number of observations
5	5	63.16	76.34	62.07	77.17	69.62	71	60	159
5	10	50.88	84.95	67.44	73.83	70.64	71	45	159
5	15	36.84	89.25	67.74	69.75	68.74	71	33	159
5	**20**	**24.56**	**93.55**	**70**	**66.92**	**68.46**	**71**	**22**	**159**
10	10	59.09	83.96	60.47	83.18	71.82	56	45	159
10	15	43.18	88.68	61.29	78.99	70.14	56	33	159
10	20	27.27	92.45	60	75.38	67.69	56	22	159
15	15	53.12	88.14	54.84	87.39	71.12	41	33	159
15	20	34.38	92.37	55	83.85	69.42	41	22	159

Non-HDL-C increase after 1st month (≥,%)	Non-HDL-C increase after 3rd month (≥,%)	PPV	NPV	Sensitivity	Specificity	AUC	Number of positives after 1st month	Number of positives after 3rd month	Number of observations
5	5	73.85	74.12	68.57	78.75	73.66	78	72	159
5	10	60	80	69.64	72.34	70.99	78	57	159
5	15	55.38	84.71	73.47	71.29	72.38	78	50	159
5	20	55.38	88.24	78.26	72.12	75.19	78	46	159
5	25	50.77	92.94	84.62	71.17	77.89	78	39	159
5	30	46.15	95.29	88.24	69.83	79.03	78	34	159
5	35	44.62	96.47	90.62	69.49	80.06	78	32	159
5	40	38.46	97.65	92.59	67.48	80.04	78	27	159
5	45	32.31	97.65	91.3	65.35	78.33	78	23	159
5	50	30.77	97.65	90.91	64.84	77.88	78	22	159
5	**55**	**26.15**	**98.82**	**94.44**	**63.64**	**79.04**	**78**	**18**	**159**
10	10	67.27	80	66.07	80.85	73.46	66	57	159
10	15	61.82	84.21	69.39	79.21	74.3	66	50	159
10	20	61.82	87.37	73.91	79.81	76.86	66	46	159
10	25	58.18	92.63	82.05	79.28	80.67	66	39	159
10	30	52.73	94.74	85.29	77.59	81.44	66	34	159
10	35	50.91	95.79	87.5	77.12	82.31	66	32	159
10	40	43.64	96.84	88.89	74.8	81.84	66	27	159
10	45	36.36	96.84	86.96	72.44	79.7	66	23	159
10	50	34.55	96.84	86.36	71.88	79.12	66	22	159
10	55	29.09	97.89	88.89	70.45	79.67	66	18	159
15	15	68.75	84.31	67.35	85.15	76.25	57	50	159
15	20	68.75	87.25	71.74	85.58	78.66	57	46	159
15	25	64.58	92.16	79.49	84.68	82.09	57	39	159
15	30	58.33	94.12	82.35	82.76	82.56	57	34	159
15	35	56.25	95.1	84.38	82.2	83.29	57	32	159
15	40	47.92	96.08	85.19	79.67	82.43	57	27	159
15	45	39.58	96.08	82.61	77.17	79.89	57	23	159
15	50	37.5	96.08	81.82	76.56	79.19	57	22	159
15	55	31.25	97.06	83.33	75	79.17	57	18	159
20	20	75	83.33	58.7	91.35	75.02	43	46	159
20	25	72.22	88.6	66.67	90.99	78.83	43	39	159
20	30	63.89	90.35	67.65	88.79	78.22	43	34	159
20	35	61.11	91.23	68.75	88.14	78.44	43	32	159
20	40	52.78	92.98	70.37	86.18	78.27	43	27	159
20	45	47.22	94.74	73.91	85.04	79.48	43	23	159
20	50	44.44	94.74	72.73	84.38	78.55	43	22	159
20	55	36.11	95.61	72.22	82.58	77.4	43	18	159
25	25	77.42	87.39	61.54	93.69	77.62	37	39	159
25	30	67.74	89.08	61.76	91.38	76.57	37	34	159
25	35	64.52	89.92	62.5	90.68	76.59	37	32	159
25	40	58.06	92.44	66.67	89.43	78.05	37	27	159
25	45	51.61	94.12	69.57	88.19	78.88	37	23	159
25	50	48.39	94.12	68.18	87.5	77.84	37	22	159
25	55	38.71	94.96	66.67	85.61	76.14	37	18	159
30	30	71.43	88.52	58.82	93.1	75.96	34	34	159
30	35	67.86	89.34	59.38	92.37	75.87	34	32	159
30	40	60.71	91.8	62.96	91.06	77.01	34	27	159
30	45	57.14	94.26	69.57	90.55	80.06	34	23	159
30	50	53.57	94.26	68.18	89.84	79.01	34	22	159
30	55	42.86	95.08	66.67	87.88	77.27	34	18	159
35	35	76.19	87.6	50	95.76	72.88	26	32	159
35	40	66.67	89.92	51.85	94.31	73.08	26	27	159
35	45	61.9	92.25	56.52	93.7	75.11	26	23	159
35	50	57.14	92.25	54.55	92.97	73.76	26	22	159
35	55	52.38	94.57	61.11	92.42	76.77	26	18	159
40	40	77.78	90.15	51.85	96.75	74.3	22	27	159
40	45	72.22	92.42	56.52	96.06	76.29	22	23	159
40	50	66.67	92.42	54.55	95.31	74.93	22	22	159
40	55	61.11	94.7	61.11	94.7	77.9	22	18	159
45	45	76.47	92.48	56.52	96.85	76.69	20	23	159
45	50	70.59	92.48	54.55	96.09	75.32	20	22	159
45	55	64.71	94.74	61.11	95.45	78.28	20	18	159
50	50	68.75	91.79	50	96.09	73.05	19	22	159
50	55	62.5	94.03	55.56	95.45	75.51	19	18	159

PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; Number of positives after 1st month: number of patients whose lipid levels outreached the 1st month threshold indicated in the first column. Number of positives after 3rd month: number of patients whose lipid levels outreached the 3rd month threshold indicated in the second column.

S4 Table. Receiver operating parameters for early lipid changes after one month to predict lipid changes after 12 months of psychotropic treatment

TC increase after 1st month (≥,%)	TC increase after 12th month (≥,%)	PPV	NPV	Sensitivity	Specificity	AUC	Number of positives after 1st month	Number of positives after 12th month	Number of observations
5	10	80	75.51	70	84.09	77.05	76	40	84
5	15	65.71	83.67	74.19	77.36	75.78	76	31	84
5	20	48.57	85.71	70.83	70	70.42	76	24	84
5	25	37.14	91.84	76.47	67.16	71.82	76	17	84
5	**30**	**34.29**	**95.92**	**85.71**	**67.14**	**76.43**	**76**	**14**	**84**
10	10	82.14	69.64	57.5	88.64	73.07	61	40	84
10	15	67.86	78.57	61.29	83.02	72.15	61	31	84
10	20	53.57	83.93	62.5	78.33	70.42	61	24	84
10	25	42.86	91.07	70.59	76.12	73.35	61	17	84
10	30	39.29	94.64	78.57	75.71	77.14	61	14	84
15	15	66.67	75	51.61	84.91	68.26	49	31	84
15	20	50	80	50	80	65	49	24	84
15	25	37.5	86.67	52.94	77.61	65.28	49	17	84
15	30	33.33	90	57.14	77.14	67.14	49	14	84
20	20	58.82	79.1	41.67	88.33	65	33	24	84
20	25	52.94	88.06	52.94	88.06	70.5	33	17	84
20	30	47.06	91.04	57.14	87.14	72.14	33	14	84
25	25	64.29	88.57	52.94	92.54	72.74	25	17	84
25	30	57.14	91.43	57.14	91.43	74.29	25	14	84

LDL increase after 1st month (≥,%)	LDL increase after 12th month (≥,%)	PPV	NPV	Sensitivity	Specificity	AUC	Number of positives after 1st month	Number of positives after 12th month	Number of observations
5	5	84.62	60.47	56.41	86.67	71.54	68	41	76
5	10	76.92	65.12	57.14	82.35	69.75	68	37	76
5	15	69.23	67.44	56.25	78.38	67.31	68	33	76
5	20	57.69	79.07	62.5	75.56	69.03	68	24	76
5	25	53.85	86.05	70	75.51	72.76	68	20	76
5	30	50	93.02	81.25	75.47	78.36	68	16	76
5	35	42.31	93.02	78.57	72.73	75.65	68	14	76
5	**40**	**42.31**	**93.02**	**78.57**	**72.73**	**75.65**	**68**	**14**	**76**
5	45	42.31	93.02	78.57	72.73	75.65	68	14	76
5	50	38.46	93.02	76.92	71.43	74.18	68	13	76
10	10	75	62.22	51.43	82.35	66.89	62	37	76
10	15	70.83	66.67	53.12	81.08	67.1	62	33	76
10	20	58.33	77.78	58.33	77.78	68.06	62	24	76
10	25	54.17	84.44	65	77.55	71.28	62	20	76
10	30	54.17	93.33	81.25	79.25	80.25	62	16	76
10	35	45.83	93.33	78.57	76.36	77.47	62	14	76
10	40	45.83	93.33	78.57	76.36	77.47	62	14	76
10	45	45.83	93.33	78.57	76.36	77.47	62	14	76
10	50	41.67	93.33	76.92	75	75.96	62	13	76
15	15	76.19	66.67	50	86.49	68.24	57	33	76
15	20	61.9	77.08	54.17	82.22	68.19	57	24	76
15	25	57.14	83.33	60	81.63	70.82	57	20	76
15	30	57.14	91.67	75	83.02	79.01	57	16	76
15	35	52.38	93.75	78.57	81.82	80.19	57	14	76
15	40	52.38	93.75	78.57	81.82	80.19	57	14	76
15	45	52.38	93.75	78.57	81.82	80.19	57	14	76
15	50	47.62	93.75	76.92	80.36	78.64	57	13	76
20	20	62.5	73.58	41.67	86.67	64.17	47	24	76
20	25	56.25	79.25	45	85.71	65.36	47	20	76
20	30	56.25	86.79	56.25	86.79	71.52	47	16	76
20	35	56.25	90.57	64.29	87.27	75.78	47	14	76
20	40	56.25	90.57	64.29	87.27	75.78	47	14	76
20	45	56.25	90.57	64.29	87.27	75.78	47	14	76
20	50	50	90.57	61.54	85.71	73.63	47	13	76
25	25	58.33	77.19	35	89.8	62.4	36	20	76
25	30	58.33	84.21	43.75	90.57	67.16	36	16	76
25	35	58.33	87.72	50	90.91	70.45	36	14	76
25	40	58.33	87.72	50	90.91	70.45	36	14	76
25	45	58.33	87.72	50	90.91	70.45	36	14	76
25	50	58.33	89.47	53.85	91.07	72.46	36	13	76

TG increase after 1st month (≥,%)	TG increase after 12th month (≥,%)	PPV	NPV	Sensitivity	Specificity	AUC	Number of positives after 1st month	Number of positives after 12th month	Number of observations
5	10	71.43	56.25	68.18	60	64.09	54	22	38
5	15	71.43	62.5	71.43	62.5	66.96	54	21	38
5	20	71.43	68.75	75	64.71	69.85	54	20	38
5	25	71.43	75	78.95	66.67	72.81	54	19	38
5	30	71.43	75	78.95	66.67	72.81	54	19	38
5	35	61.9	75	76.47	60	68.24	54	17	38
5	40	47.62	75	71.43	52.17	61.8	54	14	38
5	**45**	**47.62**	**81.25**	**76.92**	**54.17**	**65.54**	**54**	**13**	**38**
10	10	75	58.82	68.18	66.67	67.42	51	22	38
10	15	75	64.71	71.43	68.75	70.09	51	21	38
10	20	75	70.59	75	70.59	72.79	51	20	38
10	25	75	76.47	78.95	72.22	75.58	51	19	38
10	30	75	76.47	78.95	72.22	75.58	51	19	38
10	35	65	76.47	76.47	65	70.74	51	17	38
10	40	50	76.47	71.43	56.52	63.98	51	14	38
10	45	50	82.35	76.92	58.33	67.63	51	13	38
15	15	75	57.14	57.14	75	66.07	40	21	38
15	20	75	61.9	60	76.47	68.24	40	20	38
15	25	75	66.67	63.16	77.78	70.47	40	19	38
15	30	75	66.67	63.16	77.78	70.47	40	19	38
15	35	62.5	66.67	58.82	70	64.41	40	17	38
15	40	50	71.43	57.14	65.22	61.18	40	14	38
15	45	50	76.19	61.54	66.67	64.1	40	13	38
20	20	73.33	59.09	55	76.47	65.74	37	20	38
20	25	73.33	63.64	57.89	77.78	67.84	37	19	38
20	30	73.33	63.64	57.89	77.78	67.84	37	19	38
20	35	60	63.64	52.94	70	61.47	37	17	38
20	40	46.67	68.18	50	65.22	57.61	37	14	38
20	45	46.67	72.73	53.85	66.67	60.26	37	13	38
25	25	73.33	63.64	57.89	77.78	67.84	36	19	38
25	30	73.33	63.64	57.89	77.78	67.84	36	19	38
25	35	60	63.64	52.94	70	61.47	36	17	38
25	40	46.67	68.18	50	65.22	57.61	36	14	38
25	45	46.67	72.73	53.85	66.67	60.26	36	13	38
30	30	73.33	63.64	57.89	77.78	67.84	34	19	38
30	35	60	63.64	52.94	70	61.47	34	17	38
30	40	46.67	68.18	50	65.22	57.61	34	14	38
30	45	46.67	72.73	53.85	66.67	60.26	34	13	38
35	35	72.73	65.38	47.06	85	66.03	26	17	38
35	40	63.64	73.08	50	82.61	66.3	26	14	38
35	45	63.64	76.92	53.85	83.33	68.59	26	13	38

HDL decrease after 1st month (≥,%)	HDL decrease after 12th month (≥,%)	PPV	NPV	Sensitivity	Specificity	AUC	Number of positives after 1st month	Number of positives after 12th month	Number of observations
5	5	77.14	73.33	69.23	80.49	74.86	71	41	83
5	10	62.86	82.22	73.33	74	73.67	71	32	83
5	15	48.57	82.22	68	67.27	67.64	71	27	83
5	**20**	**28.57**	**93.33**	**76.92**	**62.69**	**69.8**	**71**	**15**	**83**
10	10	73.08	79.63	63.33	86	74.67	56	32	83
10	15	53.85	79.63	56	78.18	67.09	56	27	83
10	20	34.62	92.59	69.23	74.63	71.93	56	15	83
15	15	55.56	75.81	40	85.45	62.73	41	27	83
15	20	33.33	88.71	46.15	82.09	64.12	41	15	83

Non-HDL-C increase after 1st month (≥,%)	Non-HDL-C increase after 12th month (≥,%)	PPV	NPV	Sensitivity	Specificity	AUC	Number of positives after 1st month	Number of positives after 3rd month	Number of observations
5	5	81.58	61.9	65.96	78.79	72.37	78	49	83
5	10	81.58	69.05	70.45	80.56	75.51	78	45	83
5	15	68.42	73.81	70.27	72.09	71.18	78	38	83
5	20	60.53	76.19	69.7	68.09	68.89	78	34	83
5	25	50	83.33	73.08	64.81	68.95	78	26	83
5	30	50	85.71	76	65.45	70.73	78	25	83
5	35	50	90.48	82.61	66.67	74.64	78	23	83
5	40	50	95.24	90.48	67.8	79.14	78	21	83
5	**45**	**34.21**	**95.24**	**86.67**	**61.54**	**74.1**	**78**	**15**	**83**
10	10	90.62	68.75	65.91	91.67	78.79	66	45	83
10	15	78.12	75	67.57	83.72	75.64	66	38	83
10	20	71.88	79.17	69.7	80.85	75.27	66	34	83
10	25	59.38	85.42	73.08	75.93	74.5	66	26	83
10	30	59.38	87.5	76	76.36	76.18	66	25	83
10	35	59.38	91.67	82.61	77.19	79.9	66	23	83
10	40	59.38	95.83	90.48	77.97	84.22	66	21	83
10	45	40.62	95.83	86.67	70.77	78.72	66	15	83
15	15	74.07	67.92	54.05	83.72	68.89	57	38	83
15	20	66.67	71.7	54.55	80.85	67.7	57	34	83
15	25	59.26	81.13	61.54	79.63	70.58	57	26	83
15	30	59.26	83.02	64	80	72	57	25	83
15	35	59.26	86.79	69.57	80.7	75.13	57	23	83
15	40	59.26	90.57	76.19	81.36	78.77	57	21	83
15	45	44.44	94.34	80	76.92	78.46	57	15	83
20	20	68.42	67.21	39.39	87.23	63.31	43	34	83
20	25	68.42	78.69	50	88.89	69.44	43	26	83
20	30	68.42	80.33	52	89.09	70.55	43	25	83
20	35	68.42	83.61	56.52	89.47	73	43	23	83
20	40	68.42	86.89	61.9	89.83	75.87	43	21	83
20	45	52.63	91.8	66.67	86.15	76.41	43	15	83
25	25	75	78.12	46.15	92.59	69.37	37	26	83
25	30	75	79.69	48	92.73	70.36	37	25	83
25	35	75	82.81	52.17	92.98	72.58	37	23	83
25	40	75	85.94	57.14	93.22	75.18	37	21	83
25	45	56.25	90.62	60	89.23	74.62	37	15	83
30	30	75	79.69	48	92.73	70.36	34	25	83
30	35	75	82.81	52.17	92.98	72.58	34	23	83
30	40	75	85.94	57.14	93.22	75.18	34	21	83
30	45	56.25	90.62	60	89.23	74.62	34	15	83
35	35	92.31	83.58	52.17	98.25	75.21	26	23	83
35	40	92.31	86.57	57.14	98.31	77.72	26	21	83
35	45	69.23	91.04	60	93.85	76.92	26	15	83
40	40	90.91	84.06	47.62	98.31	72.96	22	21	83
40	45	63.64	88.41	46.67	93.85	70.26	22	15	83
45	45	70	88.57	46.67	95.38	71.03	20	15	83

PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve. Number of positives after 1st month: number of patients whose lipid levels outreached the 1st month threshold indicated in the first column. Number of positives after 12th month: number of patients whose lipid levels outreached the 12th month threshold indicated in the second column.

S5 Table. Linear mixed effect models fitted on lipid trait changes (%) over time in the discovery sample

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 TG 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
181	24.6% (16.1% - 33.2%)	**<0.0001**	161	34.0% (17.2% - 50.6%)	**0.0001**	95	39.8% (-0.8% - 88.1%)	**0.03**	172	-13.9% (-19.3% - (-)8.6%)	**<0.0001**	172	36.1% (22.5% - 50.6%)	**<0.0001**

Results were obtained by fitting a linear mixed model controlling for age, gender, time, baseline BMI, smoking, current psychotropic drug and early weight gain >5%, during the first three months of treatment

P-values in bold are significant.

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

S6 Table. Linear mixed effect models fitted on lipid trait changes (%) over time in the replication sample

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 TG 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
79	21.6% (10.2%-33.9%)	**<0.001**	73	28.6% (12.7% - 45.0%)	**<0.001**	45	56.5% (16.9% - 92.8%)	**0.003**	78	-21.4% (-30.6% - (-)11.8%)	**<0.001**	78	30.9% (13.8% - 49.4%)	**<0.001**

Results were obtained by fitting a linear mixed model controlling for age, gender, time, baseline BMI, smoking, current psychotropic drug and early weight gain >5% after 3 and/or 12 months of psychotropic treatment.
P-values in bold are significant.
Abbreviation: TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; non-HDL-C: non high-density lipoprotein cholesterol.

S7 Table. Demographic parameters and comparisons between patients with and without new onset dyslipidemia

	Patients without NODTC (n=64)	Patients with NODTC (n=50)	p-value	Patients without NODLDL (n=72)	Patients with NODLDL (n=43)	p-value	Patients without NODTG (n=66)	Patients with NODTG (n=18)	p-value	Patients without NODHDL (n=116)	Patients with NODHDL (n=36)	p-value	Patients without NODnonHDL (n=89)	Patients with NODnonHDL (n=38)	p-value
Age, median (IQR), y	26 (20-41)	35 (26-50)	**0.03**	26 (20-44)	35 (25-51)	**0.04**	29 (20-46)	34 (26-42)	0.39	34 (22-53)	32 (25-55)	0.98	28 (20-46)	34 (28-51)	0.06
Men, n(%)	39 (60.9)	23 (46.0)	0.11	38 (52.8)	20 (46.5)	0.52	30 (45.5)	13 (72.2)	0.04	49 (42.2)	26 (72.2)	0.002	43 (48.3)	22 (57.9)	0.32
Smoking, n(%)	31 (48.4)	21 (42.0)	0.76	30 (41.7)	21 (48.8)	0.57	29 (43.9)	10 (55.6)	0.59	39 (33.6)	22 (61.1)	0.01	37 (41.6)	19 (50.0)	0.56
Diagnosis, n(%)															
Psychotic disorders	20 (31.3)	27 (54)	**0.01**	26 (36.1)	21 (48.8)	0.18	22 (33.3)	7 (38.9)	0.66	38 (32.7)	13 (36.1)	0.71	32 (35.9)	17 (44.7)	0.35
Schizoaffective disorders	7 (1.09)	2 (4)	0.17	7 (9.7)	2 (4.7)	0.33	4 (6.1)	2 (11.1)	0.46	7 (6.0)	4 (11.1)	0.3	9 (10.1)	2 (5.3)	0.37
Bipolar disorders	5 (7.8)	5 (10.0)	0.68	7 (9.7)	3 (7)	0.61	13 (19.7)	3 (16.7)	0.77	20 (17.2)	8 (22.2)	0.5	9 (10.1)	5 (13.2)	0.62
Depressive disorders	12 (18.8)	0 (0)	**0.02**	12 (16.7)	3 (7)	0.14	11 (16.7)	4 (22.2)	0.59	22 (18.9)	2 (5.6)	0.05	14 (15.7)	4 (10.5)	0.44
Organic disorders	2 (3.1)	2 (4.0)	0.21	2 (2.8)	0 (0)	0.27	0 (0)	0 (0)		3 (2.6)	1 (2.8)	0.95	2 (2.3)	1 (2.6)	0.9
Other	5 (7.8)	7 (14.0)	0.29	6 (8.3)	4 (9.3)	0.86	7 (10.6)	0 (0)	0.15	9 (7.7)	4 (11.1)	0.53	7 (7.9)	4 (10.5)	0.63
Not available	13 (20.3)	7 (14.0)	0.38	12 (16.7)	10 (23.3)	0.39	9 (13.6)	2 (11.1)	0.78	17 (14.7)	4 (11.1)	0.59	16 (18.0)	5 (13.2)	0.5
Medication, n(%)															
Amisulpride	9 (14.1)	5 (10.0)	0.51	10 (13.9)	4 (9.3)	0.47	7 (10.6)	1 (5.6)	0.52	11 (9.5)	3 (8.3)	0.84	11 (12.4)	1 (2.6)	0.09
Aripiprazole	10 (15.6)	4 (8.0)	0.22	11 (15.3)	1 (2.3)	**0.03**	10 (15.2)	2 (11.1)	0.66	16 (13.8)	3 (8.3)	0.39	13 (14.6)	3 (7.9)	0.3
Clozapine	3 (4.7)	4 (8.0)	0.47	2 (2.3)	8 (18.6)	**0.004**	4 (6.1)	2 (11.1)	0.46	8 (6.9)	1 (2.8)	0.36	4 (4.5)	7 (18.4)	**0.01**
Haloperidol	0 (0)	0 (0)		0 (0)	1 (2.3)	0.19	0 (0)	0 (0)		1 (0.9)	0 (0)	0.58	0 (0)	0 (0)	
Lithium	2 (3.1)	1 (2.0)	0.71	5 (6.9)	1 (2.3)	0.28	5 (7.6)	1 (5.6)	0.77	9 (7.8)	3 (8.3)	0.91	6 (6.7)	1 (2.6)	0.35
Mirtazapine	1 (1.6)	0 (0)	0.38	1 (1.4)	0 (0)	0.44	1 (1.5)	0 (0)	0.6	3 (2.6)	2 (5.7)	0.38	2 (2.3)	0 (0)	0.35
Olanzapine	14 (21.9)	12 (24.0)	0.79	1419.4)	11 (25.6)	0.44	12 (18.2)	2 (11.1)	0.48	22 (18.9)	7 (19.4)	0.95	18 (20.2)	8 (21.1)	0.92
Quetiapine	15 (23.4)	20 (40.0)	0.06	20 (27.8)	14 (32.6)	0.59	17 (25.7)	9 (50.0)	0.05	35 (30.2)	9 (25.0)	0.55	24 (27.0)	14 (36.8)	0.27
Risperidone	5 (7.8)	4 (8.0)	0.97	5 (6.9)	3 (7.0)	0.99	6 (9.1)	1 (5.6)	0.63	7 (6.0)	4 (11.1)	0.3	6 (6.7)	4 (10.5)	0.47
Valproate	5 (7.8)	0 (0)	**0.04**	4 (5.6)	0 (0)	0.12	4 (6.1)	0 (0)	0.29	4 (3.5)	4 (11.1)	0.07	5 (5.6)	0 (0)	0.14
Obesity prevalence (BMI ≥ 30kg/m^2), n(%)															
Baseline	6 (10.3)	6 (9.1)	0.83	4 (5.9)	6 (16.7)	0.08	6 (10.0)	1 (5.9)	0.6	10 (9.4)	5 (15.6)	0.32	6 (7.3)	5 (14.7)	0.22
1 year	4 (13.8)	6 (27.3)	0.23	2 (6.5)	5 (31.3)	**0.02**	4 (17.4)	0 (0)	0.24	6 (30.0)	5 (6.0)	0.05	3 (8.3)	7 (33.3)	**0.02**
Early weight gain (≥5%), n(%)	9 (14.8)	12 (24.5)	0.2	12 (17.4)	10 (23.8)	0.41	5 (7.7)	6 (35.3)	**0.003**	19 (17.1)	10 (28.6)	0.14	13 (15.1)	10 (27.0)	0.12
Psychiatric illness duration, median (IQR) *years*	3 (1-8)	6 (2-10)	0.16	4 (2-10)	4 (1-13)	0.86	3.5 (1-10.5)	5 (3-10)	0.33	4 (1-10)	3 (1-9)	0.35	4 (1-10)	4 (3-10)	0.55
Baseline lipid levels[1], median (IQR), *mmol/l*	3.9 (3.5-4.3)	4.4 (4.1-4.7)	**0.0001**	2.1 (1.8-2.4)	2.4 (2.0-7.8)	**0.003**	1 (0.7-1.2)	1.2 (1.1-1.6)	**0.004**	1.5 (1.3-1.8)	1.2 (1.2-1.4)	**<0.0001**	2.7 (2.2-3.1)	3.2 (2.9-3.5)	**<0.0001**

Only patients with no dyslipidemia at baseline are included.

NODTC: new-onset hypercholesterolemia, defined either by plasma levels of total cholesterol ≥5 mmol/l (193 mg/dL) and/or by prescription of a lipid-lowering agent.

NODLDL: new-onset LDL hypercholesterolemia, defined either by plasma levels of LDL cholesterol ≥3 mmol/l (116 mg/dL)and/or by prescription of a lipid-lowering agent.

NODTG: new-onset hypertriglyceridemia, defined either by plasma levels of triglycerides ≥2 mmol/l (177 mg/dL) and/or by the prescription of a lipid-lowering agent.

NODHDL: new-onset HDL hypocholesterolemia, defined either by plasma levels of HDL cholesterol ≤1 mmol/l (39 mg/dL) and/or by the prescription of a lipid-lowering agent.

NODnonHDL: new-onset nonHDL hypercholesterolemia, defined either by plasma levels of non-HDL cholesterol ≥4 mmol/l (154 mg/dL) and/or by the prescription of a lipid-lowering agent.

[1] 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.

p-values were calculated using ranksum tests (for continuous variables) and chi^2 tests (for categorical variables) between groups. Values in bold are significant.

S8 Table. Risk factors for new onset TC- and LDL hypercholesterolemia, hypertriglyceridemia, HDL-hypocholesterolemia and non-HDL hypercholesterolemia in patients receiving psychotropic treatment

	NODTC (n=114)		NODLDL (n=115)		NODHDL (n=152)		NODTG (n=84)		NODnonHDL (n=127)	
	estimate (SE)	p-value	estimate (SE)	p-value	estimate (SE)	p-value	estimate (SE)	p-value	estimate (SE)	p-value
Age		NS		NS	0.03 (0.01)	0.02		NS		NS
Sex		NS		NS	1.62 (0.60)	0.007	2.69 (1.02)	0.008		NS
Baseline BMI		NS		NS		NS		NS		NS
Smoking status		NS		NS		NS		NS		NS
Early lipid increase[1]	1.25 (0.41)	0.002	1.65 (0.56)	0.003	1.84 (0.54)	0.0007	2.6 (1.24)	0.04		NS
Psychotropic medication group[2]		NS	0.88 (0.30)	0.003		NS		NS	0.62 (0.27)	0.02
Early weight gain[3]	0.83 (0.41)	0.04		NS		NS	2.2 (0.69)	0.001	1.10 (0.43)	0.01

Results were obtained by fitting Cox regressions controlling for age, gender, baseline BMI, smoking status, current psychotropic drug category and early weight gain >5% group.

[1] Early lipid change groups constructed according to 5% thresholds (≥5% versus <5% of TC increase for NODTC model, ≥5% versus <5% of LDL-C increase for NODLDL model, ≥5% versus <5% of TG increase for NODTG model, ≥5% versus <5% of HDL-C decrease for NODHDL model and (≥5% versus <5% of non-HDL-C increase for NODnonHDL model).

[2] Psychotropic medication categories were defined according to their expected metabolic effect drugs i.e. olanzapine, clozapine and valproate being associated with the highest risk of dyslipidemia, mirtazapine, lithium, risperidone and quetiapine conferring an intermediate risk, and aripiprazole, amisulpride and haloperidol being at lower risk.

[3] Early weight gain groups were constructed according to the 5% threshold after one month of treatment (≥5% versus <5%).

Abbreviation: SE: standard error; NS: non significant; NODTC: new onset hypercholesterolemia for total cholesterol; NODLDL: new onset hypercholesterolemia for low-density lipoprotein cholesterol; NODTG: new onset hypertriglyceridemia; NODHDL: new onset hypocholesterolemia for high-density lipoprotein cholesterol; NODnonHDL: new onset hypercholesterolemia for non-high-density lipoprotein cholesterol.

S9 Table. Influence of the number of exceeded early thresholds on new onset dyslipidemia during psychotropic treatment.

Risk of developing one or more new onset dyslipidemia

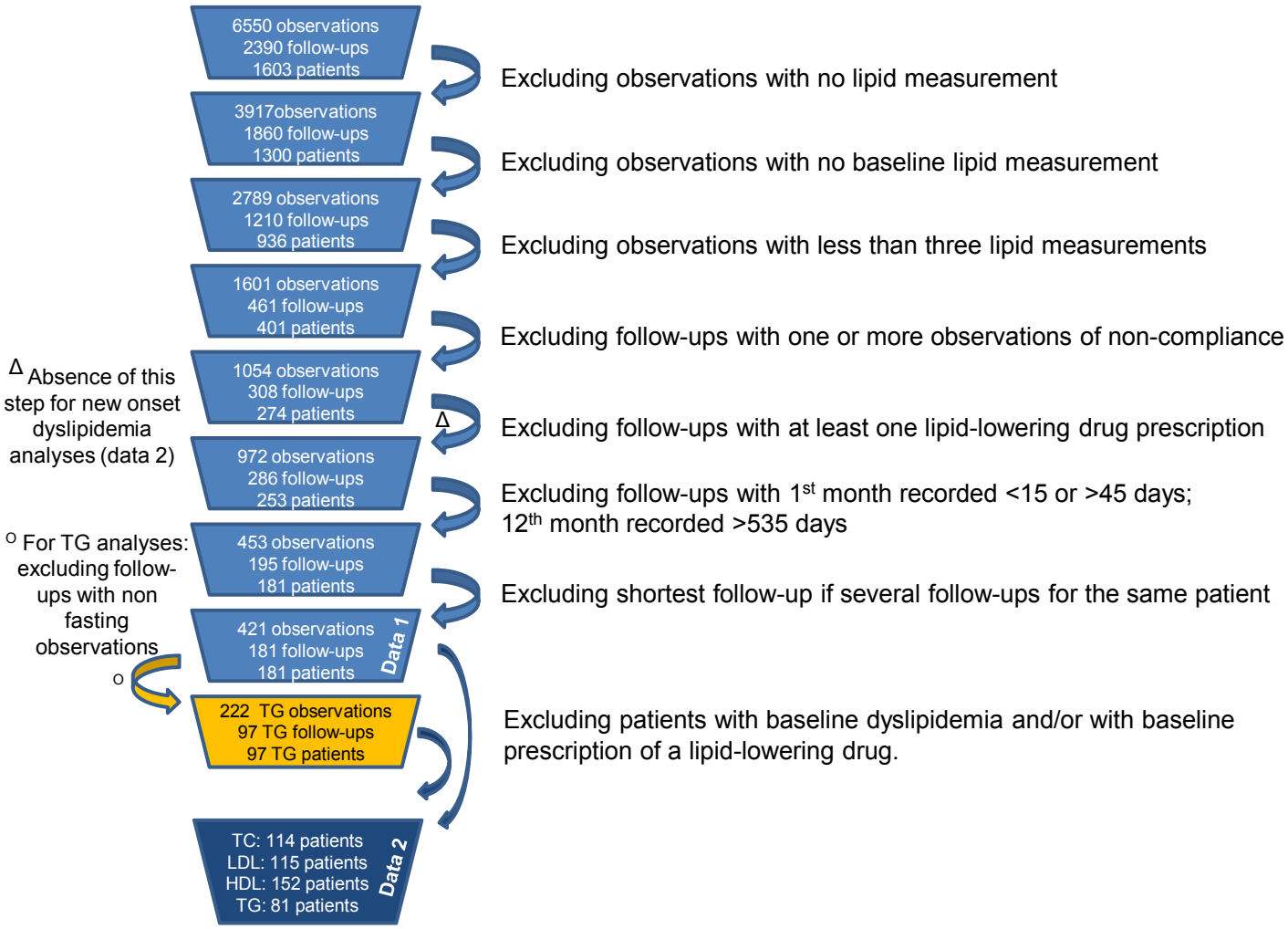
Number of early exceeded thresholds [1]		Patients developing **at least one** dyslipidemia during psychotropic treatment, n/total (%)	Non adjusted analyses		Adjusted analyses	
			Fisher		Logistic mixed model	
			Odd-ratio (CI 95%)	p-value	Adjusted odd-ratio (CI 95%)[2]	p-value
Control	0	3/12 (25%)	5.5 (1.2 - 34.5)	0.01	14.4 (1.5 - 137.6)	0.02
Case	1,2,3 or 4	47/72 (65%)				
Control	0,1	7/24 (29%)	6.0 (1.9 - 20.4)	0.0005	10 (2.1 - 47.2)	0.004
Case	2,3 or 4	43/60 (72%)				
Control	0,1,2	22/49 (45%)	4.8 (1.7 - 15.7)	0.002	5.8 (1.7 - 19.8)	0.005
Case	3 or 4	28/35 (80%)				

Risk of developing two or more new onset dyslipidemia

Number of early exceeded thresholds [1]		Patients developing **at least two** dyslipidemia during psychotropic treatment, n/total (%)	Non adjusted analyses		Adjusted analyses	
			Fisher		Logistic mixed model	
			Odd-ratio (CI 95%)	p-value	Adjusted odd-ratio (CI 95%)[2]	p-value
Control	0,1	3/24 (13%)	6.0 (1.5 - 34.8)	0.005	6.8 (1.1 - 42.1)	0.04
Case	2,3 or 4	28/60 (47%)				
Control	0,1,2	9/49 (18%)	7.3 (2.5 - 23.1)	0.00007	9.2 (2.4 - 36.1)	0.001
Case	3 or 4	22/35 (63%)				
Control	0,1,2,3	21/73 (29%)	23.8 (3.1 - 1087.9)	0.0001	42.8 (3.4 - 540)	0.004
Case	4	10/11 (91%)				

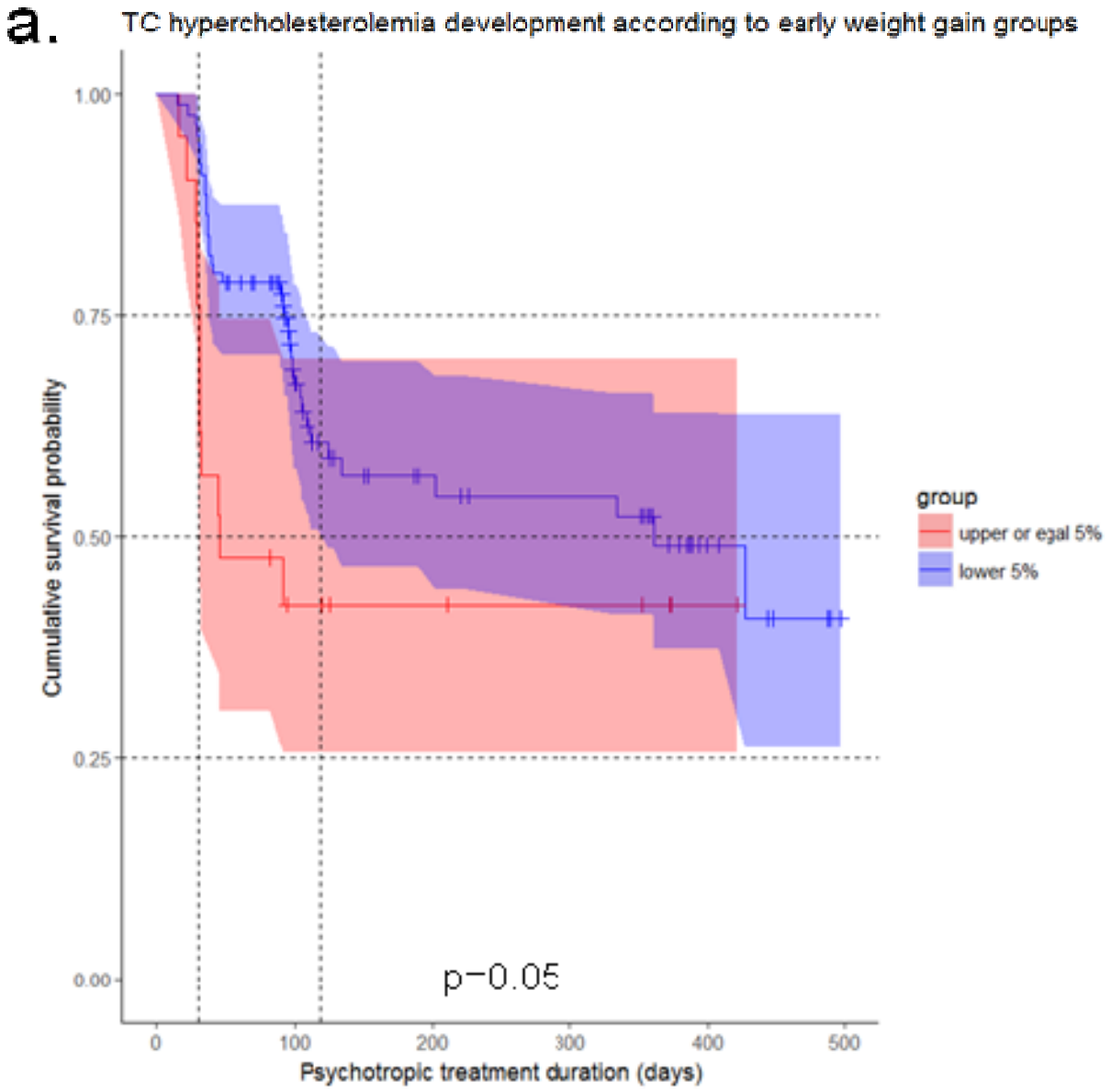
[1] Number of early exceeded thresholds refers to TCi≥5%, LDLi≥5%, TGi≥5% and/or HDLd≥5%

[2] Logistic mixed models were adjusted for age, sex, baseline BMI, smoking status, psychotropic drug category and early weight gain group.



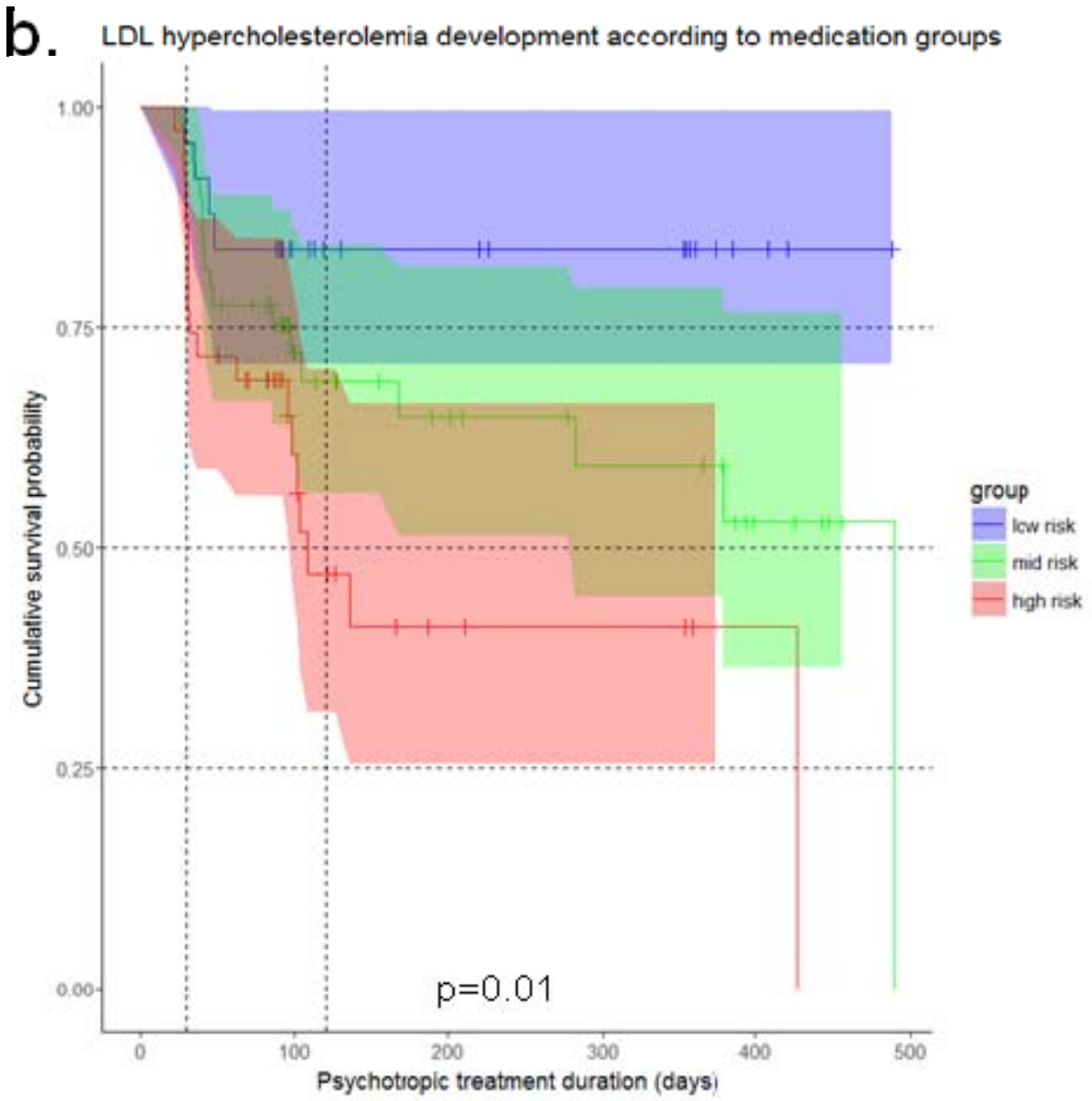
S1 Figure. Flow chart of patient selection

Data 1 constitute data used for the determination of thresholds of early lipid changes to predict long-term lipid change, in patients with no lipid-lowering medication at any time of treatment (see paragraphs 1.1 and 1.2).
Data 2 constitute data used for the analysis of thresholds of early lipid changes to predict new onset dyslipidemia, i.e. in patients with no dyslipidemia at baseline (see paragraphs 1.1 and 1.2).
Of note, replication samples of data 1 and data 2 include patients with less strict criteria of drug-adherence, i.e. patients with at least one observation with adherence ascertained, without any observations of non-adherence, but with one or several observations without adherence measurement.



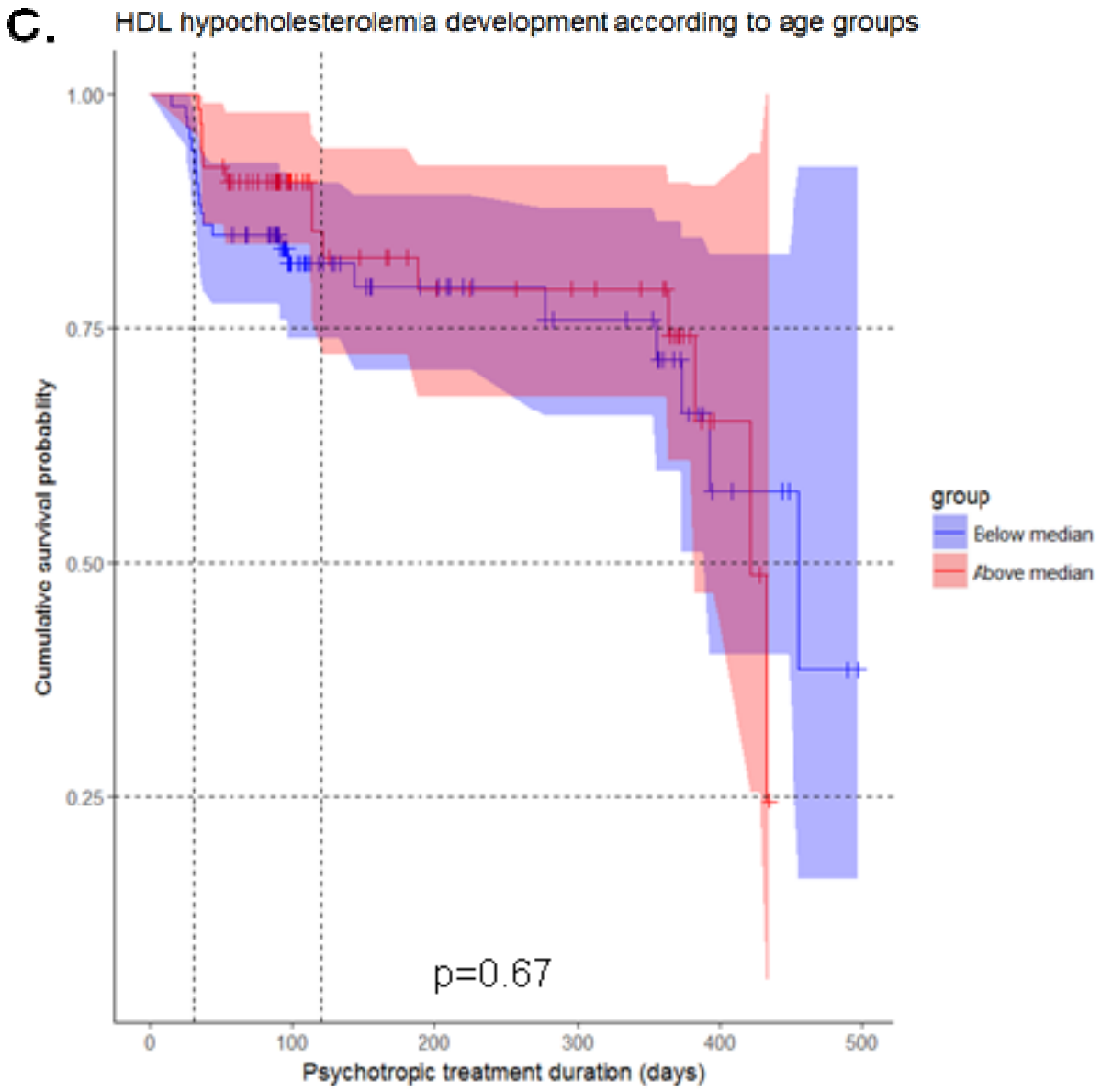
S2 Figure. Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters

a. Survival curves for NODTC (new onset hypercholesterolemia) according to weight gain threshold groups (n=114). Kaplan-Meier p-value is shown.



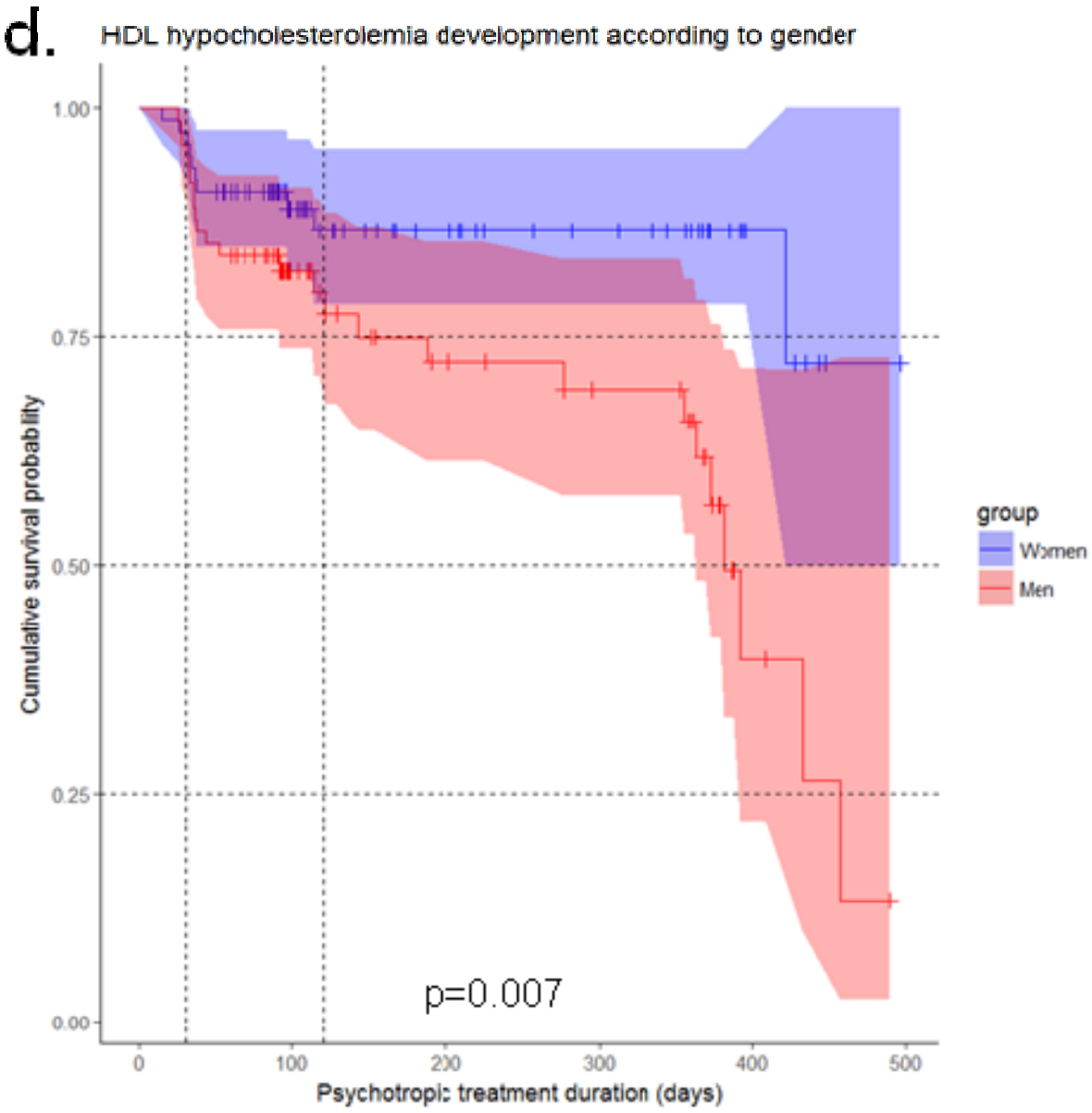
S2 Figure. Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters

b. Survival curves for NODLDL (new onset LDL hypercholesterolemia) according to psychotropic medication groups (low risk group includes patients receiving amisulpride or aripiprazole; mid risk group includes patients receiving mirtazapine, haloperidol, lithium, quetiapine, risperidone or paliperidone; high risk group includes patients receiving clozapine, olanzapine or valproate) (n=115). Kaplan-Meier p-value is shown.



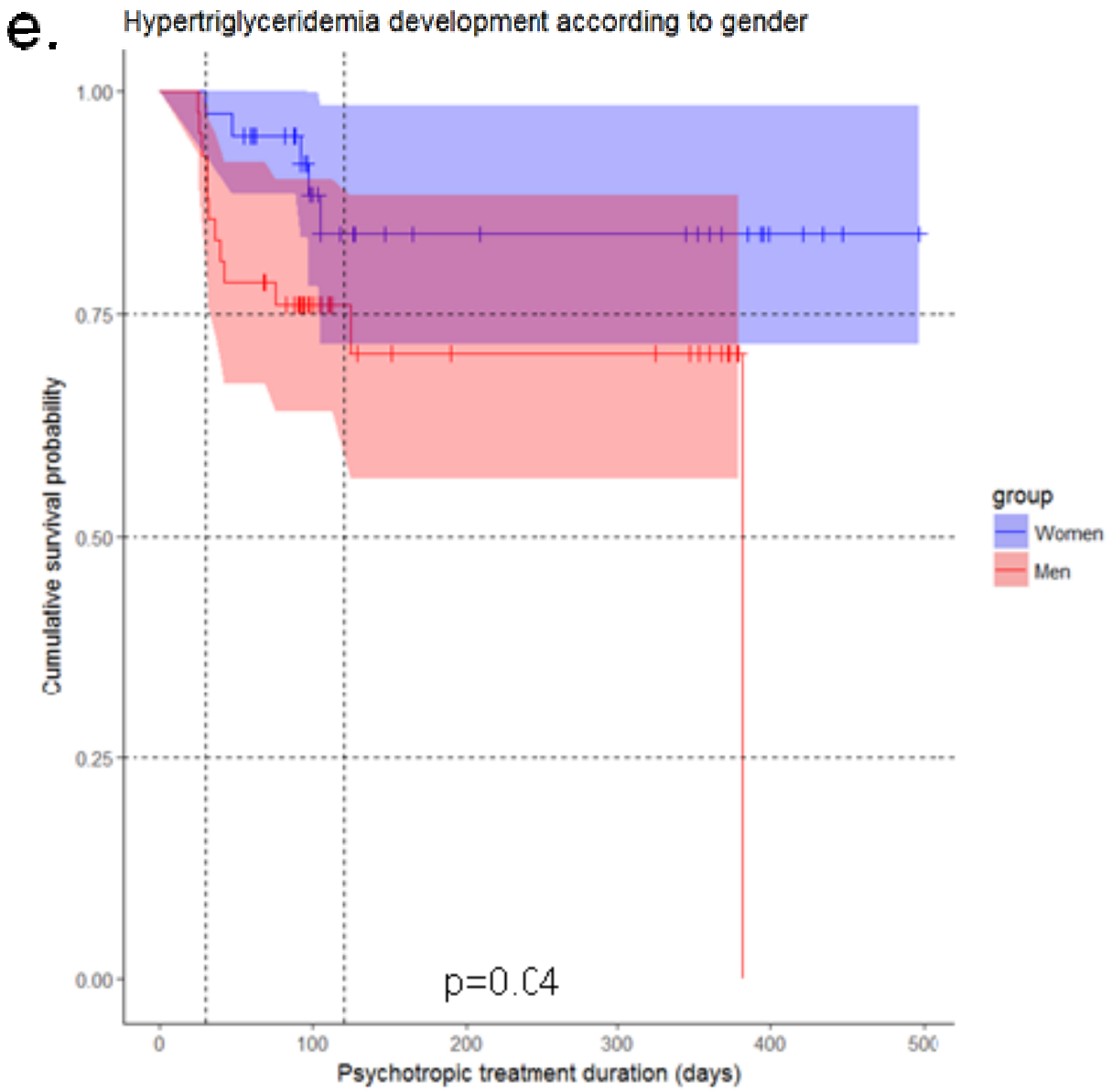
S2 Figure. Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters

c. Survival curves for NODHDL (new onset HDL hypocholesterolemia) according to age groups (median=40 years old) (n=152). Kaplan-Meier p-value is shown.



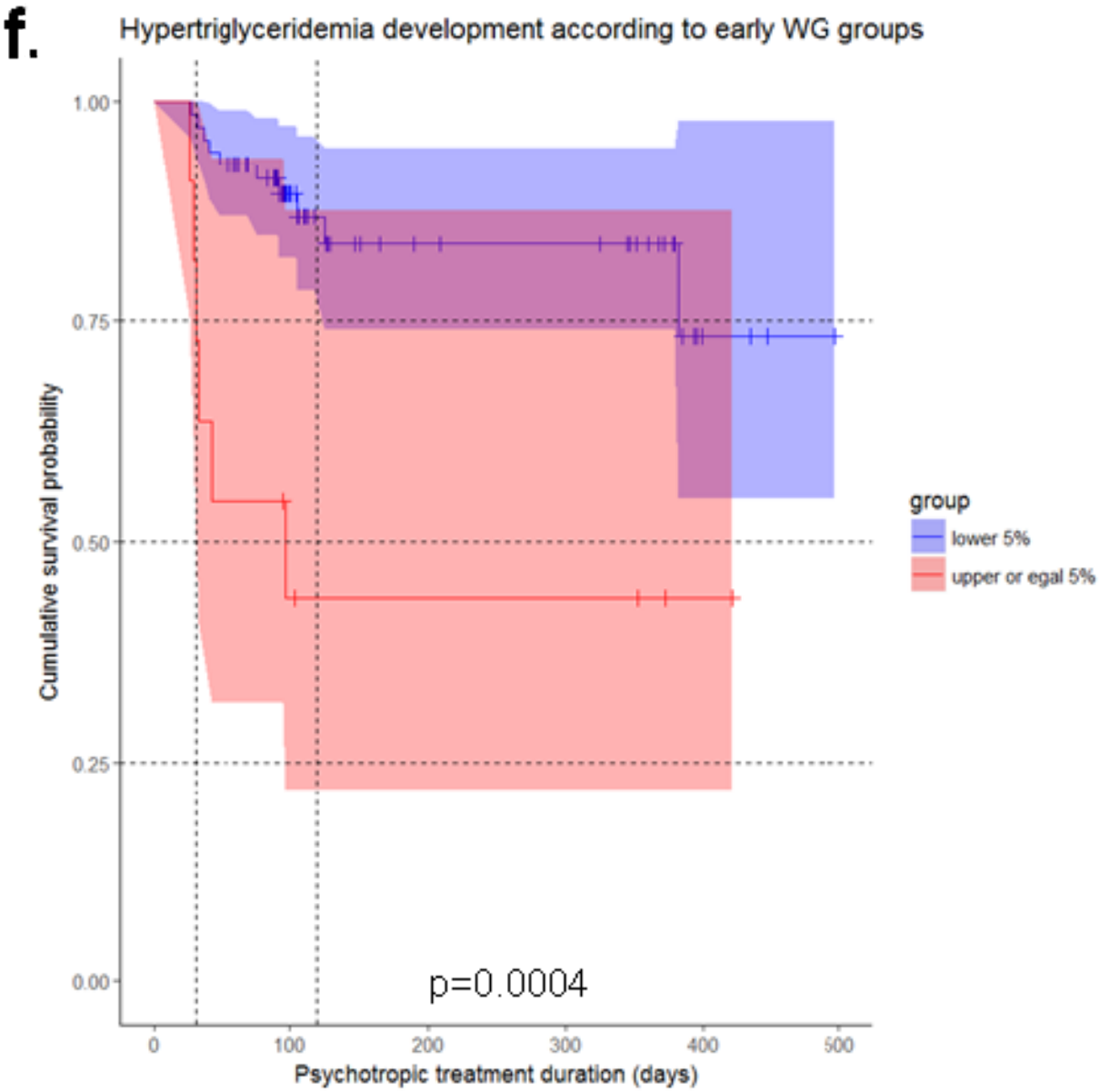
S2 Figure. Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters

d. Survival curves for NODHDL (new onset HDL hypocholesterolemia) according to gender (n=152). Kaplan-Meier p-value is shown.



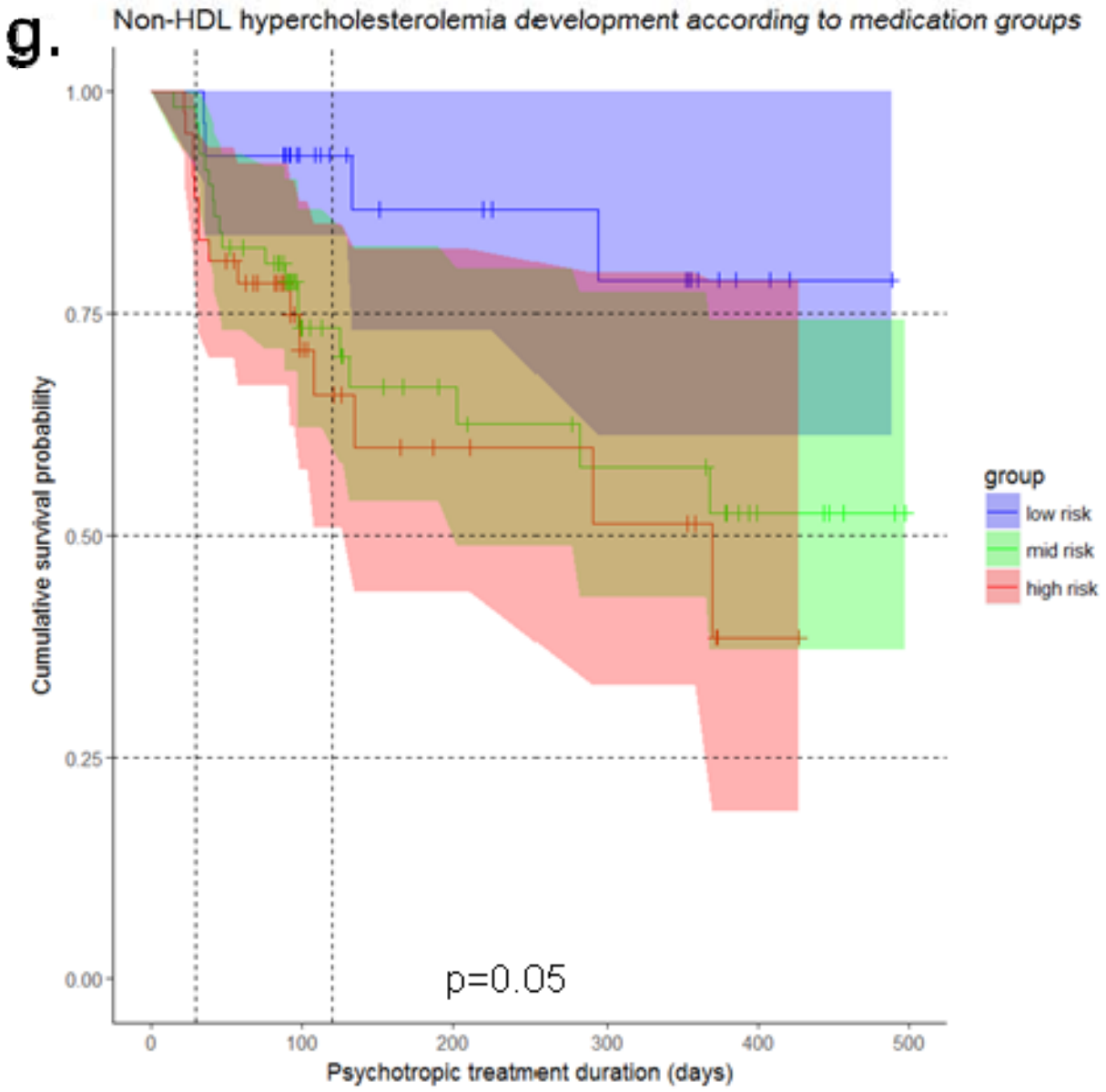
S2 Figure. Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters

e. Survival curves for NODTG (new onset hypertriglyceridemia) according to gender (n=84). Kaplan-Meier p-value is shown.



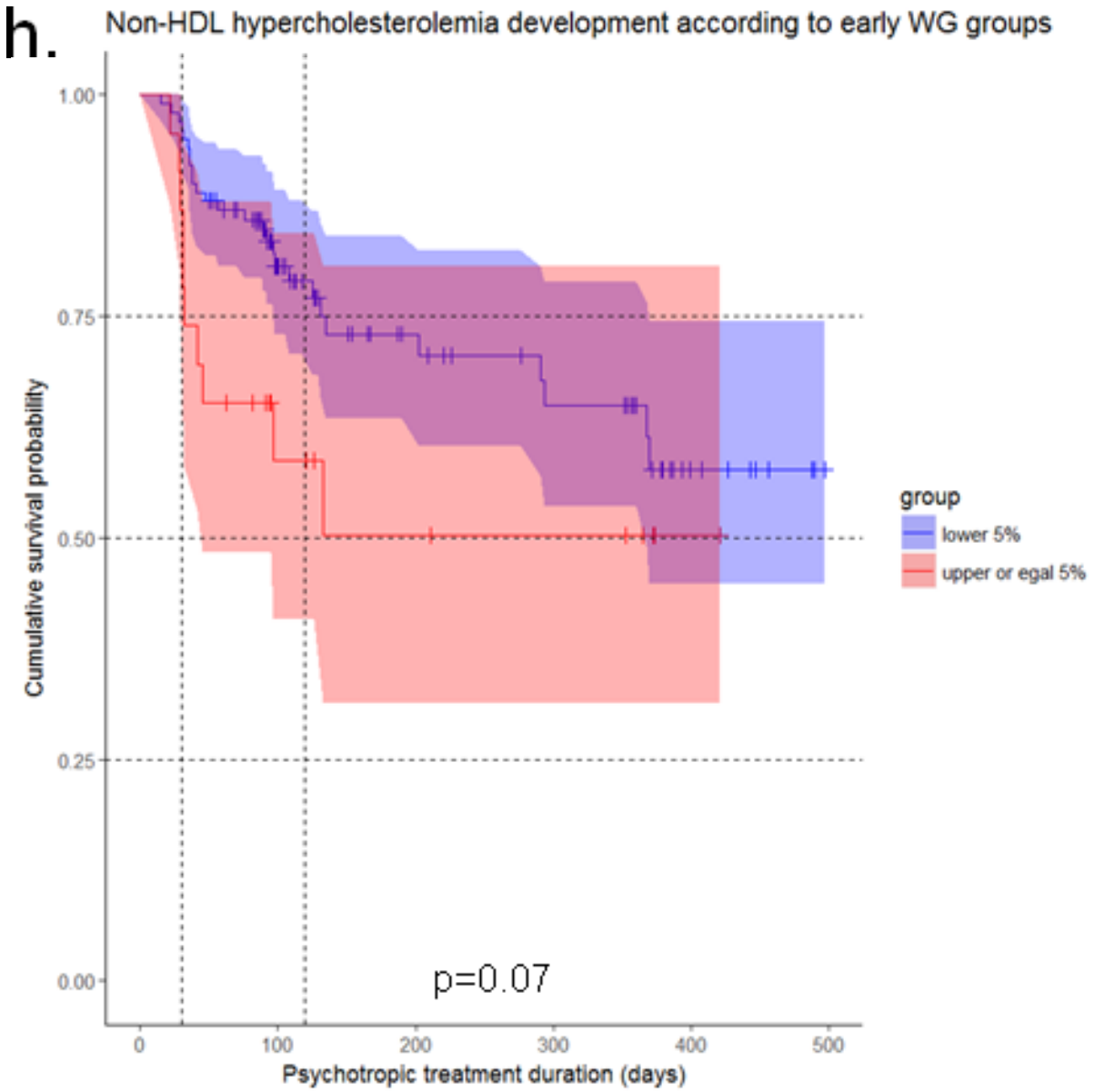
S2 Figure. **Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters**

f. Survival curves for NODTG (new onset hypertriglyceridemia) according to weight gain threshold groups (n=84). Kaplan-Meier p-value is shown.



S2 Figure. Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters

g. Survival curves for NODnonHDL (new onset non-HDL hypercholesterolemia) according to psychotropic medication groups (low risk group includes patients receiving amisulpride or aripiprazole; mid risk group includes patients receiving mirtazapine, haloperidol, lithium, quetiapine, risperidone or paliperidone; high risk group includes patients receiving clozapine, olanzapine or valproate) (n=127). Kaplan-Meier p-value is shown.



S2 Figure. Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters

h. Survival curves for NODnonHDL (new onset non-HDL hypercholesterolemia) according to weight gain threshold groups (n=127). Kaplan-Meier p-value is shown.

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