UNIL | Université de Lausanne

Unicentre
CH-1015 Lausanne
http://serval.unil.ch

Year : 2017

PHARMACOGENETIC AND CLINICAL STUDY ON METABOLIC SIDE EFFECTS INDUCED BY PSYCHOTROPIC DRUGS: FOCUS ON WEIGHT GAIN AND ON LIPID DISTURBANCES

Delacretaz Aurélie

Delacretaz Aurélie, 2017, PHARMACOGENETIC AND CLINICAL STUDY ON METABOLIC SIDE EFFECTS INDUCED BY PSYCHOTROPIC DRUGS: FOCUS ON WEIGHT GAIN AND ON LIPID DISTURBANCES

Originally published at : Thesis, University of Lausanne

Posted at the University of Lausanne Open Archive http://serval.unil.ch
Document URN : urn:nbn:ch:serval-BIB_0D5BADA032555

Droits d'auteur
L'Université de Lausanne attire expressément l'attention des utilisateurs sur le fait que tous les documents publiés dans l'Archive SERVAL sont protégés par le droit d'auteur, conformément à la loi fédérale sur le droit d'auteur et les droits voisins (LDA). A ce titre, il est indispensable d'obtenir le consentement préalable de l'auteur et/ou de l'éditeur avant toute utilisation d'une oeuvre ou d'une partie d'une oeuvre ne relevant pas d'une utilisation à des fins personnelles au sens de la LDA (art. 19, al. 1 lettre a). A défaut, tout contrevenant s'expose aux sanctions prévues par cette loi. Nous déclinons toute responsabilité en la matière.

Copyright
The University of Lausanne expressly draws the attention of users to the fact that all documents published in the SERVAL Archive are protected by copyright in accordance with federal law on copyright and similar rights (LDA). Accordingly it is indispensable to obtain prior consent from the author and/or publisher before any use of a work or part of a work for purposes other than personal use within the meaning of LDA (art. 19, para. 1 letter a). Failure to do so will expose offenders to the sanctions laid down by this law. We accept no liability in this respect.

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Département de Psychiatrie

PHARMACOGENETIC AND CLINICAL STUDY ON METABOLIC SIDE EFFECTS INDUCED BY PSYCHOTROPIC DRUGS: FOCUS ON WEIGHT GAIN AND ON LIPID DISTURBANCES

Thèse de doctorat ès sciences de la vie (PhD)

présentée à la

Faculté de biologie et de médecine

de l'Université de Lausanne

par

Aurélie DELACRETAZ

Biologiste diplômée, Université de Lausanne

Jury

Prof. Olivier Staub, Président
Prof. Chin Bin Eap, Directeur de thèse
Prof. Jacques Fellay, Expert
Dr. Ariane Giacobino, Expert

Prilly-Lausanne 2017

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Ecole Doctorale

Doctorat ès sciences de la vie

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Président· e	Monsieur Prof. Olivier **Staub**
Directeur· rice de thèse	Monsieur Prof. Chin B. **Eap**
Experts· es	Monsieur Prof. Jacques **Fellay**
	Madame Dre Ariane **Giacobino**

le Conseil de Faculté autorise l'impression de la thèse de

Madame Aurélie Delacrétaz

Maîtrise universitaire en science de l' Université de Lausanne

intitulée

PHARMACOGENETIC AND CLINICAL STUDY ON METABOLIC SIDE EFFECTS INDUCED BY PSYCHOTROPIC DRUGS: FOCUS ON WEIGHT GAIN AND ON LIPID DISTURBANCES

Lausanne, le 10 novembre 2017

pour le Doyen
de la Faculté de biologie et de médecine

Prof. Olivier Staub

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Département de Psychiatrie

PHARMACOGENETIC AND CLINICAL STUDY ON METABOLIC SIDE EFFECTS INDUCED BY PSYCHOTROPIC DRUGS: FOCUS ON WEIGHT GAIN AND ON LIPID DISTURBANCES

Thèse de doctorat ès sciences de la vie (PhD)

présentée à la

Faculté de biologie et de médecine

de l'Université de Lausanne

par

Aurélie DELACRETAZ

Biologiste diplômée, Université de Lausanne

Jury

Prof. Olivier Staub, Président
Prof. Chin Bin Eap, Directeur de thèse
Prof. Jacques Fellay, Expert
Dr. Ariane Giacobino, Expert

Prilly-Lausanne 2017

Table of contents

Acknowledgments

First and foremost, I would like to express my gratitude to my thesis director, Prof. Chin Eap, for offering me the chance to pursue working in his team after my master project, for his unconditional support throughout these years and for the inspiring discussions we shared. I learnt a lot from his scientific and leadership expertise.

I would like to thank the jury president, Prof. Olivier Staub, and the experts, Prof. Jacques Fellay and Dr. Ariane Giacobino, for having accepted to evaluate the present work and for their constructive suggestions and reflections.

Many thanks also to Prof. Philippe Conus and Prof. Armin von Gunten for supporting the clinical and pharmacogenetic study and for their accurate review of articles. Thanks to the medical and nursing staff who contributed to patient inclusion and to all patients who gave their consent for the present study.

I am very grateful to all colleagues of the Unit of Pharmacogenetics and Clinical Psychopharmacology for their constant enthusiasm which contributed to the rewarding working environment in the lab. Special thanks to Dr Lina Quteineh, Dr Frederik Vandenberghe, Dr Nuria Saigi Morgui, Dr Etienne Weisskopf, Anaïs Glatard, Axel Levier, Céline Dubath and master students for the scientific discussions and the great moments.

I would like also to warmly thank Dr Mehdi Gholam-Rezaee for his precious help in the statistical methodology.

My gratefulness goes also to Prof Wassim Raffoul, Prof Lee-Ann Laurent-Applegate and Dr. Paris Jafari for their implication in the recruitment of adipose samples. Starting this project from the beginning was a very enriching experience for me.

I also thank Prof. Pierre-Yves Bochud and Dr Stéphanie Bibert for having provided the equipment for methylation analyses.

Finally, I would like to express my gratitude to Didier, my family, in-laws and friends for their support, trust, patience and who encouraged me throughout these years.

Abbreviations

5-HT_{1A}R	Serotonin receptor 1A
5-HT_{2A}R	Serotonin receptor 2A
5-HT_{2C}R	Serotonin receptor 2C
5-HT_{6}R	Serotonin receptor 6
5-HT_{7}R	Serotonin receptor 7
5-HTR	Serotonin receptor
BMI	Body mass index
CRTC1	CREB Regulated Transcription Coactivator 1
D_2R	Dopamine receptor 2
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
EPS	Extrapyramidal symptoms
FDA	United States food and drug administration
FG	Fasting glucose
GWAS	Genome-wide association study
H_1R	Histamine receptor 1
HDL	High-density lipoprotein cholesterol
LDL	Low-density lipoprotein cholesterol
MCH	Melanin-concentrating hormone
MCHR2	Melanin-concentrating hormone receptor 2
MCHR2-AS1	MCHR2 antisense RNA 1
MDD	Major depressive disorder
meQTL	Methylome quantitative trait loci
MetS	Metabolic syndrome
NOD	New-onset dyslipidemia
NPY	Neuropeptide Y
POMC	Pro-opiomelanocortin
PRS	Polygenic risk score
RABEP1	Rabaptin, RAB GTPase Binding Effector Protein 1
SBP	Systolic blood pressure
SH2B1	Src-homology 2B Adaptor Protein 1
SNP	Single-nucleotide polymorphism
SREBP	Sterol-regulatory element-binding proteins
TC	Total cholesterol
TDM	Therapeutic drug monitoring
TG	Triglyceride
UPPC	Unit of Pharmacogenetics and Clinical Psychopharmacology
WC	Waist circumference
WG	Weight gain

Summary

Patients suffering from mental disorders have a significantly reduced life expectancy compared to the general population. This is mainly attributed to cardiovascular diseases resulting in part from the use of certain psychotropic treatments. Thus, many antipsychotics, some mood stabilizers and certain antidepressants can induce substantial metabolic disturbances. The aim of the present work was to identify whether and which clinical and/or genetic factors are associated with metabolic effects induced by psychotropic drugs, and to determine whether these factors can predict the worsening of metabolic parameters, in particular dyslipidemia, during treatment. Firstly, a candidate gene study on *MCHR2* identified a significant association between *MCHR2* rs7754794C>T and body mass index (BMI), with TT carriers having significantly lower BMI (-0.84 kg/m^2) compared to C allele carriers (n=736). This association was also recognized in the general population, particularly in patients suffering from atypical depression (n=453). A second study was conducted to determine whether BMI-related single genetic polymorphisms (SNPs) in population-based samples are associated with cardiometabolic phenotype worsening in the psychiatric population during treatment. Using a hierarchical statistical approach, this study showed that *SH2B1* rs3888190C>A (n=406) and *RABEP1* rs1000940A>G (n=369) were significantly associated with blood levels of LDL-cholesterol and fasting glucose, respectively. The third study, focusing on polygenic risk scores combining multiple SNPs, demonstrated significant associations between the scores and blood lipid levels in the psychiatric population (n=336). Finally, another project aimed to determine the predictive power of early (i.e. after the first month of treatment) changes of lipid levels on longer-term (after three and twelve months) changes of lipid levels and on new onset dyslipidemia. This study showed that early lipid change of ≥5% after the first month was the best predictor for important lipid deterioration in longer-term treatment (n=181). These findings provide new insights into the mechanisms underlying metabolic disturbances induced by psychotropic drugs and emphasize the importance of clinical and genetic parameters to predict dyslipidemia in patients receiving these drugs, providing possible steps towards personalized medicine.

Résumé

Les patients souffrant de troubles psychiatriques ont une espérance de vie significativement réduite par rapport à la population générale, principalement attribuée aux maladies cardiovasculaires résultant notamment de l'utilisation de certains psychotropes. En effet, de nombreux antipsychotiques ainsi que certains stabilisateurs de l'humeur et antidépresseurs peuvent induire des troubles métaboliques importants. Ce travail vise à identifier quels sont les facteurs cliniques et/ou génétiques associés aux effets secondaires métaboliques induits par les psychotropes, ainsi qu'à déterminer si ces facteurs peuvent prédire la détérioration métabolique, en particulier la dyslipidémie, durant le traitement. En premier lieu, une étude gène candidat a identifié une association significative entre le *MCHR2* rs7754794C>T et l'indice de masse corporel (IMC), avec les patients porteurs du génotype rs7754794C>T TT ayant un IMC significativement plus bas (-0.84 kg/m^2) que les porteurs de l'allèle C (n=736). Cette association a également été identifiée dans la population générale, en particulier chez les patients souffrant de dépression atypique (n=453). Une deuxième étude a été conduite afin de déterminer si des polymorphismes nucléotidiques simples (« single nucleotide polymorphisms » ou SNPs) associés à l'IMC dans la population générale étaient associés à la déterioration cardiométabolique observée chez les patients psychiatriques durant le traitement. A l'aide d'une approche statistique hiérarchique, cette étude a montré que *SH2B1* rs3888190C>A (n=406) et *RABEP1* rs1000940A>G (n=369) étaient significativement associés aux taux sanguins de cholestérol-LDL et de glucose, respectivement. La troisième étude, focalisée sur les scores de risque polygéniques combinant de nombreux SNPs, a démontré des associations significatives entre les scores et les taux sanguins lipidiques (n=336). Finalement, un autre projet visait à évaluer la puissance prédictive de modifications lipidiques précoces (c.-à-d. après le premier mois de traitement) sur les changements lipidiques à plus long terme (c.-à-d. après trois et douze mois) et sur le développement de dyslipidémie. Cette étude a montré que les modifications lipidiques précoces ≥5% sont les meilleurs prédicteurs pour une péjoration lipidique importante sur le long terme (n=181). Ces résultats fournissent de nouvelles connaissances sur les mécanismes impliqués dans les troubles métaboliques induits par les psychotropes et soulignent l'importance des paramètres cliniques et génétiques dans la prédiction de la dyslipidémie chez les patients recevant ces médications, ouvrant de possibles perspectives vers une médecine personnalisée.

Résumé large public

Les maladies métaboliques comme l'obésité ou d'autres maladies cardiovasculaires (diabète de type 2, perturbations des lipides dans le sang, etc.) représentent un enjeu de santé majeur en psychiatrie. En effet, de nombreux antipsychotiques ainsi que certains stabilisateurs de l'humeur et antidépresseurs, couramment utilisés pour traiter les symptômes liés à la schizophrénie et aux troubles de l'humeur, peuvent induire des effets secondaires métaboliques importants. Le but de ce travail est d'étudier les facteurs de risque associés aux effets métaboliques induits par les psychotropes, et de déterminer si ces facteurs peuvent être utilisés pour prédire le développement des effets secondaires métaboliques (en particulier les dyslipidémies) durant le traitement. En premier lieu, des analyses génétiques ont mis en évidence l'importance d'un gène impliqué dans la régulation de l'appétit, le *MCHR2*, sur l'indice de masse corporelle des patients. Une deuxième étude, utilisant une approche différente, a déterminé des associations significatives entre des modifications génétiques au sein de deux gènes (*SH2B1* et *RABEP1)* et les taux sanguins de cholestérol LDL et de glucose, respectivement. Une autre étude a montré des associations significatives entre les scores de risque génétique (combinant de nombreuses variations génétiques) et les taux sanguins de lipides (cholestérol LDL, cholestérol HDL, cholestérol total et triglycérides). Finalement, une étude a été menée afin d'évaluer l'effet d'une détérioration précoce des taux de lipides dans le sang (après le premier mois de traitement psychotrope) sur une détérioration ultérieure des lipides. Les analyses ont montré qu'une augmentation des taux lipidiques égale ou supérieure à 5% après le premier mois de traitement permettait de prédire une détérioration lipidique importante ainsi que la survenue d'une dyslipidémie à plus long terme (après trois et douze mois de traitement). En résumé, les résultats de cette thèse permettent de mieux comprendre les mécanismes impliqués dans les troubles métaboliques, notamment lipidiques, associés aux psychotropes. De plus, ils apportent de nouveaux outils cliniques afin de prévoir et si possible éviter les effets lipidiques associés à la prescription de nombreux psychotropes.

Preface

The present work was conducted at the Unit of Pharmacogenetics and Clinical Psychopharmacology (UPPC), in the Center for Psychiatric Neurosciences in Lausanne University Hospital. The UPPC lab is involved in different fields of activity, providing medico-technical services in relation to therapeutic drug monitoring (TDM), including plasma and urinary psychotropic drug quantification, for which result interpretations and eventually psychopharmacological advices are provided. Medico-technical services for molecular biology related to pharmacogenetics are also supplied. A program of pharmacovigilance (i.e. drug safety) and clinical psychopharmacology intervisions are also proposed to some services in the Department of Psychiatry and to external physicians.

In the UPPC lab, clinical and pharmacogenetic research aims to determine whether and which clinical and genetic factors are associated with psychotropic-related side effects.

Weight gain (WG) and metabolic complications are major side effects induced by some psychotropic drugs, increasing the risk of cardiovascular events and long-term morbidity and mortality in psychiatric populations. Since 2007, the Department of Psychiatry has implemented an internal guideline requiring that patients being prescribed psychotropic drugs (antipsychotics, some antidepressants and mood stabilizers) must be followed for metabolic side-effects. To date, informed consent was obtained from more than 1500 patients whose clinical data, genetic data and DNA samples are available.

The aim of the present thesis was to improve the current understanding of metabolic side effects induced by psychotropic drugs. For that purpose, different approaches were used to elucidate whether clinical and/or genetic factors are associated with metabolic side effects, and to which extent these factors predict these adverse effects.

INTRODUCTION

In the psychiatric population, a high prevalence of therapeutic failure and medication-associated side effects are observed, partly due to the high inter-individual variability in drug responses for efficacy, safety and tolerability. Drug responses depend on many personal factors including age, sex, ethnicity but also environmental (e.g. smoking, concomitant medication, diet) and genetic factors.

Since the pathophysiology of psychiatric disorders is only partially elucidated, drug development in mental health care has been essentially based on experimental observations. Thus, the first antipsychotic drug was discovered by accident in the 1950s when one drug with antihistaminic properties (chlorpromazine) was observed to have antipsychotic effects in schizophrenic patients. This discovery has been considered as one of the major advances in the history of psychopharmacology (1). By the 1970s, the ability of antipsychotics to block dopamine-2 receptors (D_2R) was recognized as the mechanism through which they reduced positive symptoms of schizophrenia (i.e delusions and hallucinations). However, these compounds were linked with movement disorders, defined as acute extrapyramidal symptoms (EPS), and were limited by their inability to treat the full range of psychotic symptoms. In the early 1970s, the first second-generation antipsychotic introduced (i.e. clozapine) showed a lower tendency to induce EPS and a significant increase in efficacy on both positive (hallucinations, disorganized behavior) and negative symptoms (social withdrawal, apathy) due to their affinities for a larger spectrum of central receptors (2). Nowadays, as a result of an increasing number of diagnoses of mental health conditions but also of many off-label uses, the use of antipsychotic drugs has raised significantly.

Therapeutic and side effects – mechanisms of action

Although the pathophysiology of psychiatric disorders is only partially explained, the most commonly accepted hypothesis to describe schizophrenia is based in part on an hyperactivity of dopamine tone in the mesolimbic dopamine pathway, postulated to cause the positive symptoms of psychosis (3). This pathway is involved in the transmission of dopamine from the

ventral tegmental area to the nucleus accumbens and it regulates many reward-related processes. By blocking D_2R in the mesolimbic pathway, antipsychotics reduce positive symptoms, i.e. delusions and hallucinations. On the other hand, this antagonism may generate a loss of reward, contributing to anhedonia and apathy which may induce or worsen negative symptoms of schizophrenia. In addition, instead of being specific to the mesolimbic dopamine pathway, antipsychotics target D_2R from the entire brain region, which can contribute to the development of numerous adverse effects. Thus, D_2R antagonism in the nigrostriatal dopamine pathway may produce movement disorders, i.e. EPS, occasionally leading to tardive dyskinesia in the long-term, a highly debilitating and potentially irreversible movement disorder (4). Moreover, D_2R antagonism in the tuberoinfundibular pathway may induce hyperprolactinemia, a condition interfering with fertility in women, as well as a decrease in mineral bone density (5). First-generation antipsychotics also have other important pharmacological properties, including blockage of muscarinic cholinergic receptors, related with dry mouth, blurred vision, constipation and cognitive blunting, and a blockage of histamine-1 receptors (H_1R), causing weight gain and drowsiness and blockade of alpha-1 adrenergic receptors, which may induce cardiovascular side effects (3). Because antipsychotics differ in their pharmacological profiles, they differ in their side-effects profile. Indeed, some are more sedating than others and some have more ability to cause EPS than others.

Atypical antipsychotics or second generation antipsychotics are distinguished from classical antipsychotics by their pharmacological profile. Several serotonin receptors (5-HTR), such as 5-$HT_{2A}R$, 5-$HT_{2C}R$, 5-$HT_{1A}R$, 5-HT_6R and 5-HT_7R, may contribute to the mechanism of action of atypical antipsychotics (6). Dopaminergic modulations, including a low affinity for dopamine D_2R and a partial D_2R agonism and glutamatergic regulations may also be involved in the pharmacological background of “atypicality”. Compared to first generation antipsychotics, some second generation antipsychotics (i.e. clozapine and quetiapine) have a lower affinity for D_2R and a faster D_2R dissociation, thereby contributing to their lower propensity to induce EPS. Additionally, 5-$HT_{2A}R$ antagonism confers atypical antipsychotics a reduction of negative

symptoms and a reduction of hyperprolactinemia and of extrapyramidal symptoms. These drugs also display affinities for many other central receptors such as histaminic, muscarinic and adrenergic receptors (**Table 1**).

Table 1 summarizes the pharmacological profile of various typical and atypical antipsychotics. Equilibrium constant (i.e. the concentration (in nanomolar) of antipsychotics needed to block 50% of the receptors) is indicated for each drug and receptor (6-14). Most typical antipsychotics have a propensity to antagonize D_2R more potently than 5-$HT_{2A}R$. On the other hand, most atypical antipsychotics possess more potent 5-$HT_{2A}R$ antagonism than D_2R antagonism, resulting in a D_2R /5-$HT_{2A}R$ ratio >1 (6).

Table 1. Receptor affinities for some antipsychotics (Adapted from: Kusumi et al., Psychiatry and Clinical Neurosciences, 2014)

	Ki (nM)													Ratio
	D_1	D_2	D_3	D_4	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_6	5-HT_7	α-1	α-2	AchM	H_1	D_2/5-HT_{2A}
Typical antipsychotics														
Nemonapride	>5000	0.16	0.26	0.31	1.8	34	224	ND	ND	178	2655	>5000	2617	0.0047
Bromperidol	214	1.2	5	35	3163	47	>5000	ND	ND	15	>5000	>5000	796	0.026
Haloperidol	270	1.4	21	11	3081	25	>5000	>5000	380	19	>5000	4669	727	0.056
Chlorpromazine†	71††	2.6††	2.4††	8.3††	3115	12	6.1	4‡‡	21‡‡	0.3	184	67	0.18	0.56
Mosapramine	143	1.8	1.0	3.2	327	2.4	709	ND	ND	43	ND	2237	117	0.75
Clocapramine	243	13	9.1	164	306	1.9	17	ND	ND	85	1076	>5000	1076	6.8
Zotepine	84	13	16	39	330	0.91	2.9	1.2‡‡	10	3.4	960	550	3.4	14
Pipamperone	2450	93	480	5.1	2600	1.2	120	ND	150	66	680	>5000	>5000	78
Atypical antipsychotics														
Amisulpride‡	>10 000	3.0	3.5	2369	>10 000	8304	>10 000	4154	12	>10 000	1114	>10 000	>10 000	0.00036
Aripiprazole§	1960	0.74	1.0	510	5.6	8.7	76	570	10	26	74	6780	25	0.085
Blonanserin¶	1070	0.14	0.49	150	804	0.81	26	42	183	27	530	100	765	0.17
Quetiapine	4240	310	650	1600	320	120	3820	ND	290	58	1000§§	1020	19	2.6
Perospirone	1111	1.3	4.4	1.8	1.3	0.22	5.5	ND	ND	2.5	245	>5000	2.2	5.9
Olanzapine	250	17	54	28	2720	1.9	7.1	2.5	120	60	170§§	26	3.5	8.9
Paliperidone	670	4.0	7.5	30	380	0.25	71	ND	1.3	4	17	3570	10	16
Risperidone	620	3.3	13	16	250	0.16	63	420	1.6	2.3	7.5	>5000	2.6	21
Ziprasidone	330	9.7	7.5	39	12	0.31	13	76§§	4.9	12	310§§	>5000	5.3	31
Clozapine	540	150	360	40	180	3.3	13	4	21	23	160	34	2.1	45

All data without notes are based on Schotte *et al.* (1995) and Schotte *et al.* (1996).
†Based on Horacek *et al.* ‡Based on Abbas *et al.* §Based on Shapiro *et al.* ¶Based on Une and Kurumiya. ††Based on Gross and Drescher. ‡‡Based on Roth *et al.* §§Based on Schmidt *et al.*
ND, not determined.

Table 2. Target receptors of antipsychotic drugs and their associated metabolic side effects (Balt et al., Clinical pharmacology and therapeutics, 2011)

Receptor	Side effect	Mechanism
Serotonin 5-HT 2C	Diabetes	Antagonists disrupt sympathetic regulation of peripheral glucose metabolism; also inhibit skeletal muscle and hepatic glucose uptake
	Weight gain	Antagonists disinhibit hypothalamic NPY neurons (resulting in elevated NPY) and inhibit POMC neurons (resulting in decreased α-MSH); may also play a role in leptin resistance
Serotonin 5-HT 1A	Diabetes	Antagonists inhibit skeletal muscle and hepatic glucose uptake and downregulate pancreatic β-cell sensitivity to glucose
	Weight gain	Agonists increase food intake; partial agonists may mitigate 5-HT2C antagonism; partial agonists may also decrease carbohydrate craving
Histamine H1	Weight gain	Antagonists cause increased hypothalamic AMPK activity, mimicking depletion of cellular energy stores and causing increased appetite
	Diabetes	Antagonists disrupt sympathetic regulation of adipose tissue
	Sedation	Antagonists inhibit cholinergic neurons of basal forebrain and serotonergic neurons of dorsal raphe
Dopamine D2	Weight gain	Antagonists cause overall decrease in limbic dopaminergic activity, possibly leading to increased engagement reward-seeking behaviors such as food intake; agonists (psychostimulants, cocaine) are appetite suppressants
	Extrapyramidal side effects	Antagonists disinhibit indirect descending motor pathway in basal ganglia
	Endocrine effects	Antagonists disinhibit prolactin release from posterior hypothalamus, also contributing to weight gain
Muscarinic M1	Anticholinergic effects	Antagonists cause dry mouth, urinary retention, cognitive dysfunction, urinary retention, and constipation
Muscarinic M3	Diabetes	Antagonists cause impaired glucose tolerance and reduced insulin secretion from pancreatic β cells

α-MSH, α-melanocyte-stimulating hormone; AMPK, AMP-related kinase; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

Metabolic side effects induced by psychotropic drugs

Psychotropic medications such as antipsychotics (mostly atypical but also some typical ones), mood stabilizers (e.g. lithium and valproate) and some antidepressants (e.g. mirtazapine) can increase the risk of metabolic disorders including obesity, dyslipidemia and type 2 diabetes (15). This excess cardio-metabolic risk contributes to a reported 10 year- shorter life expectancy in psychiatric patients, compared to the general population (16). In addition, the high prevalence and poor tolerability of metabolic effects induced by psychotropic medications frequently lead to suboptimal medication compliance and high rates of treatment discontinuation, resulting in relapse and poor patient outcomes in the long-term.

Obesity and weight gain

Patients with severe mental disorders have a significantly higher risk of being overweight or obese compared to the general population (17-19). Weight gain is a well-established side effect

of psychotropic drugs, affecting between 15% and 72% of patients (20). As reported by many studies, psychotropic treatments differ in their propensity to induce weight gain (20-23). A recent meta-analysis comparing 15 antipsychotics to placebo corroborated these findings (**Figure 1**), showing that clozapine and olanzapine are associated with greatest weight gain, quetiapine, risperidone and paliperidone confer an intermediate risk and aripiprazole, amisulpride and lurasidone have a lower effect on body weight (24). It is worth noting that some first-generation antipsychotics such as chlorpromazine and other sedative first generation antipsychotics are also associated with significant weight gain compared to placebo (24). Thus, the so-called low-potency agents (such as chlorpromazine) have a higher weight gain potential than high-potency drugs such as haloperidol (20, 25). In addition, certain mood stabilizers (e.g. lithium, valproate) and antidepressants (e.g. mirtazapine, amitriptyline) were also described for their propensity to induce weight gain and other metabolic disturbances (20, 26-31).

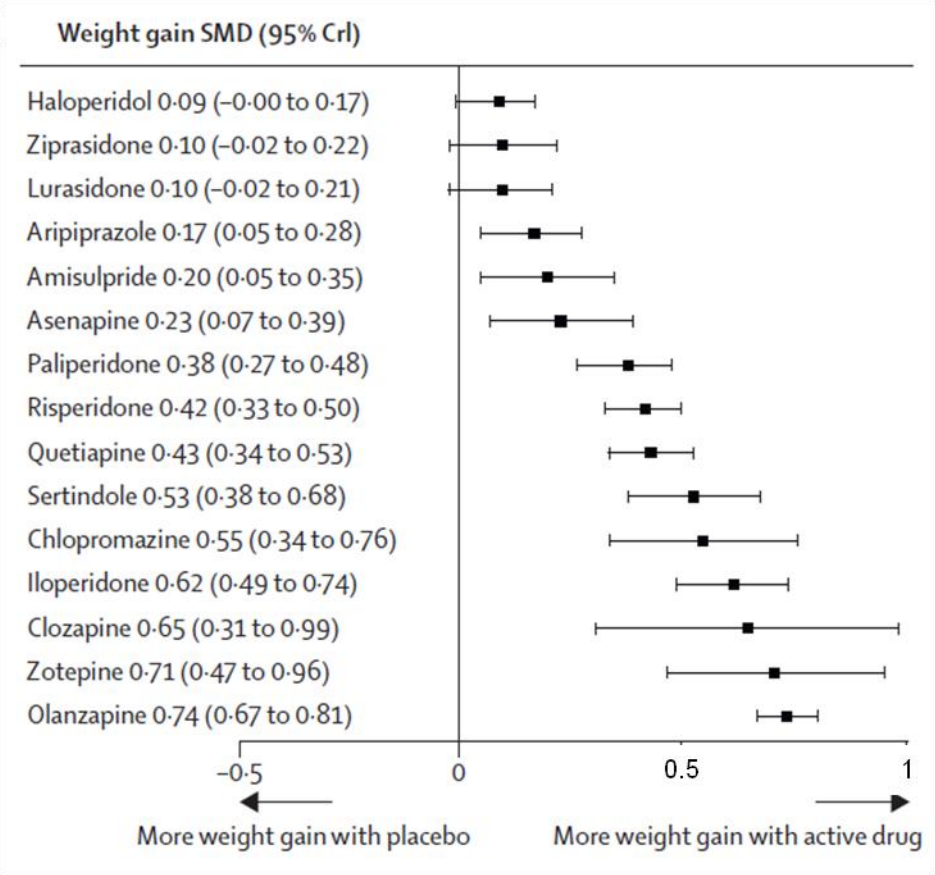


Figure 1. Forest plot for weight gain induced by antipsychotics compared with placebo (Adapted from Leucht et al., Lancet, 2013)

Metabolic syndrome (MetS) is a clinical condition defined by a combination of central obesity, high blood pressure, low high-density lipoprotein cholesterol (HDL), elevated triglyceridemia and/or hyperglycemia. As reported by Vancampfort and collaborators, individuals with severe mental disorder (i.e. schizophrenia, bipolar disorders and major depressive disorder) have a 1.6 increased risk for metabolic syndrome and its components compared to the general population (32). In the same study, people treated with antipsychotics were more likely to suffer from MetS compared to antipsychotic-naïve participants, highlighting the ability of antipsychotics to worsen metabolic parameters. In accordance with weight gain-related studies, clozapine and olanzapine were also found at higher risk for MetS as compared to other molecules (32-35). Interestingly, in agreement with data shown in Figure 1 above, Vancampfort and collaborators demonstrated that certain first generation antipsychotics such as chlorpromazine were not devoid of metabolic

side effect as they had a higher tendency to induce metabolic disturbances than aripiprazole (32).

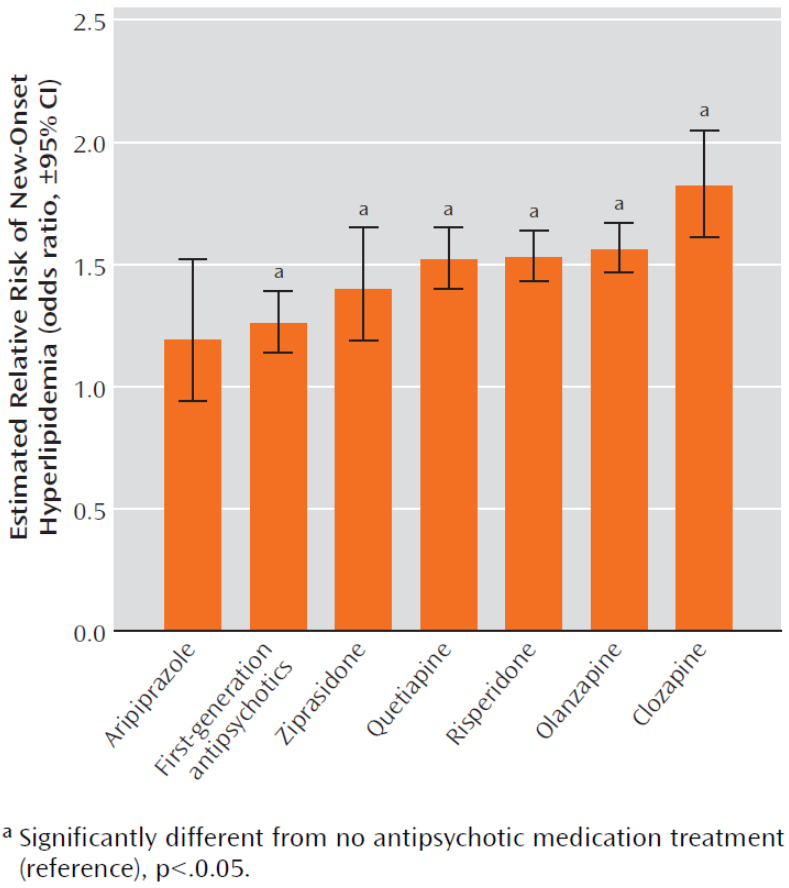


Figure 2. Association of antipsychotic medication treatment with new-onset hyperlipidemia in adults with psychotic disorders (Adapted from: Olfson et al., The American journal of psychiatry, 2006)

Lipid levels

There is accumulating evidence showing that some psychotropic medications can increase the risk of dyslipidemia, i.e. the risk to develop an imbalance of lipid components, encompassing elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglyceride (TG) or reduced HDL levels. By examining individual cardio-metabolic abnormalities in schizophrenic patients, Mitchell and collaborators observed that at least 2 in 5 patients had lipid

abnormalities (36). More interestingly, they noticed that patients taking antipsychotics were more likely to suffer from hypertriglyceridemia and HDL hypocholesterolemia compared to untreated patients (36). These findings are in accordance with a case-control study reporting a significant increased risk of developing hyperlipidemia in patients with schizophrenia or mood disorders receiving antipsychotic medications compared to patients not treated with these drugs (37) and with studies in patients with depression or bipolar disorders receiving these medications (38, 39). **Figure 2** shows that treatment with clozapine, olanzapine, risperidone, quetiapine and with first-generation antipsychotics (but not with aripiprazole) is associated with a significantly greater risk of new-onset hyperlipidemia compared to no-antipsychotic treatment (37). Although antipsychotic drugs are known to be associated with different degrees of weight gain, larger studies and meta-analyses are needed to determine how these drugs alter the lipid profile and whether their rank of risks is similar to weight gain. Despite their well-known propensity to induce weight gain, the influence of antidepressants on lipid levels remains scarce (40). Among mood stabilizers, lithium was shown to have a nominal influence on lipid traits (41), possibly through its influence on hypothyroidism leading to weight gain (42). Finally, valproate has been linked with lower TC and LDL levels in epileptic children (43) and in patients with bipolar disorders (44) despite its positive association with weight gain, triglycerides and glucose (45). Psychotropic-induced dyslipidemia has long been considered as resulting from psychotropic-drug induced weight gain. However, new data has revealed that these lipogenic adverse effects may occur very early during treatment and may even precede weight gain, displaying weight-independent molecular effects in addition to weight-related ones (46-51). A prospective longitudinal study conducted to determine the course of weight gain and other cardiometabolic abnnormalities in first-episode patients treated with antipsychotics showed that the weight was substantially increased within the first months of treatment (**Figure 3**). Similarly, within the same period of antipsychotic treatment, TC, LDL and TG levels were also drastically increased, and then remained relatively constant. On the contrary, HDL plasma levels remained stable during the first year and decreased only thereafter (**Figure 3**).

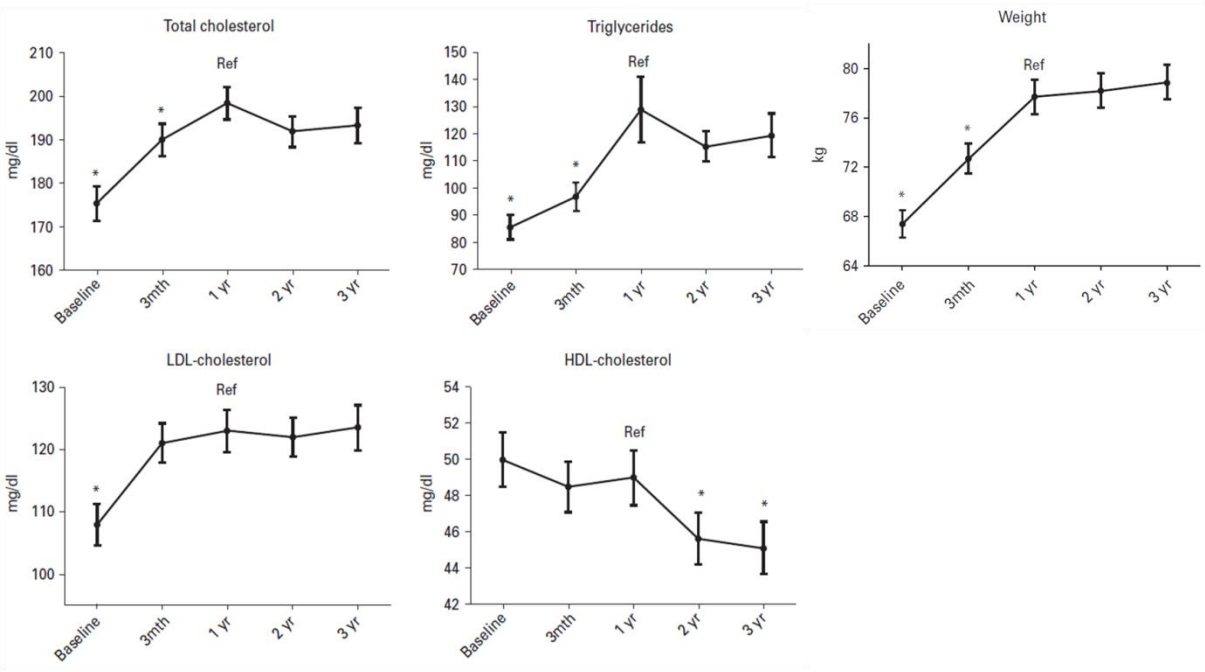


Figure 3. Evolution of weight and lipid values during the first three years of antipsychotic treatment (Adapted from: Perez-Iglesias el al., The international journal of neuropsychopharmacology, 2014)

Glucose levels

Glucose dysregulation may occur following psychotropic treatments in patients with schizophrenia or bipolar disorders (52), with approximately 20% of patients having significant hyperglycemia (36). This side effect may be provoked peripherally, independently of weight gain (53). Indeed, in healthy volunteers receiving olanzapine or placebo for 3 days, although no significant difference was detected between both treatments in terms of body weight, olanzapine provoked an important deterioration of oral glucose tolerance test (54). The weight-independent impaired glucose homeostasis was corroborated in a recently published inpatients study with a longer olanzapine treatment (9 days) (55). However, glucose impairment may also occur as a result of antipsychotic-induced weight gain. Although a recent meta-analysis determined that antidepressants increase the likelihood of new-onset type 2 diabetes (56), no causal relationship could be established and future randomized studies are needed to confirm this

association. In addition, the use of mood stabilizers was also reported to increase the occurrence of type 2 diabetes in patients with major depression (57). Thus, certain mood stabilizers such as valproate were associated with an elevated risk for the development of insulin resistance (58).

Possible mechanisms of psychotropic drug-induced metabolic effects

To date, mechanisms underlying psychotropic-induced metabolic side effects are only partially understood. One possible hypothesis to explain these mechanisms is the increase in appetite, which is often observed in treated patients. Thus, some receptors targeted by psychotropic drugs are also involved in the regulation of food intake (59). Because antagonism of 5-HT_{2C}R in the hypothalamus was shown to enhance food intake (60) and 5-HT_{2C}R genetic variants were extensively associated with obesity, glucose intolerance and susceptibility for weight gain in patients receiving psychotropic treatments (61, 62), this receptor represents a good candidate to explain psychotropic drug-induced weight gain and other metabolic abnormalities. However, certain drugs (such as ziprasidone) have a low ability to induce weight gain despite their high affinity for 5-HT_{2C}R (63) (**Table 1**), suggesting many other possible receptor affinities to explain the orexigenic potencies of antipsychotic drugs. For instance, since H_1 antihistamines were reported to be orexigenic in rats (64) and in humans (65), the histaminergic neurotransmission was also proposed to play a role in the homeostatic and hedonic aspects of feeding (53, 66). Antipsychotics associated with the greatest degree of weight gain (i.e. olanzapine and clozapine) are those that have the most potent antagonist action simultaneously on H_1R and on 5-HT_{2C}R (6, 67). Therefore, it is recognized that a concomitant antagonism on H_1R and 5-HT_{2C}R, together with many other receptors, may explain the metabolic profile of psychotropic drugs (3). **Table 2** shows target receptors of antipsychotics and their possible associated metabolic side effects (68). It is worth mentioning that, in addition to their actions on the central nervous system, antipsychotics also target peripheral receptors (i.e. receptors in pancreas, liver, muscle and adipose tissue) (53). Through convergent

molecular pathways including signaling of these above-mentioned receptors, central and peripheral targets may interact to induce synergistic effects in metabolic disturbances induced by psychotropic drugs (53).

Beside their direct pharmacodynamic activities, psychotropic drugs can also induce other mechanisms involved in the hypothalamic regulation of appetite. Thus, the transcription of some hormones involved in energy homeostasis (i.e. either anorexigenic or orexigenic) can be affected by certain psychotropic drugs. For instance, the expression of melanin-concentrating hormone (MCH) and its receptors may be up-regulated during antipsychotic treatment, which may enhance the rewarding aspects of food (69). Additionally, significant changes of mRNA levels were observed for neuropeptide Y (NPY) and pro-opiomelanocortin (POMC) following olanzapine treatment (70). A prospective trial reported a significant appetite increase in schizophrenic patients receiving olanzapine treatment, even in conditions of high leptin levels, demonstrating the development of leptin resistance (71). Finally, a recent meta-analysis showed that antipsychotics inducing the most important weight gain (i.e. olanzapine, clozapine) were associated with the most important increase of blood leptin levels in schizophrenia patients (72). The mechanisms through which psychotropic drugs influence markers of gene transcription are far from being fully defined. During the last decade, many studies have determined methylation changes associated with psychotropic drugs, including atypical antipsychotics (73-75) and mood stabilizers (76-78). A recent review discussed the possible influence of these drugs on the modulation of gene expression markers such as epigenetics (DNA methylation and histone modification), intracellular signaling pathways and post-transcription processes (microRNAs) (79). These molecular modifications can rescue molecular aberrations observed in patients with psychiatric diseases (80), but can also be linked to psychotropic drug-metabolic side effects. Two recent studies have drawn attention to associations between certain methylation sites and insulin resistance (81, 82). However, prospective studies are lacking and it remains to be asserted whether methylation modulations are tissue-specific and/or reversible. Many other possible molecular modifications induced by psychotropic drugs may participate in metabolic

side effects, in particular modulations in microRNA levels induced by antipsychotics (83), mood stabilizers (84-86) and some antidepressants (87). Future research placing a greater emphasis on gene transcription markers will need to be conducted to further disentangle mechanisms underlying metabolic side effects induced by psychotropic medications.

Metabolic changes associated by psychotropic drugs do not seem to arise only from mechanisms regulating appetite homeostasis. Thus, some studies found that metabolic side effects such as lipid parameters and insulin resistance occurred before changes in hunger, satiety and food intake and were weight-gain independent, suggesting that psychotropic drugs can exert direct effects on peripheral tissues, independently from mechanisms regulating eating behavior (51, 55, 88-90).

Lipid levels

Adverse effects on serum lipids induced by psychotropic drugs should be considered as a possible direct or collateral consequence of these drugs, either through pharmacodynamic and/or transcription-related mechanisms (25, 47, 91). Although the exact mechanisms are only partially understood, certain changes of gene transcription levels were recognized. For instance, biochemical pathways involving sterol-regulatory element-binding proteins (SREBP), the most important transcriptional regulators of cellular lipid and cholesterol synthesis (92, 93), may be altered by a variety of antipsychotics (48, 94-97). Some studies suggested that lipid abnormalities associated with psychotropic drugs arise from increased leptin levels and an increase in lipid oxidation (98). In addition, the expression of lipoprotein lipase, involved in the hydrolysis of triglycerides into free fatty acids, was shown to be suppressed during clozapine treatment in adipocytes, in a dose-dependent manner (99). In agreement with this study, a case-report demonstrated a rapid increase of lipoprotein lipase levels, coupled with rapid triglyceride normalization after olanzapine cessation due to severe hypertriglyceridemia (100). A review on mechanisms underlying psychotropic induced hypertriglyceridemia has drawn attention to distinct direct and indirect mechanisms (101). Finally, results from animal studies

suggest that valproic acid modifies cholesterol metabolism by enhancing hepatic peroxisomal b-oxidation (102). To date, the precise central and peripheral receptors mediating changes in the lipid profile are still to be elucidated, and there are many other possible mechanisms to explain drug induced alteration of the lipid profile.

Glucose levels

Similarly, hyperglycemia and/or diabetes following psychotropic treatment should be considered as a possible direct or collateral consequence of these drugs. On one hand, psychotropic-induced diabetes may follow psychotropic-induced weight gain, assuming that high levels of free fatty acids may blind insulin sensitivity, leading to insulin resistance and increased glycemia. On the other hand, the mechanisms driving the obesogenic and diabetogenic effects of psychotropic drugs appear to be partially independent. Thus, many molecular mediators were proposed to confer the diabetogenic potential of psychotropic drugs, partially or completely independently of weight gain (53, 103, 104). For instance, antagonism on several receptors in pancreatic beta-cells such as muscarinic-3-receptor (M_3R), 5-$HT_{1A}R$ or 5-$HT_{2C}R$ may directly damage insulin secretion of these cells (68, 105, 106).

Individual variations in metabolic side effects

There are considerable inter-individual variations in weight gain and other metabolic side effects associated with psychotropic drugs, regardless of the type of medication (67). For a given agent, some individuals lose weight, others remain stable and a proportion of patients gain weight (23). This variability can be explained in part by the combination of certain clinical and genetic risk factors, described below.

Clinical factors

Factors that influence the risk of psychotropic-drug induced metabolic abnormalities include personal factors, illness characteristics and treatment-related factors. For instance, patients

whose baseline body mass index (BMI) is low (<25 kg/m^2) and who are young have a high susceptibility to gain weight and develop other metabolic disturbances during psychotropic treatment (46). In addition, some studies, albeit controversial, suggested that women have a greater vulnerability to psychotropic drug-induced weight gain than men (91, 107). In addition, drug naïve and/or first-episode psychotic patients are more prone to gain substantial weight following psychotropic treatment, compared to patients with a long treatment history (23, 108). Finally, patients who gained more than 5% of their initial weight during the first month of treatment are at higher risk to gain substantial weight during psychotropic treatment (109), underlining the importance of metabolic monitoring during treatment with psychotropic drugs.

Genetic factors

Genetic variability can contribute to inherited differences in drug effectiveness and tolerability. With the rapid emergence of technical innovations in genotyping tools (such as genome-wide association studies (GWAS)) and competitive genotyping costs, a growing interest to include pharmacogenetics in clinical settings has emerged in the last two decades. To date, some polymorphisms across multiple genes involved in pharmacokinetics and pharmacodynamics of psychotropic drugs have been identified. Although pharmacogenetic testing in psychiatry is not yet included in standard clinical practice, it seems likely that this tool will enable an improvement of psychotropic treatment optimization.

Pharmacokinetics and pharmacodynamic genes for drug response

Of note, as the present work did not focus on pharmacogenetics of drug response, this paragraph is only a short summary of the topic. Even if psychotropic drugs are effective for the treatment of many psychiatric disorders, therapeutic responses are unfortunately not satisfactory for many patients (110). Thus, patients differ substantially in their ability to absorb, distribute, metabolize and excrete drugs, in part due to genetic differences in pharmacokinetic genes, i.e. in enzymes responsible for drug metabolism (e.g. *CYP2D6*). Besides, even though pharmacodynamic genes are less represented for preventing drug response than to predict

adverse effects, some genetic variants in *DRD2* and *COMT* were linked with psychotropic drug responses (111-113).

Pharmacokinetics and pharmacodynamic genes for adverse effects

A better understanding of the variability in drug plasma concentration would be clinically valuable to prevent adverse effects linked with drug plasma levels. Some variants in pharmacokinetic genes such as *CYP2D6* were related to certain adverse effects, such as EPS and tardive dyskinesia (114). However, studies are inconclusive on whether metabolic changes induced by psychotropic drugs are dose- and/or plasma concentration-dependent (115), which may explain the lack of association between pharmacokinetic genes and metabolic side effects induced by psychotropic drugs. Although some studies reported associations between weight gain and dose for clozapine, olanzapine and quetiapine (116-120), most studies did not corroborate these associations (115, 119, 121-127). Clozapine plasma levels were found to be positively associated with insulin and hypertriglyceridemia, but not with weight gain (116, 128, 129). To date, the association between metabolic disorders and psychotropic drug plasma concentration is still insufficient to justify the utility of TDM in clinical practice to prevent metabolic side effects.

On the other hand, pharmacogenetics of psychotropic-induced metabolic diseases has been extensively studied through candidate gene approaches focused on pharmacodynamic targets. A recent review showed that the most replicated genetic variants associated with weight gain and metabolic syndrome induced by psychotropic drugs were *HTR2C* -759C/T, *LEP* -2548G/A, *MC4R* rs489693 and one genetic variant near *OGFRL1* (130). Additionally, other genes in receptors (e.g. D_2R and H_1R), in leptin-melanocortin pathways (e.g. *LEPR*, *NPY*), in the endocannabinoid system (*CNR1*) or in genes involved in fatty acid and cholesterol production (insulin-induced gene 2 (*INSIG2*)) showed an association with psychotropic-induced weight gain (62). Research conducted in our unit showed associations between other candidate genes coding for enzymes involved in energy balance, appetite regulation and glucose homeostasis

and psychotropic drug-induced weight gain (i.e. genetic variants in 11β-hydroxysteroid desydrogenase (*11βHSD1*)(131), CREB-regulated transcriptional coactivator 1 (*CRTC1*)(132) and phosphoenolpyruvate carboxykinase 1 (*PCK1*)(133)). Although mechanisms underlying psychotropic-induced dyslipidemia are only partially understood, recent studies suggested a role of the sterol regulatory element-binding protein (SREBP) pathway (48). Thus, olanzapine, clozapine and risperidone were shown to promote the up-regulation of *SREBP* leading to enhanced lipid and cholesterol synthesis in mice (95, 96). Many other genetic susceptibilities remain to be discovered to further understand the etiology of psychotropic-drug induced metabolic effects.

Notably, many studies considering combinations of multiple loci yielded significant findings, while the examination of single markers provided nominal or non significant results with small effect sizes (134, 135). This puts emphasis on the probable polygenic inheritance of psychotropic drug-induced metabolic abnormalities, and the need for future studies to give more consideration to gene interactions and combinations (136). Two recent GWAS meta-analyses were conducted to reveal associations between abnormal lipid levels and single nucleotide polymorphisms (SNPs) in the general population (137, 138). Considering that these genetic variants have shown minor effects on lipid phenotypes, an alternative method of testing individual SNP effect would be to construct a polygenic risk score (PRS), which allows a better integration of the global information of these numerous small effects (139). While several PRS were determined as significant predictors of obesity, diabetes and dyslipidemia in the general population (140-142), associations between PRS and dyslipidemia among the psychiatric population have never been established.

Furthermore, GWAS enabled identifying many SNPs associated with obesity located in or near genes whose role in obesity remains unclear. Part of this lack of understanding may be due to a focus on the genes in closest proximity to SNPs. However, new evidence suggests that SNPs may regulate genes that are located far away. For instance, a recent study demonstrated

that, in the human brain, obesity-associated SNPs in *FTO* were associated with the expression of *IRX3*, a gene located more than a half million base pairs downstream of the index SNP (143). Many other examples were described (144, 145). Thus, obesity-associated SNPs might act through long-range interactions and potentially through epigenetic mechanisms. The epigenome represents the pattern of chemical and structural modifications to DNA that are heritable but which do not involve changes in the DNA sequence. In particular, DNA methylation is a reversible and heritable attachment of a methyl group most commonly to the 5-carbon position of the cytosine residues within CpG dinucleotides of the mammalian genome (146). Epigenetic mechanisms, encompassing DNA methylation, have the potential to modify gene expression. In the last decade, some studies have determined methylation changes associated with psychotropic drugs, including atypical antipsychotics (73-75) and mood stabilizers (76-78). In addition, many studies reported SNPs associated with changes of DNA methlyation (i.e. methylome quantitative trait loci, meQTLs) in different tissues, such as in adipose tissue (147, 148) and blood (149-151). Besides, recent evidence has drawn attention to the involvement of epigenetic mechanisms in the pathogenesis of obesity (152, 153). However, whether psychotropic-drug induced metabolic abnormalities may result from epigenetic mechanisms has not yet been addressed.

Management of metabolic effects induced by psychotropic drugs

As argued previously, there is clear evidence that certain psychotropic drugs such as antipsychotics, mood stabilizers and certain antidepressants are involved in the incidence and/or pejoration of metabolic comorbidities. In addition, many studies emphasized that the early months of treatment are a critical period for potential metabolic deterioration (47, 154). Therefore, regular monitoring for metabolic parameters in patients receiving the above-mentioned 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 (i.e. antipsychotics, mood stabilizers and some antidepressants), including close

monitoring during the first three months of treatment (155, 156). In our department, a clinical monitoring guideline for patients starting such drugs was established in 2007 (157). This monitoring helps psychiatrists to identify patients who gained important weight early and to use preventive approaches, which has the potential to be more effective, acceptable, cost-efficient and beneficial. Some interventions, such as education for healthy lifestyle including nutritional counseling, may help patients with schizophrenia to reduce or attenuate psychotropic-induced weight gain (156, 158). Healthy behavioral education, instruction or intervention should always be used prior to considering switching to a less weight offending agent or adding comedication that reduces weight and/or reverses metabolic abnormalities (159-161). The decision to switch to another antipsychotic should consider the whole psychiatric and physical condition of the patient as well as the pharmacological profiles of the proposed and current drugs (162). Finally, certain medications such as metformin can be added to counteract metabolic adverse effects induced by psychotropic drugs, after a careful consideration of the add-on benefit (155, 156, 163).

The ultimate goal is to adopt a personalized medicine approach in order to prevent metabolic adverse effects induced by psychotropic drugs. Nowadays, a trial and error approach is commonly used by physicians to maximize the treatment efficacy and safety. Alternatively, a personalized approach based on personal, clinical and genetic factors sounds more efficient in terms of treatment- time- and cost-effectiveness. However, solid evidence regarding the usefulness of considering personal, environmental and pharmacogenetic testing in the prescription of psychotropic drugs is still lacking. The global aim of the present thesis was to improve the current understanding of psychotropic-induced metabolic side effects and to identify the possible clinical and genetic predictors of these adverse effects.

AIMS

The overall objective of the present thesis is to improve the current understanding of psychotropic-induced metabolic side effects and to identify the possible clinical and genetic predictors of these adverse effects, using different strategies.

Project I: To examine the influence of tagging SNPs of the melanin-concentrating hormone receptor 2 (*MCHR2*) on BMI during treatment with psychotropic drugs in three independent psychiatric samples.

Influence of MCHR2 and MCHR2-AS1 Genetic Polymorphisms on Body Mass Index in Psychiatric Patients and In Population-Based Subjects with Present or Past Atypical Depression

Manuscript published in PLOS ONE, 2015

Project II: To determine whether population-based genetic variants related to BMI are associated with cardiometabolic phenotypes in patients from two psychiatric samples taking psychotropic drugs.

Association of variants in SH2B1 and RABEP1 with worsening of low-density lipoprotein and glucose parameters in patients treated with psychotropic drugs

Manuscript published in Gene, 2017

Project III: To investigate whether polygenic risk score combining multiple risk-associated SNPs from two lipid meta-analyses are associated with dyslipidemia-related traits in patients receiving psychotropic drugs known to induce worsening of metabolic parameters.

Influence of polygenic risk scores on lipid levels and dyslipidemia in a psychiatric population receiving weight gain-inducing psychotropic drugs

Manuscript published in Pharmacogenetics and Genomics, 2017

Project IV: To study how plasma lipid changes during first month of treatment can predict mid- and long-term plasma lipid changes and new onset dyslipidemia (NOD) in patients taking psychotropic drugs.

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

Manuscript accepted in Journal of Clinical Lipidology, in press

			PROJECTS	I	II	III	IV
			Approaches	G E N E T I C S			CLINICS
				Gene candidate study	Hierarchical analysis	Polygenic risk score	Predictive analyses (ROC)
				Parameters under investigation			
	Phenotype	Variable		*MCHR2* gene	BMI-SNPs from GWAS	Lipid-SNPs from GWAS	Threshold of early lipid changes
OUTCOME	Obesity	BMI WC		✓	✓		
	Lipids	TC LDL HDL TG			✓	✓	✓
	Blood pressure	SBP DBP			✓		
	Glucose	GLC			✓		

METHODS

Full methods are described in each corresponding project. All results are based on three non-interventional clinical studies, described below:

Etude suivi des effets secondaires métaboliques (Study on metabolic follow-up)

According to international recommendations, a metabolic follow-up is ongoing since 2007 in the Department of Psychiatry at the Lausanne University Hospital, in which inpatients and outpatients are monitored when starting a pharmacological treatment known to have a potential risk to induce metabolic disturbances. These treatments include clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, lithium, valproate and/or mirtazapine. Several regular metabolic check-ups for metabolic parameters (weight, blood pressure, waist circumference) are recorded at baseline, and at one, two, three, six months and one year following the introduction of treatment. Blood samples are collected at baseline, and after one, three and twelve months in order to measure metabolic parameters (i.e. lipid profile, glucose) and drug plasma concentration. This cohort with metabolic-follow up constitutes the "PsyClin" study. A subset of patients within PsyClin signed an informed consent to participate in a pharmacogenetic study (PsyMetab). As of May 2017, a total of 1851 patients have been included in the routine metabolic follow-up (PsyClin), and among them, 1017 patients gave their written informed consent to be included in the pharmacogenetic study (PsyMetab).

Etude Ambulatoire (Ambulatory study)

This ongoing study started in 2010. Similarly to PsyMetab, this ongoing cross-sectional observational study follows outpatients treated with clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, lithium, valproate and/or mirtazapine for more than one year. Similar regular metabolic check-ups are recorded, once a year. As of May 2017, informed consents were received from 375 patients.

Etude poids Genève (Weight study Geneva)

A cross-sectional observational and retrospective study was performed between June 2006 and May 2008 in two out-patient psychiatric centers at Geneva University Hospital, enrolling patients between 18 and 65 years old receiving psychotropic drugs for more than three months. Current weight was measured, and initial weight was either self-reported or extracted from medical files. Blood samples were collected in order to measure lipid profile and drug concentration and to perform genetic analyses. 196 patients treated with clozapine (n=28), olanzapine (n=31), quetiapine (n=35), risperidone (n=42), lithium (n=35) and valproate (n=25) were included.

Of note, from January 2014, patients treated with first generation antipsychotics and tricyclic antidepressants were also included in the metabolic follow-up (i.e. in PsyMetab and in *Ambulatory study*). In addition, patients treated with newly commercialized molecules such as lurasidone were included since their commercialization. Further details of the three psychiatric samples are presented in a previously published paper (164). Noteworthy, since no baseline lipid trait data were recorded in the *Ambulatory study* and *Weight study Geneva*, analyses conducted to determine the influence of clinical and/or genetic factors on lipid level worsening were only led in PsyMetab.

RESULTS

Project I: Influence of MCHR2 and MCHR2-AS1 Genetic Polymorphisms on Body Mass Index in Psychiatric Patients and In Population-Based Subjects with Present or Past Atypical Depression

PLOS | ONE

RESEARCH ARTICLE

Influence of *MCHR2* and *MCHR2-AS1* Genetic Polymorphisms on Body Mass Index in Psychiatric Patients and In Population-Based Subjects with Present or Past Atypical Depression

Aurélie Delacrétaz[1], Martin Preisig[2], Frederik Vandenberghe[1], Nuria Saigi Morgui[1], Lina Quteineh[1], Eva Choong[1], Mehdi Gholam-Rezaee[2], Zoltan Kutalik[3,4,5], Pierre Magistretti[6,7], Jean-Michel Aubry[8], Armin von Gunten[9], Enrique Castelao[2], Peter Vollenweider[10], Gerard Waeber[10], Philippe Conus[11], Chin B. Eap[1,12]*

1 Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland, **2** Centre of Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland, **3** Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital, Lausanne, Switzerland, **4** Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland, **5** Swiss Institute of Bioinformatics, Lausanne, Switzerland, **6** Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland, **7** Laboratory of Neuroenergetics and Cellular Dynamics, Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, **8** Division of Psychiatric Specialties, University Hospital of Geneva, Geneva, Switzerland, **9** Service of Old Age Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland, **10** Department of Medicine, Lausanne University Hospital, Lausanne, Switzerland, **11** Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland, **12** School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland

* chin.eap@chuv.ch

CrossMark
click for updates

OPEN ACCESS

Citation: Delacrétaz A, Preisig M, Vandenberghe F, Saigi Morgui N, Quteineh L, Choong E, et al. (2015) Influence of *MCHR2* and *MCHR2-AS1* Genetic Polymorphisms on Body Mass Index in Psychiatric Patients and In Population-Based Subjects with Present or Past Atypical Depression. PLoS ONE 10(10): e0139155. doi:10.1371/journal.pone.0139155

Editor: Neil R. Smalheiser, University of Illinois-Chicago, UNITED STATES

Received: March 16, 2015

Accepted: September 8, 2015

Published: October 13, 2015

Copyright: © 2015 Delacrétaz et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This work has been funded in part by the Swiss National Research Foundation grants 320030-120686 and 324730-144064 (CBE and PC) and by the National Center of Competence in Research "SYNAPSY-The Synaptic Bases of Mental Diseases" financed by the Swiss National Science Foundation grant 51AU40_125759. The CoLaus|PsyCoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine

Abstract

Obesity development during psychotropic treatments represents a major health issue in psychiatry. Melanin-concentrating hormone receptor 2 (MCHR2) is a central receptor involved in energy homeostasis. *MCHR2* shares its promoter region with *MCHR2-AS1*, a long antisense non-coding RNA. The aim of this study was to determine whether tagging single nucleotide polymorphisms (tSNPs) of *MCHR2* and *MCHR2-AS1* are associated with the body mass index (BMI) in the psychiatric and in the general population. The influence of *MCHR2* and *MCHR2-AS1* tSNPs on BMI was firstly investigated in a discovery psychiatric sample ($n_1 = 474$). Positive results were tested for replication in two other psychiatric samples ($n_2 = 164$, $n_3 = 178$) and in two population-based samples (CoLaus, $n_4 = 5409$; GIANT, $n_5 = 113809$). In the discovery sample, TT carriers of rs7754794C>T had 1.08 kg/m^2 ($p = 0.04$) lower BMI as compared to C-allele carriers. This observation was replicated in an independent psychiatric sample (-2.18 kg/m^2; $p = 0.009$). The association of rs7754794C>T and BMI seemed stronger in subjects younger than 45 years (median of age). In the population-based sample, a moderate association was observed (-0.17 kg/m^2; $p = 0.02$) among

of Lausanne, and the Swiss National Science Foundation (grants 3200B0–105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468 and 33CS30-148401). ZK received support from the Leenaards Foundation and the Swiss National Science Foundation (31003A-143914). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: Drs. Waeber, Vollenweider, and Preisig received two unrestricted grants from GlaxoSmithKline to build the CoLaus and PsyCoLaus cohorts and complete the physical and psychiatric baseline investigations. There are no patents, products in development or marketed products to declare. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.

younger individuals (<45y). Interestingly, this association was totally driven by patients meeting lifetime criteria for atypical depression, i.e. major depressive episodes characterized by symptoms such as an increased appetite. Indeed, patients with atypical depression carrying rs7754794-TT had 1.17 kg/m^2 (p = 0.04) lower BMI values as compared to C-allele carriers, the effect being stronger in younger individuals (-2.50 kg/m^2; p = 0.03; interaction between rs7754794 and age: p-value = 0.08). This study provides new insights on the possible influence of *MCHR2* and/or *MCHR2-AS1* on obesity in psychiatric patients and on the pathophysiology of atypical depression.

Introduction

Compared to the general population, patients with chronic severe mental disorders have an estimated shorter life expectancy of 15 to 25 years due to the psychiatric disorder and/or physical comorbidities (i.e obesity or other metabolic disorders) but also in the use of psychotropic treatments[1]. Indeed, many antipsychotics, in particular atypical antipsychotics, and some mood stabilizers and antidepressants are associated with important weight gain[2]. The variability of weight gain observed in patients sharing similar clinical risk factors (i.e gender, age and psychotropic treatment)[3], together with the heritability of weight regulation observed in twin, adoption and family studies[4] support the key role of genetic factors in the development of obesity. Moreover, recent changes in Western lifestyle (ubiquitous access of industrial/palatable food and poor physical activity) strongly increase the influence of genetic risk factors towards the development of obesity. However, genome-wide association (GWAS) and candidate gene studies have only explained a small variance of the body mass index (BMI)[5]. Therefore, the identification of new genetic predictors for the development of obesity in psychiatric patients is not only of great interest for a better understanding of the mechanisms underlying excessive weight increase, but also for the future personalized prescription of psychotropic drugs.

The regulation of food intake, a major component in energy balance, is achieved in part by highly specialized hypothalamic neurons that are able to sense and integrate peripheral feeding cues. The exact mechanisms by which peripheral cues-related signals interact within the hypothalamus to modulate the response are only partially understood. However, in this highly complex system of regulation, some specific pathways have been characterized[6, 7]. The melanocortin pathway, in the arcuate nucleus of the hypothalamus, is a major axis through which peripheral peptides and hormones converge and act to modulate the energy balance. Recent studies have enlightened the involvement of the melanin-concentrating hormone receptor 2 (MCHR2) in the transduction of central orexigenic signals. More specifically, melanin-concentrating hormone (MCH), the agonist of MCHR2, has been shown to be a critical hypothalamic regulator involved in energy homeostasis in mammals[8, 9]. Mice lacking *MCH* gene have been observed to be lean, having decreased feeding behavior and increased energy expenditure[10]. Even though *MCHR2* is not expressed in rodents, a recent study showed that induction of *MCHR2* expression in mice protected against diet-induced obesity[11]. In humans, *MCH* was shown to be expressed in neurons of the lateral hypothalamus, an area that coincides with *MCH* receptors sites of expression[9]. Moreover, in a French general population, a linkage with childhood obesity was identified on chromosome 6q16.3-q24.2[12] and two single nucleotide polymorphisms (SNPs) within *MCHR2* were further associated with childhood obesity[13]. Of note, some atypical antipsychotics have been reported to affect

neuropeptide hormone levels involved in energy homeostasis[14–16]. Specifically, the expression of *MCH* as well as its receptors may be upregulated during antipsychotic treatments, which may enhance rewarding aspects of food[17]. Moreover, the first genome scan targeting obesity as a side effect of antipsychotics has observed an implication of the pro-melanin-concentrating hormone (*PMCH*), the precursor of *MCH*[18].

Interestingly, during the preparation of the present study, gene region analyses revealed that the *MCHR2* SNP associated with BMI in a Caucasian population-based sample (i.e *MCHR2/MCHR2-AS1* rs6925272)[13], lies not only in the promoter of *MCHR2* but also in the promoter of another gene transcribed in an antisense way, *MCHR2-AS1* (*MCHR2*-antisense RNA). *MCHR2-AS1* is a RNA gene affiliated to the long non-coding RNA (lncRNA) class. Although this class of genes is still poorly understood, recent studies have linked some lncRNAs with the development of different diseases[19–21].

Because of the high prevalence of obesity, of metabolic abnormalities and of mortality rate within the psychiatric population, the probable involvement of MCHR2 in the phenotype of obesity and the absence of studies examining the possible influence of genetic polymorphisms of *MCHR2* on BMI in psychiatric patients, we examined associations between tagging SNPs of *MCHR2* and of *MCHR2-AS1* with BMI in three independent psychiatric samples treated with psychotropic drugs that were likely to induce weight (i.e clozapine, olanzapine, quetiapine, risperidone, lithium, valproate, mirtazapine, aripiprazole and/or amisulpride). In order to further investigate whether these above-mentioned associations are valid in the general population as well or are only specific to psychiatry, we then attempted to replicate the results in two population-based samples, one of which had subjects with psychiatric evaluations.

Results

Demographic and clinical characteristics of three psychiatric Caucasian populations are presented in S1 Table. In the discovery sample, the prevalence of obesity at the end of the follow-up was lower (17%) than in both replication samples (39% and 28%), which could in part be explained by the longer treatment duration in the latter samples. The median age of patients in the discovery sample was higher (50 years) than in both replication samples (43 and 42 years), the former sample containing geriatric patients, which is not the case for both replication samples. In each of these three independent psychiatric samples, almost half of patients gained more than 5% of initial weight during the current psychotropic treatment (41%, 56% and 51%), with a median duration of treatment of 6, 27 and 35 months, respectively.

MCHR2 and *MCHR2-AS1* tagging SNPs are presented in S2 Table. rs9403322 and rs4559096 deviated from Hardy-Weinberg equilibrium in the discovery sample (p-values$\leq$0.05). These two SNPs were therefore not further analyzed. Therefore, a total of twelve SNPs were analyzed in this study. Minor allele frequencies (MAF) in our combined sample were comparable to those reported in HapMap (Caucasians).

Associations between *MCHR2* and *MCHR2-AS1* Tagging Polymorphisms and BMI in the Psychiatric Sample

In the discovery sample, three tagging SNPs of *MCHR2* (i.e. *MCHR2* rs4840109, *MCHR2* rs2001456 and *MCHR2* rs7754794) were significantly associated with BMI, with carriers of the G allele (for rs4840109), G allele (for rs2001456) and TT genotype (for rs7754794) having lower BMI values as compared to others, respectively (more details in S3 Table). Multiple comparison tests in the discovery sample using the false discovery rate method correcting for 12 independent tests revealed p-corrected-values of 0.04 for each of these three SNPs. The remaining *MCHR2* and *MCHR2-AS1* tagging SNPs were not associated with BMI. *MCHR2*

rs4840109, *MCHR2* rs2001456 and *MCHR2* rs7754794 were tested for replication in replication samples 1 and 2. P-values of replication analyses were corrected for 3 independent tests using false discovery rate correction. Both rs4840109 and rs2001456 were not replicated and were therefore not considered for further analyses. rs7754794 was significantly associated with BMI in the replication sample 1, for which carriers of TT genotype had 2.18 kg/m^2 lower BMI as compared to C-allele carriers ($p_{corrected}$ = 0.009). A significant association was also observed within the combined sample, with TT carriers having 0.84 kg/m^2 lower BMI as compared to others ($p_{corrected}$ = 0.02; Table 1). Fig 1 presents the evolution of BMI during psychotropic treatment in patients of the combined sample according to rs7754794 genotype. In carriers with the TT genotype, the BMI remained stable over time, whereas the BMI of CC or CT carriers increased along the treatment duration. The difference across genotypes reached the threshold of significance after six months of treatment.

Associations between *MCHR2* rs7754794C>T and BMI in Age-Stratified Subgroups of the Combined Sample

The influence of rs7754794 polymorphism on BMI was assessed in age-stratified psychiatric subgroups of the combined sample (interaction between rs7754794 and age: p-value = 0.08). Only patients younger than 45 years (the median of age in the psychiatric sample) appeared to be concerned with this genetic effect on BMI, with carriers of TT genotype having 1.59 kg/m^2 lower BMI as compared to others (p = 0.003) (Table 2). Of note, in the discovery sample, rs7754794-TT carriers younger than 45 years had significantly lower waist circumference (WC) as compared to others (-4.34 cm; p = 0.02; S4 Table).

MCHR2 and *MCHR2-AS1* Tagging SNPs Haplotype Analysis

Four haplotype blocks were observed (S1 Fig). Combinations formed from the first three haplotype blocks did not show any significant association with BMI in the combined psychiatric sample (data not shown). Regarding the block 4 (within *MCHR2-AS1*), by combining SNPs rs11155243, rs9484646 and rs12214805, four different combinations were formed. Wild-type carriers for these three SNPs (i.e. GGC, frequency of this combination: 0.5) had 2.02 lower unit BMI as compared to others (p = 0.04). Age-stratified analyses could not be conducted due to an insufficient number of observations.

Replication of *MCHR2* rs7754794C>T Association with BMI in Population-Based Samples

The association of *MCHR2* rs7754794 with BMI was further investigated for replication in two population-based samples (CoLaus and GIANT) using rs7749425, a proxy of rs7754794 (r^2 = 0.97). The rs7754794 association with BMI was not replicated in these samples (Table 3). However, in CoLaus, age-stratified analyses revealed that individuals younger than 45 years and carrying rs7754794-TT had a significantly lower BMI and WC than others. Of note, in order to avoid bias, the same threshold (i.e. 45 years old) was used both in psychiatric and in population-based samples. Age-stratified data were not available in GIANT.

In PsyCoLaus, the subset of CoLaus with psychiatric evaluations, stratifications according to depression subtypes revealed some differences between atypical and non-atypical subgroups. Women were more prevalent among those with atypical depression (74%) than among the other depressives (63%; S5 Table). As expected, in the former subgroup, the proportion of subjects with increased appetite, which is one of the 5 diagnostic criteria for this depression subtype, was much higher (41%) than in the latter subgroup (5%). Moreover, subjects with

Table 1. Association of *MCHR2* rs7754794C>T with BMI in three independent Caucasian psychiatric samples.

MCHR2 rs7754794C>T	Discovery sample n = 441			Replication sample 1 n = 153			Replication sample 2 n = 142			Combined sample n = 736		
	β (95% CI) (kg/m^2)	p-value	Ex. var (%)	β (95% CI) (kg/m^2)	p-value	Ex. var (%)	β (95% CI) (kg/m^2)	p-value	Ex. var (%)	β (95% CI) (kg/m^2)	p-value	Ex. var (%)
CC/CT	ref			ref			ref			ref		
TT	-1.08 (-2.11–(-) 0.35)	**0.04**	0.46	-2.18 (-3.87–(-) 1.01)	**0.009**	2.78	0.79 (-0.81–3.01)	0.42		-0.84 (-1.52–(-) 0.32)	**0.02**	0.28

Results were obtained by fitting Generalized Additive Mixed Models for patients, controlling for age, sex, smoking status, current psychotropic drug and comedications possibly causing weight-gain. β: estimate. p-value: corrected for multiple tests.Ex. var (%): explained variance by the polymorphism, only calculated for significant results. ref: reference.

doi:10.1371/journal.pone.0139155.t001

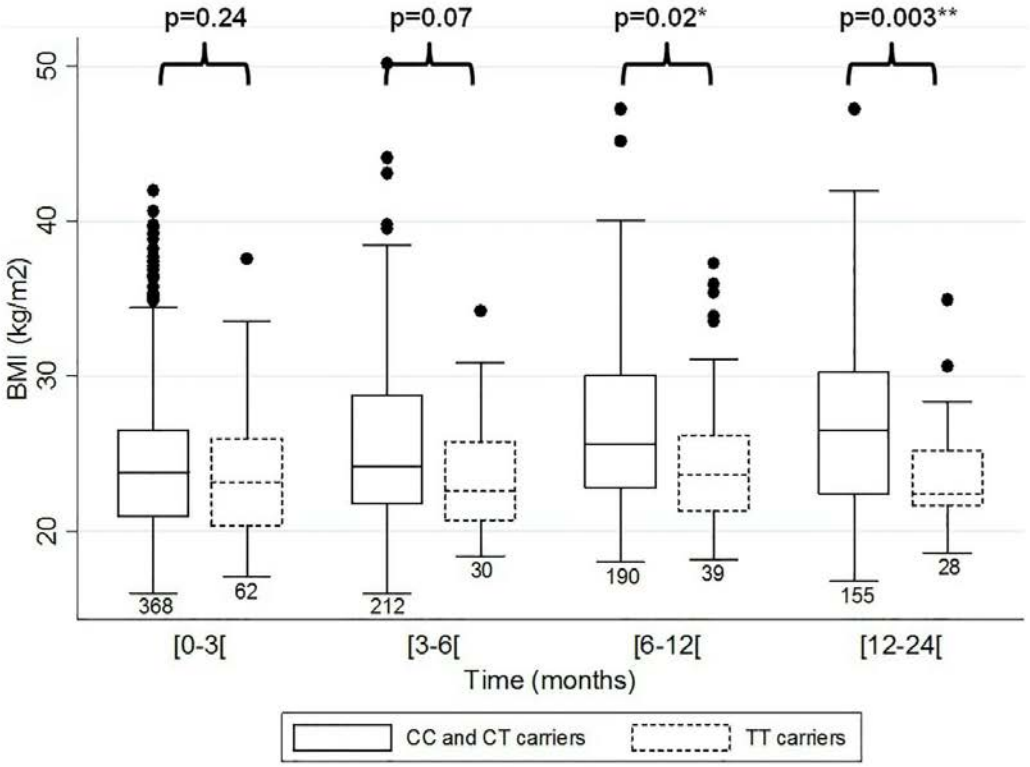


Fig 1. BMI evolution during psychotropic treatment according to protective or risk *MCHR2* rs7754794C>T genotype. Caucasian patients carrying protective (TT) or risk (CC or CT) rs7754794C>T variant. Median, interquartiles and number of observations for each box are indicated.

doi:10.1371/journal.pone.0139155.g001

Table 2. Age-stratified analysis for *MCHR2* rs7754794C>T association with BMI.

MCHR2 rs7754794C>T	Combined sample			
	n	β (95% CI) (kg/m^2)	p-value	Ex. var (%)
Age≤45	374			
CC/CT		ref		
TT		-1.59 (-2.65–(-)0.46)	**0.003**	1.11
Age>45	366			
CC/CT		ref		
TT		-0.23 (-1.09–0.75)	0.35	

Results were obtained by fitting Generalized Additive Mixed Models for patients, controlling for age (whenever appropriate), sex (whenever appropriate), smoking status, current psychotropic drug and comedications possibly causing weight-gain. β: estimate. Ex. var (%): explained variance by the polymorphism, only calculated for significant results. ref: reference.

doi:10.1371/journal.pone.0139155.t002

atypical depression were more frequently in a current episode at the moment of the evaluation than the other subjects with a major depressive disorder (28% versus 13%), which is likely to explain the higher proportion of antidepressant use (23% versus 13%, respectively). In the PsyCoLaus sample, there was no association between rs7754794 and BMI (Table 4). However, there was an interaction (p = 0.04) between the rs7754794-TT genotype and a lifetime major depressive episode with DSM-IV atypical depression regarding the BMI. Indeed, among subjects with atypical depression features, those carrying rs7754794-TT had a significantly lower BMI (-1.17 kg/m^2) as compared to C-allele carriers (p = 0.04), whereas the BMI of individuals with no history of an atypical depression was not influenced by this genetic polymorphism. Age-stratified analyses revealed that this association was also observed in individuals younger than 45 years with atypical depression (-2.50 kg/m^2; p = 0.03). Of note, no significant association was found between rs7754794 and BMI in subjects without lifetime major depressive episode (data not shown). Finally, no difference of rs7754794 frequency was observed between subgroups of diagnosis of PsyCoLaus (S6 Table). Subgroups of diagnosis were not available in the combined sample.

Discussion

The present results suggest a contribution of *MCHR2* and/or *MCHR2-AS1* in the regulation of human body weight, which is consistent with the proposed role of MCH and MCHR2 pathway in the literature[9] and with the only other genetic study on *MCHR2* which reported an association of *MCHR2* genetic polymorphism with obesity in the general population[13]. To our knowledge, this is the first study performed in psychiatric subjects, i.e. a population with a high prevalence of obesity or overweight phenotypes. Specifically, this study showed a significant association of *MCHR2/MCHR2-AS1* genetic polymorphisms with BMI in the psychiatric population as well as in a psychiatric subgroup of a population-based sample. Moreover, a haplotype combination of three *MCHR2-AS1* tagging SNPs was also significantly associated with BMI in the psychiatric population.

Interestingly, the association of *MCHR2* rs7754794 with BMI was only observed in patients younger than 45 years old. Because a first treatment exposure has been previously described as an important risk factor for important weight gain[22], it could be hypothesized that age would be a proxy of first-treatment exposure in younger patients. However, most of the young patients had already received previous psychiatric drug treatment before inclusion and there

Table 3. Replication analyses in Caucasian population-based samples.

rs7749425C>T (proxy of rs7754794C>T)	ALL SUBJECTS						≤45 years subjects					
	BMI			WC			BMI			WC		
	n	β (kg/m^2)	p-value	n	β (cm)	p-value	n	β (kg/m^2)	p-value	n	β (cm)	p-value
GIANT	113809	ref										
		0.0032	0.47		NA			NA			NA	
CoLaus	5409	ref		5409	ref		1463	ref		1463	ref	
		-0.0492	0.22		-0.0381	0.34		-0.17	**0.02**		-0.15	**0.04**

Results were obtained by using robust regression, adjusted for age and sex. BMI: body mass index; WC: waist circumference. ref: reference (i.e carriers of the C allele at rs7749425 locus). β: estimate. NA: non applicable.

doi:10.1371/journal.pone.0139155.t003

was no association between *MCHR2* rs7754794 and BMI in a subgroup of the discovery sample with a newly diagnosed psychiatric disorder (see Supporting information for further details). Therefore, *MCHR2* rs7754794 seems to be associated with BMI in younger patients independently of the psychotropic treatment exposure status. *MCHR2* has been described as one of the components acting in the hypothalamic regulation of food intake[23, 24], a system of regulation involved early in the development of obesity. Additionally, age has been found to affect appetite regulation with elderly individuals having a less efficient hypothalamic regulation of food intake[25, 26]. These elements may suggest that genetic risk factors involved in the regulation of food intake in young individuals may be more important than in the elderly. Interestingly, replication analyses in the population-based sample (CoLaus) was in accordance with this hypothesis, where the association between *MCHR2* genetic polymorphism and BMI was only significant in younger individuals. Moreover, the only reported study that associated *MCHR2* with obesity also observed an age-dependent genetic susceptibility in obesity, with the younger being more concerned[13]. The association between *MCHR2/MCHR2-AS1* with BMI found in the discovery sample was confirmed in replication sample 1 but not in replication

Table 4. Replication analyses in PsyCoLaus, the subset of CoLaus with psychiatric evaluations.

rs7749425C>T (proxy of rs7754794C>T)	ALL SUBJECTS						≤45 years subjects					
	BMI			WC			BMI			WC		
	n	β (kg/m^2)	p-value	n	β (cm)	p-value	n	β (kg/m^2)	p-value	n	β (cm)	p-value
PsyCoLaus:	3938	ref		3938	ref		907	ref		907	ref	
All subjects		-0.15	0.42		-0.58	0.26		-0.28	0.38		-1.33	0.13
PsyCoLaus:	1580	ref		1580	ref		404	ref		404	ref	
Depression		-0.21	0.46		-0.52	0.5		-0.35	0.45		-1.73	0.16
PsyCoLaus:	1127	ref		1127	ref		278	ref		278	ref	
Non-atypical depression		0.18	0.56		0.17	0.85		0.37	0.44		-0.36	0.79
PsyCoLaus:	453	ref		453	ref		126	ref		126	ref	
Atypical depression		-1.17	**0.04***			0.12		-2.5	**0.03***		-5.59	**0.05**

Results were obtained by using robust regression, adjusted for age and sex. BMI: body mass index; WC: waist circumference. ref: reference (i.e carriers of the C allele at rs7749425 locus). β: estimate.

*Interaction between atypical depression and rs7749425 significant (p = 0.04).

doi:10.1371/journal.pone.0139155.t004

sample 2. In the latter sample, the positive association between rs7754794 and BMI in patients older than 45 years may have hampered replication when considering the whole replication sample 2 (see Supporting information for further details). Additionally, the longer treatment duration in replication sample 2 (median of 35 months) as compared to the two other samples (6 and 27 months, respectively) may have also contributed to the observed differences.

Interestingly, within the PsyColaus replication sample, MDD (major depressive disorder) subtypes stratification revealed that individuals with present or past depression with atypical features were concerned with the protective effect of rs7754794 on BMI, whereas other individuals (i.e those without depression or those with depression with non-atypical features) were not. Atypical depression has been characterized by an improved mood in response to positive events, featuring some symptoms such as an increased appetite, weight gain and hypersomnia [27]. In PsyCoLaus, the atypical subtype of MDD has been described as a strong predictor of obesity[28]. Of note, several common biological states linking obesity and depression have been determined, such as the dysregulation of the hypothalamic-pituitary-adrenocortical axis [29, 30]. Moreover, the *MCH* pathway has been involved in both body weight and mood status regulation in rats[31]. In the present study, no difference of rs7754794 frequency was observed in the atypical depression subgroup of PsyCoLaus, as compared to others (data not shown), suggesting that *MCHR2/MCHR2-AS1* variant is not a risk factor for atypical depression but rather for BMI increase during atypical depression. BMI increase in patients with atypical depression may result from several factors, including illness symptoms, such as an increased appetite and/or a sleeping dysregulation. Interestingly, *MCH* has been associated with the regulation of both atypical depression features in humans[32, 33]. Exploratory association analyses of *MCHR2* rs7754794 with appetite conducted in the discovery sample and in the atypical depression subgroup revealed no significant association (see Supporting information for further details). It would be interesting to investigate in the future whether this genetic variant is associated with sleep regulation. Of note, *MCHR2* rs7754794 effect on BMI was higher in the psychiatric population than in replication population-based samples. In addition, positive results found in the general population appear to be totally driven by the subgroup of subjects with present or past atypical depression. It can however not be excluded that *MCHR2* rs7754794 does contribute to BMI regulation in other populations, including non psychiatric individuals as well.

Interestingly, *MCHR2* rs7754794 is not only a tagging SNP of *MCHR2*, but is also a proxy of rs6925272 ($r^2 = 0.97$), a *MCHR2-AS1* tagging SNP lying in the promoter region of both *MCHR2* and *MCHR2-AS1*. Therefore, our results could be directly linked with a differential *MCHR2* and/or *MCHR2-AS1* genotype-dependent expression. Analyses of *MCHR2* and *MCHR2-AS1* expression have been conducted in peripheral blood mononuclear cells in a subset of the discovery sample. Unfortunately, these two genes were not expressed in these cells (data not shown). Even when focusing on patients receiving olanzapine, a medication having been described as a potent inducer of MCH receptor[17], no expression of these two genes could be detected in peripheral cells (data not shown). Further expression analyses of *MCHR2* and *MCHR2-AS1* within their functional tissue are of particular interest and will help to understand their implication in the development of obesity. Regarding the possible biological function of long antisense non-coding genes, a recent study observed an epigenetic-conducted transcription of a gene (i.e *APOA1*; apolipoprotein A1) by a lncRNA in its antisense direction (*APOA1-AS1*)[34]. However, further studies are needed to better characterize the role of long noncoding antisense RNAs in the pathophysiology of obesity.

Several limitations of this study need to be acknowledged. Firstly, this study was restricted to Caucasian patients and results cannot be extrapolated to other ethnicities. Secondly, we could not link any *MCHR2* and/or *MCHR2-AS1* tagging-variants with their expression to

functionally validate our hypotheses. Thirdly, we were not able to determine whether the polymorphism associated with BMI lies in *MCHR2*, *MCHR2-AS1* or in the promoter region of both genes. On the other hand, the fact that the results were replicated in one independent sample and in a psychiatric subgroup of a population-based sample, the latter used as a proof of concept of the polymorphism effect, strengthens the validity of our data.

In conclusion, this is the first genetic study linking *MCHR2* and/or *MCHR2-AS1* tagging polymorphisms and BMI in psychiatric patients under psychotropic treatments. The present results are in agreement and expand those from the lone study preformed until now, showing a significant association between *MCHR2* and BMI in the general population[13]. Moreover, the significant interaction found between *MCHR2/MCHR2-AS1* and BMI in population-based subjects with present and/or previous history of atypical depression but not non-atypical depression provides new clues to the pathophysiology of atypical depression.

Materials and Methods

Psychiatric Samples

Discovery sample (Lausanne follow-up prospective psychiatric study). Since 2007, a prospective cohort study is ongoing in the Psychiatric University Hospital of Lausanne including 474 Caucasian patients with newly prescribed psychotropic drugs (see Supporting Information). Clinical variables and body weight were prospectively recorded at several time points during the first 12 months of treatment, according to published recommended monitoring guidelines (i.e before starting the psychotropic treatment and at months 1,2,3,6 and 12)[35].

Replication sample 1 (Geneva retrospective psychiatric study). From 2006 to 2008, a study was conducted in out-patient psychiatric centers of Geneva University Hospital. 163 Caucasian patients treated for more than 3 months with psychotropic drugs were included (see Supporting Information).

Replication sample 2 Lausanne retrospective study). From 2010 to 2011, a study was conducted in two out-patient psychiatric centers of Lausanne (Lausanne University Hospital and a private psychiatric center). 178 Caucasian patients treated with psychotropic drugs were recruited (see Supporting Information).

In the three samples, demographic data, history of treatment and comedications were obtained from medical files. At inclusion, body weight and height were measured with participants standing without shoes in light clothes. Body weight was measured in kilograms to the nearest kg. Height was measured to the nearest cm using a height gauge. Body mass index (BMI) was defined as weight/height^2 (kg/m^2). BMI values between 25–30 kg/m^2 and equal or higher than 30 kg/m^2 were used to define overweight and obese patients, respectively. Psychiatric diagnoses were established by physicians according to the ICD-10 classification. Most patients had already received other psychotropic treatments before the current treatment. For patients in replication samples 1 and 2, clinical variables, body weight and height were measured during the interview, while their previous weight data (i.e. weight before the beginning of the current treatment and/or weight at different times during the current treatment) were either collected from medical files or self-reported. Full description of these samples was published elsewhere[36]. Written informed consents were obtained from patients or their legal representatives for the three psychiatric cohorts and these studies were approved by the Ethics Committee of Geneva and Lausanne University Hospitals.

Population-Based Samples

Results were replicated in two population-based samples: CoLaus/PsyCoLaus, n = 5 409 [37, 38] and Genetic Investigation of ANtropometric Traits (GIANT, n = 123 865)[5].

CoLaus/PsyCoLaus. Participants aged from 35 to 75 years were recruited between June 2003 and May 2006, as previously described for CoLaus[37]. The assessment included cardiovascular risk factors such as body mass index (BMI), fat mass, waist circumference (WC), blood pressure, blood glucose, triglycerides and high density lipoprotein cholesterol. In addition, all Caucasians (91% of the sample) underwent a genetic exam (GWAS; n = 5409). All participants of CoLaus in the age range of 35 to 66 years were also asked to participate in a psychiatric evaluation (PsyCoLaus) based essentially on a semi-structured diagnostic interview [38]. In PsyCoLaus, we could subtype depressive individuals by atypical features according to the DSM-IV. Combined genetic and psychiatric data were available for 3938 participants. Genotyping for the CoLaus/PsyCoLaus subjects was performed using the Affymetrix GeneChipR Human Mapping 500K array set. Demographic and clinical characteristics of PsyCoLaus are shown in results.

Genetic Investigation of ANtropometric Traits (GIANT) consortium. The GIANT consortium performed a meta-analysis of GWAS data with a discovery set of 123 865 individuals of European ancestry from 46 studies for height [39], BMI [5] and waist-to hip ratio [40].

Genotyping and Candidate Gene Polymorphisms

rs6925272 was first selected based on a previous study[13] and genotyped using Taqman allelic discrimination assay (ABI PRISM 7000 Sequence Detection System; Applied Biosystems, Rotkreuz, Switzerland). Tagging SNPs within *MCHR2* and *MCHR2-AS1* where then selected using HapMap Genome Browser (release #28, NCBI build 36, dbSNP b126). Ten tagging polymorphisms within *MCHR2* and twelve within *MHCR2-AS1* were obtained by limiting the search to SNPs with a minor allele frequency >5% in the Caucasian population and r^2 cutoff of 0.8. *MCHR2* tagging SNPs were customized and added to the Illumina 200K cardiometabochip [41], whereas four among twelve *MCHR2-AS1* tagging SNPs were added to the cardiometabochip. Due to technical issues, proxies of SNPs were chosen in some cases (S7 Table). A good concordance was observed between genotypes obtained using Taqman and those obtained in the Cardiometabochip.

Statistical Analysis

Associations between tagging SNPs of *MCHR2* and of *MCHR2-AS1* and BMI were first tested in the discovery sample. Only SNPs significantly associated with BMI were tested for replication in the two replication psychiatric samples and the population based samples. For the assessment of association between BMI and tagging SNPs in psychiatric samples, a generalized additive mixed model (GAMM) was fitted, adjusting for age, gender, smoking status, current psychotropic drug and comedications potentially inducing weight gain (S8 Table), allowing a smooth trend for the response in time based on multiple observations for each patient. GAMMs were fitted using the mgcv package of R, in which parameter uncertainties (confidence intervals and p-values) were computed using 1000 bootstrap replicates with replacement, performed on patient level. Replication analyses in population-based samples were conducted using robust regression adjusted for age and sex. P-values of these two-sided models ≤ 0.05 were considered as statistically significant. All the analyses were performed using Stata 12 (StataCorp, College Station TX, USA) and R version 2.13.0 software. Haploview 4.2 [42] was used to define haplotype blocks and linkage disequilibrium (LD) between different *MCHR2* or *MCHR2-AS1* SNPs (D' and r^2). The haplo.stat package of R was used for haplotype analysis. P-values were defined using asymptotic chi-squared tests of haplo scores.

Supporting Information

S1 Fig. *MCHR2* and *MCHR2-AS1* SNPs haplotype blocks.
(DOCX)

S1 Table. Characteristics of psychiatric Caucasian samples: discovery, replication and combined samples.
(DOCX)

S2 Table. Genotype frequencies of *MCHR2* and *MCHR2-AS1* SNPs in three Caucasian psychiatric samples.
(DOCX)

S3 Table. Associations of *MCHR2* and *MCHR2-AS1* tagging SNPs with BMI in the Caucasian discovery psychiatric sample.
(DOCX)

S4 Table. *MCHR2* rs7754794C>T tagging SNP association with waist circumference in the discovery sample*.
(DOCX)

S5 Table. Characteristics of PsyCoLaus sample.
(DOCX)

S6 Table. Genotype frequencies of *MCHR2* rs7749425C>T according to subgroups of diagnosis in PsyCoLaus sample.
(DOCX)

S7 Table. *MCHR2* and *MCHR2-AS1* tagging SNPs referenced in HapMap.
(DOCX)

S8 Table. Comedications considered as weight-inducers in statistical analyses.
(DOCX)

Acknowledgments

The authors thank Dr. S. Crettol, C. Brogli, V. Hodel (logistical assistance), E. Retamales (bibliographical help), A. C. Aubert, M. Brocard, N. Cochard, M. Delessert, A. Vuilloud, M. Brawand, K. Powell Golay, S. Jaquet, M. Jonzier (sample analysis). We thank the GIANT consortium for access to their BMI association result in 123 807 individuals. CardioMetabochip genotyping was performed at the iGE3 genomics platform of the University of Geneva (http://www.ige3.unige.ch/genomics-platform.php).

Author Contributions

Conceived and designed the experiments: CBE. Performed the experiments: AD FV NSM LQ. Analyzed the data: AD ZK EC. Contributed reagents/materials/analysis tools: AD MP FV NSM LQ EC MGR ZK PM JMA AVG EC PV GW PC CBE. Wrote the paper: AD MP MGR CBE.

References

1. Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M, et al. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. The Journal of clinical psychiatry. 2004; 65 Suppl 7:4–18; quiz 9–20. PMID: 15151456.

2. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013; 382 (9896):951–62. doi: 10.1016/S0140-6736(13)60733-3 PMID: 23810019.
3. Malhotra AK, Correll CU, Chowdhury NI, Muller DJ, Gregersen PK, Lee AT, et al. Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug-induced weight gain. Archives of general psychiatry. 2012; 69(9):904–12. doi: 10.1001/archgenpsychiatry.2012.191 PMID: 22566560; PubMed Central PMCID: PMC4166499.
4. Comuzzie AG, Allison DB. The search for human obesity genes. Science. 1998; 280(5368):1374–7. PMID: 9603720.
5. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nature genetics. 2010; 42 (11):937–48. doi: 10.1038/ng.686 PMID: 20935630; PubMed Central PMCID: PMC3014648.
6. Abbott CR, Kennedy AR, Wren AM, Rossi M, Murphy KG, Seal LJ, et al. Identification of hypothalamic nuclei involved in the orexigenic effect of melanin-concentrating hormone. Endocrinology. 2003; 144 (9):3943–9. doi: 10.1210/en.2003-0149 PMID: 12933668.
7. Gao Q, Horvath TL. Neurobiology of feeding and energy expenditure. Annual review of neuroscience. 2007; 30:367–98. doi: 10.1146/annurev.neuro.30.051606.094324 PMID: 17506645.
8. Kishi T, Elmquist JK. Body weight is regulated by the brain: a link between feeding and emotion. Molecular psychiatry. 2005; 10(2):132–46. doi: 10.1038/sj.mp.4001638 PMID: 15630408.
9. Pissios P, Bradley RL, Maratos-Flier E. Expanding the scales: The multiple roles of MCH in regulating energy balance and other biological functions. Endocrine reviews. 2006; 27(6):606–20. Epub 2006/06/ 22. doi: 10.1210/er.2006-0021 PMID: 16788162.
10. Shimada M, Tritos NA, Lowell BB, Flier JS, Maratos-Flier E. Mice lacking melanin-concentrating hormone are hypophagic and lean. Nature. 1998; 396(6712):670–4. doi: 10.1038/25341 PMID: 9872314
11. Chee MJ, Pissios P, Prasad D, Maratos-Flier E. Expression of melanin-concentrating hormone receptor 2 protects against diet-induced obesity in male mice. Endocrinology. 2013. Epub 2013/10/31. doi: 10. 1210/en.2013-1738 PMID: 24169555.
12. Meyre D, Lecoeur C, Delplanque J, Francke S, Vatin V, Durand E, et al. A genome-wide scan for childhood obesity-associated traits in French families shows significant linkage on chromosome 6q22.31-q23.2. Diabetes. 2004; 53(3):803–11. PMID: 14988267.
13. Ghoussaini M, Vatin V, Lecoeur C, Abkevich V, Younus A, Samson C, et al. Genetic study of the melanin-concentrating hormone receptor 2 in childhood and adulthood severe obesity. The Journal of clinical endocrinology and metabolism. 2007; 92(11):4403–9. doi: 10.1210/jc.2006-2316 PMID: 17698913.
14. Perez-Iglesias R, Vazquez-Barquero JL, Amado JA, Berja A, Garcia-Unzueta MT, Pelayo-Teran JM, et al. Effect of antipsychotics on peptides involved in energy balance in drug-naive psychotic patients after 1 year of treatment. Journal of clinical psychopharmacology. 2008; 28(3):289–95.
15. Sentissi O, Epelbaum J, Olie JP, Poirier MF. Leptin and ghrelin levels in patients with schizophrenia during different antipsychotics treatment: a review. Schizophrenia bulletin. 2008; 34(6):1189–99. doi: 10.1093/schbul/sbm141 PMID: 18165262; PubMed Central PMCID: PMC2632509.
16. Esen-Danaci A, Sarandol A, Taneli F, Yurtsever F, Ozlen N. Effects of second generation antipsychotics on leptin and ghrelin. Progress in neuro-psychopharmacology & biological psychiatry. 2008; 32 (6):1434–8. doi: 10.1016/j.pnpbp.2008.03.015 PMID: 18579280.
17. Guesdon B, Denis RG, Richard D. Additive effects of olanzapine and melanin-concentrating hormone agonism on energy balance. Behavioural brain research. 2010; 207(1):14–20. doi: 10.1016/j.bbr.2009. 09.032 PMID: 19788900.
18. Chagnon YC, Merette C, Bouchard RH, Emond C, Roy MA, Maziade M. A genome wide linkage study of obesity as secondary effect of antipsychotics in multigenerational families of eastern Quebec affected by psychoses. Molecular psychiatry. 2004; 9(12):1067–74. doi: 10.1038/sj.mp.4001537 PMID: 15224101.
19. Congrains A, Kamide K, Ohishi M, Rakugi H. ANRIL: Molecular Mechanisms and Implications in Human Health. International journal of molecular sciences. 2013; 14(1):1278–92. doi: 10.3390/ ijms14011278 PMID: 23306151; PubMed Central PMCID: PMC3565320.
20. Congrains A, Kamide K, Oguro R, Yasuda O, Miyata K, Yamamoto E, et al. Genetic variants at the 9p21 locus contribute to atherosclerosis through modulation of ANRIL and CDKN2A/B. Atherosclerosis. 2012; 220(2):449–55. doi: 10.1016/j.atherosclerosis.2011.11.017 PMID: 22178423.
21. Pasic I, Shlien A, Durbin AD, Stavropoulos DJ, Baskin B, Ray PN, et al. Recurrent focal copy-number changes and loss of heterozygosity implicate two noncoding RNAs and one tumor suppressor gene at chromosome 3q13.31 in osteosarcoma. Cancer research. 2010; 70(1):160–71. Epub 2010/01/06. doi: 10.1158/0008-5472.CAN-09-1902 PMID: 20048075.

22. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nature reviews Endocrinology. 2012; 8(2):114–26. doi: 10.1038/nrendo.2011.156 PMID: 22009159.

23. Rodriguez M, Beauverger P, Naime I, Rique H, Ouvry C, Souchaud S, et al. Cloning and molecular characterization of the novel human melanin-concentrating hormone receptor MCH2. Molecular pharmacology. 2001; 60(4):632–9. PMID: 11562423.

24. Sailer AW, Sano H, Zeng Z, McDonald TP, Pan J, Pong SS, et al. Identification and characterization of a second melanin-concentrating hormone receptor, MCH-2R. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98(13):7564–9. doi: 10.1073/pnas.121170598 PMID: 11404457; PubMed Central PMCID: PMC34708.

25. MacIntosh CG, Andrews JM, Jones KL, Wishart JM, Morris HA, Jansen JB, et al. Effects of age on concentrations of plasma cholecystokinin, glucagon-like peptide 1, and peptide YY and their relation to appetite and pyloric motility. The American journal of clinical nutrition. 1999; 69(5):999–1006. PMID: 10232642.

26. Donini LM, Savina C, Cannella C. Eating habits and appetite control in the elderly: the anorexia of aging. International psychogeriatrics / IPA. 2003; 15(1):73–87. PMID: 12834202.

27. Lamers F, de Jonge P, Nolen WA, Smit JH, Zitman FG, Beekman AT, et al. Identifying depressive subtypes in a large cohort study: results from the Netherlands Study of Depression and Anxiety (NESDA). The Journal of clinical psychiatry. 2010; 71(12):1582–9. doi: 10.4088/JCP.09m05398blu PMID: 20673552.

28. Lasserre AM, Glaus J, Vandeleur CL, Marques-Vidal P, Vaucher J, Bastardot F, et al. Depression With Atypical Features and Increase in Obesity, Body Mass Index, Waist Circumference, and Fat Mass: A Prospective, Population-Based Study. JAMA psychiatry. 2014. doi: 10.1001/jamapsychiatry.2014.411 PMID: 24898270.

29. Bornstein SR, Schuppenies A, Wong ML, Licinio J. Approaching the shared biology of obesity and depression: the stress axis as the locus of gene-environment interactions. Molecular psychiatry. 2006; 11(10):892–902. doi: 10.1038/sj.mp.4001873 PMID: 16880826.

30. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Archives of general psychiatry. 1998; 55(7):580–92. PMID: 9672048.

31. Borowsky B, Durkin MM, Ogozalek K, Marzabadi MR, DeLeon J, Lagu B, et al. Antidepressant, anxiolytic and anorectic effects of a melanin-concentrating hormone-1 receptor antagonist. Nature medicine. 2002; 8(8):825–30. doi: 10.1038/nm741 PMID: 12118247

32. Barson JR, Morganstern I, Leibowitz SF. Complementary roles of orexin and melanin-concentrating hormone in feeding behavior. International journal of endocrinology. 2013; 2013:983964. doi: 10.1155/2013/983964 PMID: 23935621; PubMed Central PMCID: PMC3727095.

33. Blouin AM, Fried I, Wilson CL, Staba RJ, Behnke EJ, Lam HA, et al. Human hypocretin and melanin-concentrating hormone levels are linked to emotion and social interaction. Nature communications. 2013; 4:1547. doi: 10.1038/ncomms2461 PMID: 23462990; PubMed Central PMCID: PMC3595130.

34. Halley P, Kadakkuzha BM, Faghihi MA, Magistri M, Zeier Z, Khorkova O, et al. Regulation of the apolipoprotein gene cluster by a long noncoding RNA. Cell reports. 2014; 6(1):222–30. doi: 10.1016/j.celrep.2013.12.015 PMID: 24388749; PubMed Central PMCID: PMC3924898.

35. American Diabetes A, American Psychiatric A, American Association of Clinical E, North American Association for the Study of O. Consensus development conference on antipsychotic drugs and obesity and diabetes. Obesity research. 2004; 12(2):362–8.

36. Choong E, Quteineh L, Cardinaux JR, Gholam-Rezaee M, Vandenberghe F, Dobrinas M, et al. Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and the general adult population. JAMA psychiatry. 2013; 70(10):1011–9. doi: 10.1001/jamapsychiatry.2013.187 PMID: 23925723.

37. Firmann M, Mayor V, Vidal PM, Bochud M, Pecoud A, Hayoz D, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC cardiovascular disorders. 2008; 8:6. Epub 2008/03/28. doi: 10.1186/1471-2261-8-6 PMID: 18366642; PubMed Central PMCID: PMC2311269.

38. Preisig M, Waeber G, Vollenweider P, Bovet P, Rothen S, Vandeleur C, et al. The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. BMC psychiatry. 2009; 9:9. doi: 10.1186/1471-244X-9-9 PMID: 19292899; PubMed Central PMCID: PMC2667506.

39. Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature. 2010; 467(7317):832–8. doi: 10.1038/nature09410 PMID: 20881960; PubMed Central PMCID: PMC2955183.

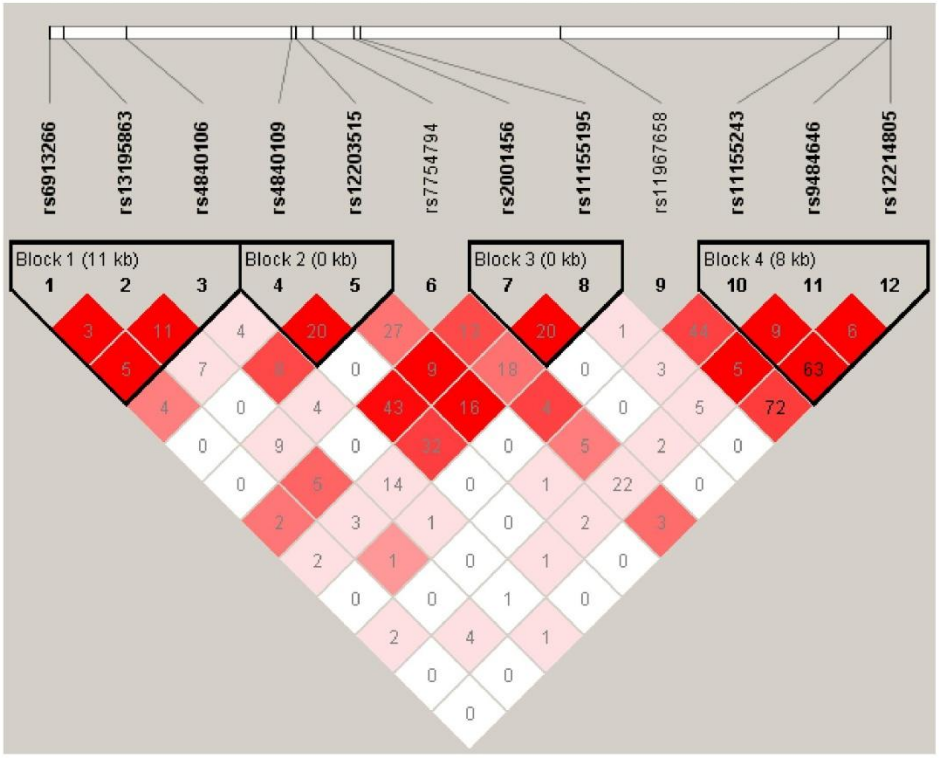
40. Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nature genetics. 2010; 42(11):949–60. doi: 10.1038/ng.685 PMID: 20935629; PubMed Central PMCID: PMC3000924.

41. Voight BF, Kang HM, Ding J, Palmer CD, Sidore C, Chines PS, et al. The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. PLoS genetics. 2012; 8(8):e1002793. doi: 10.1371/journal.pgen.1002793 PMID: 22876189; PubMed Central PMCID: PMC3410907.

42. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics. 2005; 21(2):263–5. doi: 10.1093/bioinformatics/bth457 PMID: 15297300.

S1 Fig. *MCHR2* and *MCHR2-AS1* SNPs haplotype blocks

Coefficients of correlation (r^2) between SNPs are indicated.



S1 Table. Characteristics of psychiatric Caucasian samples: discovery, replication and combined samples

Characteristics	Discovery sample	Replication sample 1	Replication sample 2	Combined sample
	n=474	n=164	n=178	n=816
Male (%)	205 (43.2)	85 (51.8)	106 (59.5)	396 (48.5)
Age, median (range) *years*	50 (12-97)	42.6 (19.5-64)	42.3 (18.7-69.1)	45.5 (12-97)
BMI				
Initial BMI, median (range), kg/m^2 [1]	23.5 (13.3-44.5)	25.2 (15.4-45.5)	24 (15.5-46.2)	23.9 (13.3-46.2)
Initial BMI 25-30 kg/m^2 (%) [1]	100 (21.1)	50 (30.6)	42 (23.6)	192 (23.5)
Initial BMI ≥30 kg/m^2 (%) [1]	69 (14.5)	21 (12.8)	26 (14.6)	116 (14.2)
Current BMI, median (range), kg/m^2 [2]	24.2 (15.2-50.2)	28.1 (16.2-42.3)	26.3 (16.7-58.4)	25.4 (15.2 - 58.4)
Current BMI 25-30 kg/m^2 (%) [2]	109 (23)	48 (29.4)	57 (32)	214 (26.2)
Current BMI ≥30 kg/m^2 (%) [2]	81 (17.1)	64 (39.2)	49 (27.5)	194 (23.7)
Medication, n(%)				
Amisulpride	38 (8)	0 (0)	17 (9.6)	55 (6.7)
Aripiprazole	39 (8.2)	0 (0)	12 (6.7)	51 (6.3)
Clozapine	34 (7.2)	24 (14.6)	18 (10.1)	76 (9.3)
Lithium	35 (7.4)	34 (20.7)	19 (10.7)	88 (10.8)
Mirtazapine	24 (5.1)	0 (0)	1(0.5)	25 (3)
Olanzapine	49 (10.3)	23 (14)	24 (13.5)	96 (11.8)
Paliperidone	1 (0.2)	0 (0)	1 (0.5)	2 (0.2)
Quetiapine	156 (32.9)	31 (18.9)	40 (22.6)	227 (27.8)
Risperidone	74 (15.6)	29 (17.8)	34 (19.1)	137 (16.9)
Valproate	24 (5.1)	23 (14)	12 (6.7)	59 (7.2)
Main diagnosis, n(%)				
Organic disorders	18 (3.8)	0 (0)	0 (0)	18 (2.2)
Psychotic disorders	138 (29.1)	37 (22.5)	68 (38.2)	243 (29.7)
Schizo-affective disorders	32 (6.7)	25 (15.2)	23 (12.9)	80 (9.8)
Bipolar disorders	85 (17.9)	50 (30.5)	28 (15.7)	163 (19.9)
Depression	87 (18.3)	23 (14.1)	25 (14.1)	135 (16.5)
Others[3]	114 (24.1)	29 (17.7)	34 (19.1)	177 (21.7)
Smoker (%)	181 (38.2)	96 (58.9)	111 (62.3)	406 (49.7)
Treatment duration, median (range) *months*	6 (1-12)	27.2 (3-333)	34.8 (1-385)	12 (1-385)
Weight-gain inducing comedications (%) [4]	137 (28.9)	104 (63.8)	73 (41)	318 (38.9)
Important weight-gain inducing treatment (%)[5]	104 (21.9)	70 (42.7)	55 (30.9)	229 (28.1)
Appetite increase (%)[6]	80 (32.9)	70 (46.7)	75 (44.1)	225 (27.5)
Important weight gain (%)[7]	196 (41.3)	93 (56.7)	91 (51.1)	380 (46.5)

[1]Initial BMI represents BMI before the current psychotropic treatment.

[2]Current BMI represents BMI value during the last interview (x months after the beggining of the current psychotropic treatment).

[3]Others include addiction, anxiety, personality disorder and mental retardation.

[4]Weight-gain inducing comedications: see S8 Table for further details.

[5]Important weight gain inducing treatment: includes patients taking either clozapine, olanzapine or valproate as main treatment.

[6]Appetite increase: includes patients incuring an appetite increase between initial and current month.

[7]Important weight gain: defined as an increase of ≥ 5% between current weight and initial weight before current psychotropic treatment

S2 Table. Genotype frequencies of MCHR2 and MCHR2-AS1 SNPs in three Caucasian psychiatric samples.

Psychiatric sample	Position	Total, n	n (%)			HWE	MAF	MAF Hap Map CEU
***MCHR2* rs6913266 C>A**	**99943715**		**AA**	**CA**	**CC**			
Discovery sample		474	4 (0.8)	96 (20.3)	374 (78.9)	0.4		
Replication sample 1		164	2 (1.2)	24 (14.6)	138 (84.2)	0.46		
Replication sample 2		177	7 (3.9)	35 (19.8)	135 (76.3)	0.04		
Combined sample		815	13 (1.6)	155 (19)	647 (79.4)	0.31	0.11	0.14
***MCHR2* rs13195863 C>A**	**99945885**		**AA**	**CA**	**CC**			
Discovery sample		474	21 (4.4)	15 (32.7)	298 (62.9)	0.88		
Replication sample 1		164	7 (4.3)	60 (36.6)	97 (59.1)	0.54		
Replication sample 2		177	8 (4.5)	59 (33.3)	110 (62.2)	0.98		
Combined sample		815	36 (4.4)	274 (33.6)	505 (62.0)	0.88	0.21	0.24
***MCHR2* rs4840106 G>A**	**99955638**		**AA**	**GA**	**GG**			
Discovery sample		474	38 (8)	201 (42.4)	235 (49.6)	0.69		
Replication sample 1		164	15 (9.2)	77 (46.9)	72 (43.9)	0.38		
Replication sample 2		177	16 (9)	68 (38.4)	93 (52.6)	0.49		
Combined sample		815	69 (8.5)	346 (42.4)	400 (49.1)	0.63	0.29	0.3
***MCHR2* rs4840109 G>A**	**99981465**		**AA**	**GA**	**GG**			
Discovery sample		474	91 (19.2)	217 (45.8)	166 (35)	0.19		
Replication sample 1		164	29 (17.7)	81 (49.4)	54 (32.9)	0.88		
Replication sample 2		177	36 (20.4)	82 (46.3)	59 (33.3)	0.44		
Combined sample		815	156 (19.2)	380 (46.6)	279 (24.2)	0.19	0.42	0.43
***MCHR2* rs12203515 C>A**	**99982186**		**AA**	**CA**	**CC**			
Discovery sample		474	19 (4)	176 (37.2)	279 (58.8)	0.17		
Replication sample 1		164	9 (5.5)	51 (31.1)	104 (63.4)	0.42		
Replication sample 2		177	8 (4.5)	55 (31.1)	114 (64.4)	0.68		
Combined sample		815	36 (4.4)	282 (34.6)	497 (61.0)	0.61	0.21	0.21
***MCHR2* rs7754794 C>T**	**99984779**		**CC**	**CT**	**TT**			
Discovery sample		474	196 (41.3)	215 (45.3)	63 (13.3)	0.74		
Replication sample 1		164	66 (40.2)	73 (44.5)	25 (15.2)	0.52		
Replication sample 2		178	75 (42.1)	82 (46.1)	21 (11.8)	0.84		
Combined sample		816	337 (41.3)	370 (45.3)	109 (13.4)	0.64	0.36	0.37
***MCHR2* rs2001456 G>A**	**99991133**		**AA**	**GA**	**GG**			
Discovery sample		474	31 (6.6)	185 (39.0)	258 (54.4)	0.78		
Replication sample 1		164	6 (3.7)	62 (37.8)	96 (58.5)	0.29		
Replication sample 2		177	15 (8.5)	63 (35.6)	99 (55.9)	0.28		
Combined sample		815	52 (6.4)	310 (38.0)	453 (55.6)	0.92	0.25	0.22
***MCHR2* rs11155195 A>G**	**99992082**		**AA**	**AG**	**GG**			
Discovery sample		474	178 (37.4)	236 (49.8)	60 (12.6)	0.18		
Replication sample 1		164	64 (39)	76 (46.4)	24 (14.6)	0.85		
Replication sample 2		177	70 (39.5)	83 (46.9)	24 (13.6)	0.94		

Combined sample		815	312 (38.3)	395 (48.5)	108 (13.2)	0.33	0.37	0.37
***MCHR2-AS1* rs11967658 G>A**	**100023410**		**GG**	**GA**	**AA**			
Discovery sample		474	373 (78.7)	96 (20.2)	5 (1.1)	0.67		
Replication sample 1		164	137 (83.5)	27 (16.5)	0 (0)	0.25		
Replication sample 2		178	149 (83.7)	26 (14.6)	3 (1.7)	0.15		
Combined sample		816	659 (80.7)	149 (18.3)	8 (1)	0.9	0.1	0.12
***MCHR2-AS1* rs11155243G>A**	**100066556**		**GG**	**GA**	**AA**			
Discovery sample		474	331 (69.8)	131 (27.7)	12 (2.5)	0.82		
Replication sample 1		164	120 (73.2)	43 (26.2)	1 (0.6)	0.17		
Replication sample 2		177	129 (72.9)	44 (24.9)	4 (2.2)	0.91		
Combined sample		815	580 (71.2)	218 (26.7)	17 (2.1)	0.51	0.15	0.17
***MCHR2-AS1* rs9484646 G>T**	**100074221**		**GG**	**GT**	**TT**			
Discovery sample		474	199 (42)	223 (47)	52 (11)	0.37		
Replication sample 1		164	70 (40.7)	78 (47.5)	16 (9.8)	0.73		
Replication sample 2		178	76 (42.7)	80 (44.9)	22 (12.4)	0.89		
Combined sample		816	345 (42.3)	381 (46.7)	90 (11)	0.32	0.34	0.31
***MCHR2-AS1* rs12214805 C>T**	**100074607**		**CC**	**CT**	**TT**			
Discovery sample		474	373 (78.7)	96 (2.02)	5 (1.1)	0.67		
Replication sample 1		164	137 (83.5)	27 (16.5)	0 (0)	0.25		
Replication sample 2		178	144 (80.9)	31 (17.4)	3 (1.7)	0.39		
Combined sample		816	654 (80.1)	154 (18.9)	8 (1)	0.75	0.1	0.11

Genomic positions (Build 37), deviation from Hardy Weinberg Equilibrium (HWE) and minor allele frequencies (MAF) observed and refered in HapMap are indicated.

S3 Table. Associations of MCHR2 and MCHR2-AS1 tagging SNPs with BMI in the Caucasian discovery psychiatric sample

MCHR2			*MCHR2-AS1*		
n=441	β (95% CI)	Corrected p-value	n=441	β (95% CI)	Corrected p-value
rs6913266			**rs11967658**		
CC	ref		GG	ref	
CA/AA	0.33 (-0.53 - 1.16)	NS	GA/AA	0.23 (-0.62 - 0.99)	NS
rs4559096			**rs11155243**		
TT	ref		GG	ref	
TC/CC	NA		GA/AA	0.71 (-0.14 - 1.52)	NS
rs13195863			**rs9484646**		
CC/CA	ref		GG	ref	
AA	-0.92 (-2.25 - 0.58)	NS	GT/TT	0.22 (-0.46 - 0.96)	NS
rs4840106			**rs12214805**		
GG	ref		CC	ref	
GA/AA	0.11 (-0.62 - 0.81)	NS	CT/TT	0.31 (-0.61 - 1.18)	NS
rs4840109					
GG/GA	ref				
AA	1.31 (0.41 - 2.14)	0.04			
rs9403322					
GG/GC	ref				
CC	NA				
rs12203515					
CC	ref				
CA/AA	-0.21 (-0.79 - 0.30)	NS			
rs2001456					
GG/GA	ref				
AA	2.38 (0.37 - 4.36)	0.04			
rs11155195					
AA	ref				
AG/GG	-0.32 (-0.98 - 0.25)	NS			
rs7754794					
CC/CT	ref				
TT	-1.08 (-2.11 - (-)0.35)	0.04			

Results were obtained by fitting Generalized Additive Mixed Models for patients, controlling for age, sex, smoking status, current psychotropic drug and comedications possibly causing weight-gain.
β: estimate.
P-value: corrected for multiple tests.
NA: non applicable (because not in HW equilibrium).
NS: non significant.
ref: reference.

S4 Table. MCHR2 rs7754794C>T tagging SNP association with waist circumference in the discovery sample*

MCHR2 rs7754794C>T	WC (cm)		
	n	β (95% CI)	p-value
All subjects			
CC/CT	428	ref	
TT		-1.55 (-4.78 - 1.74)	0.17
≤45 years subjects			
CC/CT	190	ref	
TT		-4.34 (-8.32 - (-)0.19)	**0.02**

Results were obtained by fitting Generalized Additive Mixed Models for patients, controlling for age, sex, smoking status, current psychotropic drug and comedications possibly causing weight-gain.
ref: reference
WC: waist circumference.
*WC data were not available in replication samples 1 and 2.

S5 Table. Characteristics of PsyCoLaus sample.

Characteristics	All participants	MDD status			
		Atypical	Non atypical	No MDD	
	n=3938	n=453	n=1127	n=2350	p-value[g]
Women, % [95CI]	53.9	73.5 [69.4-77.6]	63.3 [60.4-66.1]	45.7 [43.6-47.7]	**0.001**[i]
Age, mean (SD), y	54.8 (11.3)	52.2 (9.7)	53.6 (10.6)	55.9 (11.8)	**0.032**[h]
BMI, mean (SD)	25.8 (4.6)	26.5 (5.2)	25.1 (4.5)	25.9 (4.4)	**<0.001**[h]
SES[a], mean (SD)	3.4 (1.3)	3.3 (1.2)	3.4 (1.3)	3.3 (1.2)	**0.016**[h]
Married, % [95CI]	57.8	50.1 [45.5-54.7]	48.8 [45.9-51.7]	63.7 [61.8-65.6]	0.638[i]
Appetite[b], % [95CI]	NA	40.6 [36.1-45.2]	5.1 [3.9-6.4]	NA	**<0.001**[i]
Physically active[c], % [95CI]	58.1	54.8 [49.7-59.9]	59.7 [56.5-62.9]	57.9 [55.5-60.3]	0.104[i]
Smoking status, % [95CI]					
Former	34.5	30.9 [26.6-35.2]	33.7 [31.0-36.5]	35.6 [33.6-37.5]	0.282[i]
Current	25.2	29.4 [25.1-33.6]	29.4 [26.7-32.0]	22.3 [20.7-24.0]	0.996[i]
Alcohol intake[d], % [95CI]					
Low	57.8	61.1 [56.6-65.7]	57.9 [55.1-60.8]	57.1 [55.1-59.1]	0.242[i]
High	16.7	11.0 [8.1-13.9]	14.9 [12.8-17.0]	18.6 [17.0-20.1]	**0.044**[i]
Anxiety disorders[e], % [95CI]	18	33.5 [29.1-37.9]	26.3 [23.7-28.9]	11.1 [9.9-12.4]	**0.042**[i]
Substance dependence[f], % [95CI]	5.2	5.5 [3.4-7.6]	6.1 [4.7-7.5]	4.7 [3.9-5.6]	0.639[i]
Antidepressant use, % [95CI]	8.6	23.0 [19.1-26.8]	12.5 [10.6-14.4]	4.0 [3.1-4.7]	**<0.001**[i]
Age at MDD onset, mean (SD), y	NA	33.7 (14.0)	35.1 (13.9)	NA	0.141[h]
Time spent in episodes, mean (SD), wk	NA	236.9 (415.7)	157.9 (269.1)	NA	**<0.001**[h]
MDE current, % [95CI]	7.1	28.3 [24.1-32.4]	13.4 [11.4-15.4]	NA	**<0.001**[i]

MDD, major depressive disorder; MDE, major depressive episode; SES, socioeconomic status; BMI, body mass index; 95CI, 95% confidence interval; NA, not applicable.
a Hollingshead Four-Factor Index of Social Status (5 is the highest status).
b Increase of appetite during MDD.
c Physically active more than 20 minutes twice a week.
d Number of drinks per week: low = 1-13 and high = 14 or more.
e Generalized anxiety disorder, social phobia, panic disorder, or agoraphobia.
f Lifetime dependence on cocaine, heroin, stimulant, sedative, or hallucinogen.
g Comparison between atypical and non atypical depressives.
h Wilcoxon-Mann-Whitney test.
i Chi-square test.

S6 Table. Genotype frequencies of *MCHR2* rs7749425C>T according to subgroups of diagnosis in PsyCoLaus sample

	rs7749425-C allele carriers n (%)	rs7749425-TT genotype n (%)
PsyCoLaus	3413 (86.7)	525 (13.3)
PsyCoLaus: Depression	1343 (85.0)	237 (15.0)
PsyCoLaus: Non-atypical Depression	956 (84.8)	171 (15.2)
PsyCoLaus: Atypical Depression	387 (85.4)	66 (14.6)

p-value (Chi2 test)=0.24.

S7 Table. *MCHR2* and *MCHR2-AS1* tagging SNPs referenced in HapMap.

Tagging SNP	Gene	SNPs analyzed, by order of position	r^2
rs6913266 C>A	*MCHR2*	rs6913266 C>A	1
rs13195863 C>A	*MCHR2*	rs13195863 C>A	1
rs4840106 G>A	*MCHR2*	rs4840106 G>A	1
rs4840109 G>A	*MCHR2*	rs4840109 G>A	1
rs12203515 C>A	*MCHR2*	rs12203515 C>A	1
rs6925272T>C	*MCHR2*	**rs7754794 C>T**	**0.97**
rs2001456 G>A	*MCHR2*	rs2001456 G>A	1
rs11155195 A>G	*MCHR2*	rs11155195 A>G	1
rs6919506C>T	*MCHR2-AS1*	**rs11967658 G>A**	**1**
rs4240586T>C	*MCHR2-AS1*	**rs11155243G>A**	**1**
rs9484646 G>T	*MCHR2-AS1*	rs9484646 G>T	1
rs3763374C>T	*MCHR2-AS1*	**rs12214805 C>T**	**0.83**

These tagging SNPs were obtained in HapMap using MAF>5% and pairwise linkage disequilibrium $r^2 \geq 0.8$

r^2:correlation coefficient between loci.

Proxys of tagging SNPs are indicated in bold.

S8 Table. Comedications considered as weight-inducers in statistical analyses

Aldesleukin	Amisulpride	Aripiprazole
Carvedilol	Cetirizine	Chlorpromazine
Chlorprothixene	Clobazam	Clomiphene
Clomipramine	Clozapine	Danazol
Desogestrel	Dexamethasone	Doxepin
Drospirenone + Ethinylestradiol	Estradiol	Ethinylestradiol + Levonorgestrel
Etonogestrel	Etoricoxib	Flupentixol
Gabapentin	Glatiramer	Insulin
Ketazolam	Ketotifen	Levocetirizine
Levonorgestrel	Lithium	Maprotiline
Megestrol	Mianserin	Minoxidil
Mirtazapine	Olanzapine	Paliperidone
Paroxetine	Perphenazine	Pioglitazone
Pregabalin	Progesterone	Quetiapine
Risperidone	Rosiglitazone + Metformin	Rosiglitazone
Sertindole	Sulpiride	Terazosin
Tibolone	Toremifene	Valproate
Vigabatrin	Zuclopenthixol	

More details are available in (36).

Project II: Association of variants in SH2B1 and RABEP1 with worsening of low-density lipoprotein and glucose parameters in patients treated with psychotropic drugs

Gene 628 (2017) 8–15

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Research paper

Association of variants in *SH2B1* and *RABEP1* with worsening of low-density lipoprotein and glucose parameters in patients treated with psychotropic drugs

Aurélie Delacrétaz[a], Adna Zdralovic[a], Frederik Vandenberghe[a], Nuria Saigi-Morgui[a], Anaïs Glatard[a], Lina Quteineh[a], Mehdi Gholam-Rezaee[b], Wassim Raffoul[c], Lee Ann Applegate[c], Paris Jafari[c], Franziska Gamma[d], Armin von Gunten[e], Philippe Conus[f], Chin B. Eap[a,g,*]

[a] Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland
[b] Centre of Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland
[c] Department of Plastic, Reconstructive and Hand Surgery, Unit of Regenerative Therapy, University Hospital of Lausanne (CHUV), Lausanne, Switzerland
[d] Les Toises Psychiatry and Psychotherapy Center, Lausanne, Switzerland
[e] Service of Old Age Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland
[f] Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland
[g] School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland

ARTICLE INFO

Keywords:
SH2B1
RABEP1
Pharmacogenetics of psychotropic drugs
Metabolic syndrome in psychiatry
Dyslipidemia
Type 2 diabetes

ABSTRACT

Genetic factors associated with Body Mass Index (BMI) have been widely studied over the last decade. We examined whether genetic variants previously associated with BMI in the general population are associated with cardiometabolic parameter worsening in the psychiatric population receiving psychotropic drugs, a high-risk group for metabolic disturbances. Classification And Regression Trees (CARTs) were used as a tool capable of describing hierarchical associations, to pinpoint genetic variants best predicting worsening of cardiometabolic parameters (i.e total, HDL and LDL-cholesterol, triglycerides, body mass index, waist circumference, fasting glucose, and blood pressure) following prescription of psychotropic drugs inducing weight gain in a discovery sample of 357 Caucasian patients. Significant findings were tested for replication in a second Caucasian psychiatric sample (n = 140).

SH2B1 rs3888190C > A was significantly associated with LDL levels in the discovery and in the replication sample, with A-allele carriers having 0.2 mmol/l ($p = 0.005$) and 0.36 mmol/l ($p = 0.007$) higher LDL levels compared to others, respectively. G-allele carriers of *RABEP1* rs1000940A > G had lower fasting glucose levels compared to others in both samples (− 0.16 mmol/l; $p < 0.001$ and − 0.77 mmol/l; $p = 0.03$ respectively). The present study is the first to observe such associations in human subjects, which may in part be explained by a high risk towards dyslipidemia and diabetes in psychiatric patients receiving psychotropic treatments compared to population-based individuals. These results may therefore give new insight into the etiology of LDL-cholesterol and glucose regulation in psychiatric patients under psychotropic drug therapy.

1. Introduction

Cardiovascular diseases constitute a major health concern associated with high morbidity and mortality. Comorbidities such as obesity, dyslipidemia, diabetes and hypertension are complex clinical conditions and major contributing risk factors for the development of cardiovascular diseases. Such medical conditions result from the interaction between numerous genetic and environmental factors (e.g. sedentary lifestyle with excessive dietary intake) (Qi & Cho, 2008; Maes et al., 1997). Genetic risk factors were actually reported to account for up to 40 to 70% of inter-individual variability for the most extensively studied obesity-related phenotype, namely the BMI (Visscher et al., 2012; Zaitlen et al., 2013). The largest meta-analysis of Genome-Wide Association Studies (GWAS) to date has reported 97 different loci associated with BMI in 339,224 individuals (Locke et al., 2015).

In psychiatry, patients suffering from severe mental illness have a reduced life expectancy of 10 to 25 years compared to the general population due mainly to cardiovascular diseases resulting from the

* Corresponding author at: Hôpital de Cery, 1008 Prilly, Lausanne, Switzerland.
E-mail address: chin.eap@chuv.ch (C.B. Eap).

http://dx.doi.org/10.1016/j.gene.2017.07.005
Received 15 December 2016; Received in revised form 11 May 2017; Accepted 2 July 2017
Available online 08 July 2017
0378-1119/ © 2017 Elsevier B.V. All rights reserved.

psychiatric disorder and/or comorbidities, but also from the prescription of psychotropic treatments (Laursen et al., 2012). Thus, many antipsychotics, in particular atypical antipsychotics, some mood stabilizers and antidepressants induce metabolic dysfunctions by inducing weight gain (Leucht et al., 2013), dyslipidemia (Correll et al., 2015), type 2 diabetes (Sernyak et al., 2002; Kessing et al., 2010; Buse et al., 2003), and/or hypertension (Khasawneh & Shankar, 2014) to varying degrees. For instance, clozapine and olanzapine are associated with the greatest risk for developing weight gain and other metabolic effects (Leucht et al., 2013). All of these factors result in serious morbidity such as cardiovascular diseases (Newcomer, 2007) and a decreased medication adherence. Dyslipidemia, type 2 diabetes and hypertension can develop either as a direct or collateral consequence of the use of psychotropic drugs. Although precise mechanisms underlying metabolic side effects induced by psychotropic drugs are only partially elucidated to date, the dual antagonism on serotonin and dopamine receptors was shown to stimulate appetite leading to weight gain and other long-term comorbidities (Stahl, 2008). Furthermore, independent antagonism actions on adrenergic and muscarinic receptors were directly related with decreasing insulin secretion and pancreatic β-cell response (Holt & Mitchell, 2015). Over the last decade, pharmacogenetics of psychotropic-induced weight gain has been extensively studied using candidate gene approaches, in particular within dopamine and serotonin receptors (Ryu et al., 2007; Balt et al., 2011). In addition, numerous single nucleotide polymorphisms (SNPs) within genes involved in other pathways of metabolism regulation (e.g. enzymes, receptors or transcriptional coactivators involved in leptin-melanocortin pathways, genes involved in cholesterol and/or in glucose homeostasis) were also associated with weight gain in psychiatric patients taking psychotropic drugs (Lett et al., 2012; Saigi-Morgui et al., 2015; Quteineh et al., 2015; Delacretaz et al., 2015; Choong et al., 2013).

A growing body of evidence suggests that obesity and psychiatric diseases share common etiological pathways, which may be illustrated by the observed synergistic influence of genes associated with obesity and with psychiatric illness on cardiometabolic parameters (Lopresti-& Drummond, 2013). In addition, recent pharmacogenetic studies have shown stronger influence on obesity phenotypes of some BMI-associated genes in the psychiatric population treated with weight gain inducing psychotropic drugs compared to the general population (Saigi-Morgui et al., 2015; Quteineh et al., 2015; Delacretaz et al., 2015). Unfortunately, it is unknown to which extent the 97 variants associated with BMI in the general population are associated with other cardiometabolic phenotypes in the psychiatric population, despite that such populations are at very high risk for cardiometabolic disorders. Because cardiometabolic traits have a complex etiology, with an important variability, the aim of the present study was to determine whether population-based genetic variants related to BMI are associated with cardiometabolic phenotypes in patients from two psychiatric samples who were prescribed known weight gain inducing psychotropic drugs. The analyses were performed using methods capable of detecting hierarchical associations, in order to further refine the underlying biological mechanisms of cardiometabolic phenotypes in psychiatry.

2. Materials and methods

2.1. Psychiatric samples

A prospective cohort study is ongoing in the Lausanne Psychiatric University Hospital since 2007. Patients treated with atypical antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, paliperidone, risperidone), mood stabilizers (lithium, valproate) or/and mirtazapine were included. Baseline and follow-up clinical observations (1, 3, 6 and/or 12 months) were obtained during a medical examination based on the department guideline for metabolic follow-up performed on a routine basis (Choong et al., 2008). Blood samples were collected at 1st, 3rd and 12th months. Most patients had already received other psychotropic treatments before the current treatment. Ethnicity data were obtained from medical files. Diagnoses were based on the *ICD-10* classification (F00-F09 organic disorder; F20.0-F24.9 and F28-F29 psychotic disorders; F25.0-F25.9 schizoaffective disorder; F30.0-F31.9 bipolar disorder; F32.0-F33.9 depressive disorder). Written informed consents for inclusion in the study and also for the genetic analyses were obtained from patients or their legal representatives. The study was approved by the Ethics Committee of Lausanne University Hospital. Further description of the cohort study was published elsewhere (Choong et al., 2013; Vandenberghe et al., 2015).

2.2. Discovery and replication samples

97 SNPs associated with BMI in a recent population-based meta-analysis (Locke et al., 2015) were tested for association with worsening of cardiometabolic variables in the discovery sample. The discovery sample consisted of 357 Caucasian patients from the above-described prospective cohort study, with available clinical data for at least two periods including baseline data. Positive results (i.e. for a smaller subset of SNPs) were tested for replication in the replication sample, composed of 140 Caucasian patients from the same cohort study, with available clinical data for at least two periods of treatment but without baseline data (all patients with baseline data were already included in the discovery sample). Changes of metabolic parameters are more important at the beginning of treatment and including patients with baseline data in the discovery cohort increases the power to detect significant associations between SNPs and cardiometabolic parameters. Thereafter, only the strongest signals were confirmed using the replication sample.

2.3. SNP selection and genotyping

97 SNPs were selected according to the previously mentioned population-based meta-analysis (Locke et al., 2015). DNA from blood samples of psychiatric patients was extracted using the Flexigene DNA Kit or QIAamp DNA Blood Mini QIAcube Kit (Qiagen AG, Switzerland) as described by the manufacturers's instructions. Genotypes of 96 SNPs were available in the Illumina 200 K CardioMetaboChip (Voight et al., 2012). The CardioMetabochip is a custom Illumina iSelect genotyping array designed to test DNA variation of 200′000 SNPs from regions identified by large scale meta-analyses of genome wide association studies (GWAS) for metabolic and cardiovascular traits. CardioMetabochip genotyping was performed at the iGE3 genomics platform of the University of Geneva (http://www.ige3.unige.ch/genomics-platform.php). Quality control excluded samples from the analysis if gender was inconsistent with genetic data from X-linked markers, if autosomal heterozygosity was extreme, genotype call rate < 0.96, Gene Call (GC) score < 0.15 and/or minor allele frequency (MAF) < 0.10. The one remaining SNP not available in the CardioMetaboChip, namely rs11847697, was analysed using a TaqMan SNP Genotyping Assay (C_1293175_10) on ViiA™ 7 Real-Time PCR System, as described by the manufacturer instructions.

3. Functional assessment of significant SNPs

3.1. eQTL analysis

Cis-association data of the influence of significant SNPs on the expression of nearby genes were extracted from the Genotype-Tissue Expression (GTEx) project, a public source (http://www.gtexportal.org/home/) with available expression Quantative Trait Loci (eQTL) data of 7051 samples from 44 different tissues and for genome-wide genetic variations in the general population (Illumina OMNI 5M SNP Array) (GTEx Consortium, 2013).

3.2. RegulomeDB annotation

The Regulome database (http://www.regulomedb.org/) was used to assess the functional activity of significant SNPs (Boyle et al., 2012). This database defines SNPs with known and/or predicted regulatory elements located in intergenic regions of the human genome. Known and predicted regulatory elements include regions of DNAase hypersensitivity, binding sites of transcription factors and promoter regions biochemically characterized to the regulation of transcription. Sources for these data include public datasets from GEO, the ENCODE project and the published literature.

3.3. Statistical analyses

Statistical analyses were performed using Stata 12 (StataCorp, College Station TX, USA) and R version 3.1.1. Hardy-Weinberg equilibrium (HWE) testing was performed for the 97 SNPs using Pearson's chi-squared test. SNPs for which *p*-value was higher than 0.05 were considered in HWE.

Classification And Regression Trees (CARTs) are used to segregate SNPs that best predict the worsening of cardiometabolic variables during different periods of the psychotropic treatment. CARTs can be grown using the so called Recursive Partitioning and Regression Trees algorithms (Breiman et al., 1984). These algorithms are implemented in a few softwares including R environment for statistical programming and data analysis (rpart library). At each node, the split rule is applied which is based on the Generalized Gini index, the split can be performed if number of observations exceeds a certain threshold (the threshold in this study was 20). Pruning can be used in function of the desired complexity of the tree. Complexity of the constructed tree at each node is represented by the so called Complexity Parameter which is equivalent to the decrease in relative error rate of the tree if the split at each that node survives after the tree is pruned.

CARTs were first performed on the discovery sample to identify clinical (age, sex, smoking status) and genetic (97 SNPs) variables best predicting worsening of cardiometabolic features during the psychotropic treatment (i.e. increase of BMI, waist circumference (WC), total cholesterol (TC), fasting triglycerides (TG), low-density lipoprotein (LDL), fasting glucose (GLC), systolic blood pressure (SBP) and/or of diastolic blood pressure (DBP), and/or decrease of high-density lipoprotein (HDL)). Of note, patients receiving lipid-lowering, antidiabetic and/or antihypertensive drugs were excluded from TC, TG, LDL, HDL analyses, GLC analyses and SBP and DBP analyses, respectively (S1 Table). In order to determine short- and long-term risk factors associated with metabolic disturbances, CARTs were performed at several periods of treatment (i.e. from ≥ 10 to < 45 days; from ≥ 45 to < 135 days and from ≥ 135 to < 535 days of psychotropic treatment). Variables in the first three layers of the CART tree structure for each cardiometabolic phenotype and each period of psychotropic treatment were considered in further covariate-adjusted statistical analyses. Associations between the most important SNPs (in the first three layers) and cardiometabolic variables were assessed in the discovery sample (using a dominant or recessive model according to CART results) by fitting a generalized additive mixed model (GAMM) adjusting for possible confounders such as age, sex and smoking status (De Hert et al., 2011), allowing a smooth trend for the response in time based on multiple observations for each patient. Significant associations were then tested in the replication sample using the same model. GAMMs were fitted using the mgcv package of R, in which parameter uncertainties (confidence intervals and p-values) were computed using bootstrap (1000 replicates or 10,000 replicates whenever possible with replacement, performed on patient level). p-Values of two-sided models ≤ 0.05 were considered as statistically significant.

4. Results

4.1. Characteristics of psychiatric samples

S2 Table displays demographic and clinical characteristics of the two psychiatric Caucasian samples. As published elsewhere (Vandenberghe et al., 2015), values of cardiometabolic parameters in both psychiatric samples generally increased during the psychotropic treatment. Patients were slightly older in the replication sample (median of 52 years) compared to the discovery sample (median of 47 years; $p = 0.04$). Psychotic (F20.0-F24.9 and F28-F29) was the most frequent diagnosis (37% in the combined sample), and quetiapine was the most frequently prescribed psychotropic drug (33% in the combined sample). No difference of clinical or of demographical variables was observed between the discovery and replication samples ($p > 0.05$), except in the second psychotropic treatment period, namely between 45 and 135 days of treatment, in which BMI and waist circumference were higher in the replication sample (25.5 kg/m^2; 95 cm) compared to the discovery sample (23.7 kg/m^2; 91 cm; p-values = 0.04 and 0.03, respectively).

4.2. Variables predicting cardiometabolic phenotype worsening in the discovery sample

Three out of the 97 SNPs were not in Hardy Weinberg equilibrium and were therefore not used in analyses (i.e rs1075847, rs13201877 and rs657452). CARTs fitted on the different cardiometabolic phenotypes (i.e. BMI, WC, HDL, TC, TG, LDL, GLC, SBP and DBP) highlighted 57 different SNPs that best predicted worsening of at least one of the latter-mentioned cardiometabolic variable in the discovery sample during three distinct consecutive periods of psychotropic treatment. An example of a CART is presented in S1 Fig, showing, for instance, that patients carrying the variant allele of *ADCY3* rs10182181A > G (i.e. G) have a mean TC increase of 3.9%, whereas those who carry the AA genotype have a mean TC increase of 13.7% during the first period of psychotropic treatment. A summary of CART results is displayed in Table 1.

4.3. Association of SNPs with cardiometabolic phenotypes in psychiatric samples

In the discovery sample, 18 out of the 57 different SNPs were significantly associated with at least one cardiometabolic phenotype using multiple linear models adjusted for age, sex, BMI and smoking status ($p < 0.05$) (Table 2). Two out of the 18 SNPs were significantly replicated in the replication sample, with *SH2B1* rs3888190C > A and *RABEP1* rs1000940A > G being significantly associated with LDL levels ($p = 0.007$) and FG levels ($p = 0.03$), respectively (Table 3). The 16 remaining SNPs were not replicated (data not shown) and were therefore not considered in further analyses. Genotype frequencies of *SH2B1* rs3888190C > A (GRCh38.p7 16:28,878,165) and *RABEP1* rs1000940A > G (GRCh38.p7 17:5,379,957) in the discovery and replication samples are presented in the S3 Table. Both SNPs were in HWE in the two psychiatric samples, and their MAF were in accordance with those reported in HapMap for Caucasians.

4.4. Association of SH2B1 rs3888190C > A with LDL levels in psychiatric samples

In the discovery sample, rs3888190C > A was significantly associated with LDL levels, with A-allele carriers having 0.20 [0.07; 0.36] mmol/l higher LDL levels compared to patients carrying the CC genotype ($p = 0.005$) (Table 3). This observation was replicated in the second psychiatric sample (0.36 [0.08; 0.66] mmol/l; $p = 0.007$)

Table 1
SNPs and cardiometabolic variables: CART analyses.

TC		HDL		LDL		TG		BMI	
SNP	Gene[a]	SNP	Gene[a]	SNP	Gene[a]	SNP	Gene[a]	SNP	Gene[a]
rs10182181	*ADCY3*	rs10132280	*STXBP6*	rs1000940	*RABEP1*	rs1000940	*RABEP1*	rs1016287	*LINC01122*
rs10968576	*LINGO2*	rs10968576	*LINGO2*	rs10182181	*ADCY3*	rs11688816	*EHBP1*	rs10182181	*ADCY3*
rs11688816	*EHBP1*	rs11165643	*PTBP2*	rs10968576	*LINGO2*	rs12429545	*OLFM4*	rs11688816	*EHBP1*
rs12401738	*FUBP1*	rs11688816	*EHBP1*	rs1441264	*MIR548A2*	rs1528435	*UBE2E3*	rs12885454	*PRKD1*
rs17024393	*GNAT2*	rs1441264	*MIR548A2*	rs2176598	*HSD17B12*	rs29941	*KCTD15*	rs12940622	*RPTOR*
rs17094222	*HIF1AN*	rs1460676	*FIGN*	rs2287019	*QPCTL*	rs3101336	*NEGR1*	rs1441264	*MIR548A2*
rs1808579	*C18orf8*	rs1514175	*TNNI3K*	rs3736485	*DMXL2*	rs3888190	*SH2B1*	rs1808579	*C18orf8*
rs1928295	*TLR4*	rs16907751	*ZBTB10*	rs3888190	*SH2B1*	rs5014937	*CALCR*	rs2033732	*RALYL*
rs205262	*C6orf106*	rs2112347	*POC5*	rs492400	*USP37*	rs7103411	*BDNF*	rs4740619	*C9orf93*
rs492400	*USP37*	rs29941	*KCTD15*	rs7164727	*LOC100287559*			rs7903146	*TCF7L2*
rs7164727	*LOC100287559*	rs4787491	*INO80E*	rs7243357	*GRP*			rs9400239	*FOXO3*
rs7903146	*TCF7L2*	rs6804842	*RARB*	rs7715256	*GALNT10*				
rs9914578	*SMG6*	rs7103411	*BDNF*	rs9374842	*LOC285762*				
		rs7715256	*GALNT10*						
		rs7903146	*TCF7L2*						

WC		FG		SBP		DBP	
SNP	Gene[a]	SNP	Gene[a]	SNP	Gene[a]	SNP	Gene[a]
rs11583200	*ELAVL4*	rs1000940	*RABEP1*	rs10132280	*STXBP6*	rs1000940	*RABEP1*
rs12429545	*OLFM4*	rs11688816	*EHBP1*	rs10182181	*ADCY3*	rs10938397	*GNPDA2*
rs1808579	*C18orf8*	rs17203016	*CREB1*	rs1441264	*MIR548A2*	rs10968576	*LINGO2*
rs2033529	*TDRG1*	rs17405819	*HNF4G*	rs17203016	*CREB1*	rs10968576	*LINGO2*
rs2033732	*RALYL*	rs2820292	*NAV1*	rs29941	*KCTD15*	rs1167827	*HIP1*
rs205262	*C6orf106*	rs3101336	*NEGR1*	rs3810291	*ZC3H4*	rs17405819	*HNF4G*
rs2241420	*MAP2K5*	rs543874	*SEC16B*	rs7164727	*LOC100287559*	rs17724992	*PGPEP1*
rs29941	*KCTD15*	rs6567160	*MC4R*			rs3810291	*ZC3H4*
rs492400	*USP37*	rs7164727	*LOC100287559*			rs3849570	*GBE1*
		rs7239883	*LOC284260*			rs4787491	*INO80E*
		rs7903146	*TCF7L2*			rs7113874	*TRIM66*

TC: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; TG: triglycerides; BMI: body mass index; WC: waist circumference; FG: fasting glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure.
This table displays the 57 SNPs predicting the best worsening of cardiometabolic parameters (within the first three layers) according to CART analyses in the discovery sample.
[a] Nearest gene for each SNP.

(Table 3). S2 Fig.a illustrates the evolution of abnormal LDL level (i.e. LDL levels ≥ 3 mmol/l and/or with any prescribed lipid-lowering drug) prevalence according to rs3888190C > A genotypes during psychotropic treatment in the combined sample. During psychotropic treatment, the proportion of patients with abnormal LDL values significantly increased for both rs3888190-CC (from 40% at baseline to 54% in the last treatment period; p = 0.04) and rs3888190-A allele carriers (from 46% to 60%, respectively; p = 0.02), reflecting the development of dyslipidemia-induced psychotropic drug. Within subperiods of treatment, no difference of abnormal LDL proportion was detected across rs3888190C > A genotypes, possibly due to insufficient power. In contrast, when considering all observations from multiple treatment periods together (S2 Fig.b), the overall proportion of patients with abnormal LDL levels was lower for rs3888190-CC carriers (47%) compared to rs3888190-A allele carriers (53%; p = 0.03).

4.5. Association of *RABEP1* rs1000940A > G with fasting glucose levels in psychiatric samples

In the discovery sample, rs1000940A > G was significantly associated with fasting glucose. G-allele carriers had 0.16 [0.06; 0.28] mmol/l lower fasting glucose levels compared to patients carrying the AA genotype (p < 0.001) and this association was replicated in the second psychiatric sample (0.77 [0.03; 1.39] mmol/l; p = 0.03) (Table 3). S3 Fig.a displays the prevalence of abnormal fasting glucose levels (i.e. fasting GLC levels ≥ 5.6 mmol/l and/or with any prescribed antidiabetic drug) according to rs1000940A > G during the psychotropic treatment. As for *SH2B1* rs3888190C > A and LDL, no significant difference of abnormal glucose level prevalence across rs1000940A > G genotypes was observed in subperiods of psychotropic treatment. However, the overall proportion of patients with abnormal glucose levels was significantly lower for patients carrying rs1000940-G allele (20%) compared to those carrying the AA genotype (27%; p = 0.03) when considering all periods of treatment together (S3 Fig.b). Moreover, when considering each genotype separately (i.e. in carriers of rs1000940 AA genotype and in carriers of rs1000940 G allele), there was no significant difference of the prevalence of hyperglycemia after a short or after a longer period of treatment (p = 0.77 and 0.96 for AA and G allele carriers, respectively), possibly explained by a worsening of glycemia profile occurring during a longer period of treatment than the one taken into account during the present study.

Even though being non-significant due to non-adjusted analyses as well as an insufficient number of observation, S2 and S3 Fig suggest that both *SH2B1* rs3888190C > A and *RABEP1* rs1000940A > G could exert an influence on LDL and on glucose, respectively, already before the current psychotropic treatment initiation. These baseline differences may possibly be explained, at least in part, by the fact that most patients were not drug naïve when starting the current psychotropic treatment. Of note, no difference of LDL nor of glucose levels were observed between psychotropic medication groups (constructed according to their propensity to induce metabolic alterations, i.e. high-risk group (olanzapine, clozapine and valproate) versus medium-risk group (quetiapine, risperidone, mirtazapine, lithium) versus low-risk group (amisulpride, aripiprazole)), data not shown.

Although neither *SH2B1* rs3888190C > A nor *RABEP1*

Table 2
SNPs and cardiometabolic variables: discovery sample.

	n	Gene(s)[a]	SNP	β	*p*-Value
TC	309	*HIF1AN*	rs17094222 T > C	ref: TT 0.17 (− 0.04–0.35)	0.05
		C6orf106; SNRPC	rs205262 A > G	ref: AA − 0.22 (− 0.37–(−)0.05)	0.01
		EHBP1	rs11688816 G > A	ref: GG/GA 0.24 (0.06–0.47)	0.01
HDL	306	*MIR548A2*	rs1441264 G > A	ref: GG 0.07 (0.02–0.12)	0.01
		BDNF	rs7103411 C > T	ref: CC/CT − 0.23 (− 0.31–(−)0.14)	< 0.001
LDL	301	*SH2B1; APOBR; ATXN2L; SBK1; SULT1A2; TUFM*	rs3888190 C > A	ref: CC 0.20 (0.07–0.36)	0.005
		QPCTL; GIPR	rs2287019 C > T	ref: CC − 0.11 (− 0.24–0.02)	0.05
TG	290	*BDNF*	rs7103411 C > T	ref: CC 0.12 (0.01–0.25)	0.01
		SH2B1; APOBR; ATXN2L; SBK1; SULT1A2; TUFM	rs3888190 C > A	ref: CC/CA 0.13 (− 0.04–0.29)	0.05
		EHBP1	rs11688816 G > A	ref: GG/GA 0.19 (0.01–0.37)	0.02
BMI	330	*LINC01122*	rs1016287 T > C	ref: TT/TC 1.33 (− 0.28–2.85)	0.05
		FOXO3; HSS00296402	rs9400239 T > C	ref: TT 0.99 (0.22–1.88)	0.009
WC	325	*MAP2K5; LBXCOR1*	rs2241420 G > A	ref: GG/GA − 7.37 (− 10.54–(−)2.90)	< 0.001
		OLFM4	rs12429545 G > A	ref: GG − 2.18 (− 4.05–(−)0.17)	0.02
FG	287	*RABEP1*	rs1000940 A > G	ref: AA − 0.16 (− 0.28–(−)0.06)	< 0.001
		TCF7L2	rs7903146 C > T	ref: CC/CT 0.15 (− 0.01–0.31)	0.03
SBP	268	*KCTD15*	rs29941 A > G	ref: AA/AG 6.78 (− 0.42–12.2)	0.05
DBP	268	*RABEP1*	rs1000940 A > G	ref: AA − 3.34 (− 5.76–(−)1.72)	< 0.001
		ZC3H4	rs3810291 G > A	ref: GG − 1.63 (− 4.07–0.32)	0.04
		HIP1; PMS2L3; PMS2P5; WBSCR16	rs1167827 G > A	ref: GG 2.20 (0.04–3.88)	0.03

Among SNPs from CART analyses (in Table 1), 18 SNPs were significantly associated with cardiometabolic variables in the discovery sample using GAMM models, with SNPs considered as dominant or recessive according to CART results.

[a] All notable genes related to corresponding SNPs (i.e. nearest gene, gene with biological relevance to metabolic parameters, eQTL SNPs, etc) (Locke et al., 2015).

rs1000940A > G were detected as having a possible influence on BMI in CART analyses, both SNPs were tested for association with BMI in the discovery psychiatric sample. No significant association was observed between these two SNPs and BMI in the discovery sample (data not shown).

5. Discussion

The present study aimed to explore whether SNPs previously associated with BMI and other cardiometabolic variables in the general population (Locke et al., 2015) are associated with the worsening of cardiometabolic phenotypes in a psychiatric population receiving

Table 3
Association of SNPs with metabolic phenotypes in two independent Caucasian psychiatric samples.

SNP	Phenotype	n	Discovery sample	*p*-Value	n	Replication sample	*p*-Value
			β (95% CI) (mmol/l)			β (95% CI) (mmol/l)	
SH2B1 rs3888190C > A	LDL	301			105		
CC			ref	0.005		ref	0.007
CA/AA			0.20 (0.07–0.36)			0.36 (0.08–0.66)	
RABEP1 rs1000940A > G	FG	287			82		
AA			ref	< 0.001		ref	0.03
AG/GG			− 0.16 (− 0.28–− 0.06)			− 0.77 (− 1.39–0.03)	

In this Table, 2 SNPs significantly associated with cardiometabolic variables in the replication sample using GAMM models are displayed. For clarity purpose, results for these 2 SNPs in the discovery sample are repeated. These 2 SNPs appeared in the second layer of CART analyses on LDL and fasting glucose levels.
Results were obtained by fitting Generalized Additive Mixed Models for patients, controlling for age, sex, body mass index and smoking status.
β: estimate; ref.: reference; LDL:low-density lipoprotein; FG: fasting glucose.
Patients taking lipid-lowering or antidiabetic medications were excluded from LDL and FG analyses, respectively.
For FG analyses, patients in non-fasting conditions were excluded from analyses.

weight gain inducing psychotropic treatments. In particular, we aimed to better refine underlying mechanisms linking and/or discerning genetics of BMI with regard to other cardiometabolic comorbidities in the psychiatric population, considering that the prevalence of metabolic syndrome has been reported twice as high in this population compared to the general population (De Hert et al., 2009).

Our preliminary exploration using CART analyses highlighted and ranked 57 different SNPs that predicted the best metabolic parameter worsening during psychotropic treatment in the discovery sample. In the latter sample, 18 SNPs were significantly associated with cardiometabolic phenotypes but the remaining 39 SNPs were not, probably due to adjustment for covariates (i.e. age, sex, BMI and/or smoking status) in GAMM analyses, which was not performed in exploratory CART analyses. Out of the 18 SNPs, *SH2B1* rs3888190C > A and *RABEP1* rs1000940A > G were replicated in the second psychiatric replication sample. The 16 remaining SNPs were not replicated, possibly due to the lower sample size of the latter sample compared to the discovery sample and the probable minor influence of these SNPs on cardiometabolic variables.

Thus, *SH2B1* rs3888190C > A and *RABEP1* rs1000940A > G were significantly associated with low-density lipoprotein levels and fasting glucose levels, respectively, in two separate psychiatric samples. As recent population-based studies did not observe such associations (Locke et al., 2015; Lu et al., 2016) this is, to our knowledge, the first genetic study that suggested an influence of *SH2B1* rs3888190C > A on LDL as well as of *RABEP1* rs1000940A > G on fasting glucose levels. These different results between general and psychiatric populations may in part be explained by a lower risk towards dyslipidemia and diabetes in population-based individuals compared to psychiatric patients receiving psychotropic treatments (De Hert et al., 2012). Of note, since a 1% reduction in LDL-cholesterol on average was shown to reduce risks for hard coronary heart disease events by approximately 1% in short-term controlled trials (Third Report of the National Cholesterol Education Program (NCEP), 2002), the observed difference of LDL levels between *SH2B1* rs3888190C > A genotypes appears clinically relevant.

In order to differentiate SNPs according to their short- and/or long-term influence on metabolic features, CART analyses were conducted after several distinct periods of psychotropic treatment. Both *SH2B1* rs3888190C > A and *RABEP1* rs1000940A > G appeared to exert an influence already before the current psychotropic treatment initiation, which may be explained by the fact that most patients were not drug naïve when starting the current psychotropic treatment. Further studies are required to characterize how these genetic variants influence these two metabolic parameters in drug naïve patients. It is of particular interest to note that our results within this observational psychiatric sample reflect real clinical conditions.

The LDL-increasing allele of *SH2B1* rs3888190C > A in the psychiatric population, namely the A allele was associated with higher BMI values ($0.03\ kg/m^2$; $p = 3.14 * 10^{-23}$) in population-based samples (Locke et al., 2015), which is in accordance with epidemiological expectations. On the other hand, the glucose-increasing genotype of *RABEP1* rs1000940A > G in the psychiatric population, namely AA was associated with lower BMI values in the general population ($-0.019\ kg/m^2$; $p = 1.3 * 10^{-8}$) (Locke et al., 2015). This unexpected result may be explained by a differential influence of *RABEP1* rs1000940A > G on these two cardiometabolic parameters between population-based and psychiatric samples. Despite BMI being a well-described parameter associated with metabolic comorbidities including fasting glycemia in large prospective population studies (Guh et al., 2009), some recent conflicting genetic association results have been described in population-based samples (Lu et al., 2016). Thus, several loci have a more pronounced effect on body fat percentage than on BMI, suggesting a specific effect on adiposity rather than on overall body mass (Lu et al., 2016). For instance, a genetic polymorphism 500 kb upstream of *IRS1* and influencing its expression was on one hand significantly associated with an increased overall adiposity (body fat percentage) and, on the other hand, associated with a protective effect on cardiometabolic health, including a reduced risk of type 2 diabetes and cardiovascular diseases (Lu et al., 2016). These unexpected results were explained by an effect on fat distribution, as the body fat percentage increasing allele was associated with increased subcutaneous but not with metabolically more harmful visceral fat (Kilpelainen TO et al., 2011). Many other similar inconsistent cross-phenotypic genetic associations were described in population-based GWAS meta-analyses (Locke et al., 2015; Lu et al., 2016) and strikingly, most of inconsistent cross-phenotypic genetic associations encompass genes that influence insulin receptor signaling (Lu et al., 2016). Further studies are therefore needed to elucidate underlying biological mechanisms of such unexpected cross-phenotypic associations, in particular between adiposity and insulin resistance disorders.

An increasing number of studies indicate that metabolic and psychiatric diseases share common etiological pathways and have related neurobiological bases (Lopresti & Drummond, 2013). *SH2B1* rs3888190C > A as well as its 77 proxies lie in a highly conserved genetic region displaying a considerable regulatory function. *SH2B1* rs3888190C > A may alter the expression of many genes involved in cholesterol homeostasis, including Interleukin 27 (*IL27*), *SH2B1* and Apolipoprotein B receptor (*APOBR*) (S4 Fig) (Ren et al., 2007; Rui, 2014; Sheng et al., 2013; Fu et al., 2014; Hirase et al., 2013; Jin et al., 2012; Fujita et al., 2005), either through a cis-effect in the liver and/or through methylation-mediated long-range interaction with its promoter (Voisin et al., 2015). Apart from being involved in the regulation of atherosclerosis, this cytokine was associated with LDL levels in mice and humans (Fu et al., 2014; Hirase et al., 2013; Jin et al., 2012). Besides, some genes involved in the immune system have been associated with schizophrenia, bipolar disorder and major depressive disorder (MDD) in two recent genome-wide association studies (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), suggesting that cytokines may play a role in psychiatric disorders. Similarly, a recent meta-analysis reported analogies in the pattern of cytokine alterations in the above mentioned psychiatric disorders (Goldsmith et al., 2016). Taken together, published results suggest that LDL regulation and psychiatric illnesses may share common regulatory genes including *IL27*, which constitutes a possible candidate to explain the specific influence of *SH2B1* rs3888190C > A on LDL in patients with psychiatric disorders but not in individuals from the general population. A growing body of evidence suggest that *RABEP1* rs1000940A > G and its 7 proxies ($r^2 > 0.95$) may be involved in the regulation of glucose. RABEP1 was shown to interact with RAB5a, a protein required for the regulation of gluconeogenic gene (Zeigerer et al., 2015) and for insulin sensitivity (Tessneer et al., 2014; Huang et al., 2001). Additionally, NUP88 was shown to interact with several proteins including the CREB binding protein (CREBBP) involved in insulin sensitivity (Yamauchi et al., 2002). In addition, eQTL data of these SNPs showed higher expression of *NUP88* in the brain (cerebellar hemisphere) and a lower expression of *RABEP1* in the thyroid and the pituitary, two genes (tagged in part by rs1000940A > G) interacting with different proteins involved in insulin sensitivity (S5 Fig) (Zeigerer et al., 2015; Tessneer et al., 2014; Huang et al., 2001; Yamauchi et al., 2002). Within the large genetic region of *RABEP1* rs1000940A > G, three proxies may influence expression levels of *ATF2*, a transcription factor involved in part in the regulation of insulin resistance (Yamauchi et al., 2002; Ban et al., 2000; Kreisberg et al., 1994; Ausserer et al., 1994; Yang & Trevillyan, 2008). Interestingly, an overexpression of the latter transcription factor in nucleus accumbens of rats enhanced antidepressant-like responses, suggesting that this transcription factor plays a role in the regulation of emotional behavior as well (Green et al., 2008). Likewise, chronic administration of antidepressants impaired levels of ATF2 in the prefrontal cortex in rats, and similarly, levels of phosphorylated ATF2 were decreased in patients medicated with antidepressants compared to non-medicated patients in post-mortem human brains (Laifenfeld et al., 2004). The latter studies illustrate the possible role of *ATF2* in the complex

interminglement between glucose homeostasis and psychiatric illnesses and may therefore explain the specific influence of *RABEP1* rs1000940A > G on glucose levels in particular in patients with psychiatric disorders but not in individuals from the general population. More studies with larger psychiatric samples are needed to confirm our findings and to identify true causal variants, which will help to better understand mechanisms underlying the metabolic regulation of cholesterol and glucose, in particular in the psychiatric population.

Several limitations of the present study should be considered. Firstly, this study was limited to Caucasian patients and results cannot be generalized to other ethnicities. Secondly, the functional activity of *SH2B1* rs3888190C > A and of *RABEP1* rs1000940A > G could not be assessed in the psychiatric population. Third, association with *SH2B1* rs3888190C > A did not survive to multiple testing correction. However, the present results were replicated in a second psychiatric sample and functional analyses strengthen the validity of our data. Moreover, our results within this observational psychiatric sample reflect real clinical conditions.

In conclusion, this is the first genetic study to identify an association between *SH2B1* rs3888190C > A and LDL levels as well as between *RABEP1* rs1000940A > G and glucose levels. Our results are in agreement with the previously reported roles of the many probable affected genes in metabolism and provide new insight into the implication of these genes in the human regulation of cholesterol and glucose, in particular in the psychiatric population receiving psychotropic drugs. Finally, the considerable regulatory function of these genetic regions emphasizes the probable involvement of many regulatory genes and supports further studies to better understand mechanisms underlying the metabolic regulation of cholesterol and glucose, in particular in the psychiatric population.

Funding

This work has been funded in part by the Swiss National Research Foundation (CBE and PC: 320030-120686, 324730-144064 and 320030-173211). The funding sources had no role in the writing of the manuscript or in the decision to submit it for publication.

Author disclosure information

CBE received research support from Takeda and The Roche Transplantation Research Foundation in the past 3 years. CBE received honoraria for conferences or teaching CME courses from Advisis, Astra Zeneca, Lundbeck, MSD, Otsuka; Sandoz,Servier and Vifor-Pharma in the past 3 years. AVG received honoraria for a conference or workshop participation from Vifor and Bayer Sheringer in the previous 3 years. WR, PJ and LAA have no conflict of interest or Industrial funding related to the content of this paper. All authors declare no conflict of interest in relation to the content of the paper.

Acknowledgement

The authors thank Dr. S. Crettol, C. Brogli, V. Hodel (logistical assistance), E. Ponce (bibliographical help), A. C. Aubert, M. Brocard, N. Cochard, M. Delessert, A. Vuilloud, M. Brawand, K. Powell Golay, S. Jacquet (sample analysis).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.gene.2017.07.005.

References

Ausserer, W.A., Bourrat-Floeck, B., Green, C.J., Laderoute, K.R., Sutherland, R.M., 1994. Regulation of c-jun expression during hypoxic and low-glucose stress. Mol. Cell. Biol. 14 (8), 5032–5042.

Balt, S.L., Galloway, G.P., Baggott, M.J., Schwartz, Z., Mendelson, J., 2011. Mechanisms and genetics of antipsychotic-associated weight gain. Clin. Pharmacol. Ther. 90 (1), 179–183.

Ban, N., Yamada, Y., Someya, Y., Ihara, Y., Adachi, T., Kubota, A., et al., 2000. Activating transcription factor-2 is a positive regulator in CaM kinase IV-induced human insulin gene expression. Diabetes 49 (7), 1142–1148.

Boyle, A.P., Hong, E.L., Hariharan, M., Cheng, Y., Schaub, M.A., Kasowski, M., et al., 2012. Annotation of functional variation in personal genomes using RegulomeDB. Genome Res. 22 (9), 1790–1797.

Breiman, L., Friedman, J.H., Olshen, R.A., Stone, C.J., 1984. Classification and Regression Trees. Wadsworth B, CA. (editor).

Buse, J.B., Cavazzoni, P., Hornbuckle, K., Hutchins, D., Breier, A., Jovanovic, L., 2003. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. J. Clin. Epidemiol. 56 (2), 164–170.

Choong, E., Solida, A., Lechaire, C., Conus, P., Eap, C.B., 2008. Follow-up of the metabolic syndrome induced by atypical antipsychotics: recommendations and pharmacogenetics perspectives. Rev. Med. Suisse 4 (171), 1994–1999.

Choong, E., Quteineh, L., Cardinaux, J.R., Gholam-Rezaee, M., Vandenberghe, F., Dobrinas, M., et al., 2013. Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and the general adult population. JAMA Psychiat. 70 (10), 1011–1019.

Correll, C.U., Detraux, J., De Lepeleire, J., De Hert, M., 2015. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry: Off. J. World Psychiatr. Assoc. 14 (2), 119–136.

De Hert, M., Dekker, J.M., Wood, D., Kahl, K.G., Holt, R.I., Moller, H.J., 2009. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of diabetes (EASD) and the European Society of Cardiology (ESC). Eur. Psychiatry 24 (6), 412–424.

De Hert, M., Detraux, J., van Winkel, R., Yu, W., Correll, C.U., 2011. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat. Rev. Endocrinol. 8 (2), 114–126.

De Hert, M., Detraux, J., van Winkel, R., Yu, W., Correll, C.U., 2012. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat. Rev. Endocrinol. 8 (2), 114–126.

Delacretaz, A., Preisig, M., Vandenberghe, F., Saigi Morgui, N., Quteineh, L., Choong, E., et al., 2015. Influence of MCHR2 and MCHR2-AS1 genetic polymorphisms on body mass index in psychiatric patients and in population-based subjects with present or past atypical depression. PLoS One 10 (10), e0139155.

Fu, H., Tang, Y.Y., Ouyang, X.P., Tang, S.L., Su, H., Li, X., et al., 2014. Interleukin-27 inhibits foam cell formation by promoting macrophage ABCA1 expression through JAK2/STAT3 pathway. Biochem. Biophys. Res. Commun. 452 (4), 881–887.

Fujita, Y., Ezura, Y., Bujo, H., Nakajima, T., Takahashi, K., Kamimura, K., et al., 2005. Association of nucleotide variations in the apolipoprotein B48 receptor gene (APOB48R) with hypercholesterolemia. J. Hum. Genet. 50 (4), 203–209.

Goldsmith, D.R., Rapaport, M.H., Miller, B.J., 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol. Psychiatry 21 (12), 1696–1709 (doi: 101038/mp20163).

Green, T.A., Alibhai, I.N., Unterberg, S., Neve, R.L., Ghose, S., Tamminga, C.A., et al., 2008. Induction of activating transcription factors (ATFs) ATF2, ATF3, and ATF4 in the nucleus accumbens and their regulation of emotional behavior. J. Neurosci. 28 (9), 2025–2032.

GTEx Consortium, 2013. The genotype-tissue expression (GTEx) project. Nat. Genet. 45 (6), 580–585.

Guh, D.P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C.L., Anis, A.H., 2009. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 9, 88.

Hirase, T., Hara, H., Miyazaki, Y., Ide, N., Nishimoto-Hazuku, A., Fujimoto, H., et al., 2013. Interleukin 27 inhibits atherosclerosis via immunoregulation of macrophages in mice. Am. J. Physiol. Heart Circ. Physiol. 305 (3), H420–H429.

Holt, R.I., Mitchell, A.J., 2015. Diabetes mellitus and severe mental illness: mechanisms and clinical implications. Nat. Rev. Endocrinol. 11 (2), 79–89.

Huang, J., Imamura, T., Olefsky, J.M., 2001. Insulin can regulate GLUT4 internalization by signaling to Rab5 and the motor protein dynein. Proc. Natl. Acad. Sci. U. S. A. 98 (23), 13084–13089.

Jin, W., Zhao, Y., Yan, W., Cao, L., Zhang, W., Wang, M., et al., 2012. Elevated circulating interleukin-27 in patients with coronary artery disease is associated with dendritic cells, oxidized low-density lipoprotein, and severity of coronary artery stenosis. Mediat. Inflamm. 2012, 506283.

Kessing, L.V., Thomsen, A.F., Mogensen, U.B., Andersen, P.K., 2010. Treatment with antipsychotics and the risk of diabetes in clinical practice. Br. J. Psychiatry J. Ment. Sci. 197 (4), 266–271.

Khasawneh, F.T., Shankar, G.S., 2014. Minimizing cardiovascular adverse effects of atypical antipsychotic drugs in patients with schizophrenia. Cardiol. Res. Pract. 2014, 273060.

Kilpelainen TO, Zillikens, M.C., Stancakova, A., Finucane, F.M., Ried, J.S., Langenberg, C., et al., 2011. Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. Nat. Genet. 43 (8), 753–760.

Kreisberg, J.I., Radnik, R.A., Ayo, S.H., Garoni, J., Saikumar, P., 1994. High glucose elevates c-fos and c-jun transcripts and proteins in mesangial cell cultures. Kidney Int. 46 (1), 105–112.

Laifenfeld, D., Karry, R., Grauer, E., Klein, E., Ben-Shachar, D., 2004. ATF2, a member of the CREB/ATF family of transcription factors, in chronic stress and consequent to

antidepressant treatment: animal models and human post-mortem brains. Neuropsychopharmacol: Off. Publ. Am. Coll. Neuropsychopharmacol. 29 (3), 589–597.
Laursen, T.M., Munk-Olsen, T., Vestergaard, M., 2012. Life expectancy and cardiovascular mortality in persons with schizophrenia. Curr. Opin. Psychiatry 25 (2), 83–88.
Lett, T.A., Wallace, T.J., Chowdhury, N.I., Tiwari, A.K., Kennedy, J.L., Muller, D.J., 2012. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. Mol. Psychiatry 17 (3), 242–266.
Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., et al., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382 (9896), 951–962.
Locke, A.E., Kahali, B., Berndt, S.I., Justice, A.E., Pers, T.H., Day, F.R., et al., 2015. Genetic studies of body mass index yield new insights for obesity biology. Nature 518 (7538), 197–206.
Lopresti, A.L., Drummond, P.D., 2013. Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 45, 92–99.
Lu, Y., Day, F.R., Gustafsson, S., Buchkovich, M.L., Na, J., Bataille, V., et al., 2016. New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk. Nat. Commun. 7, 10495.
Maes, H.H., Neale, M.C., Eaves, L.J., 1997. Genetic and environmental factors in relative body weight and human adiposity. Behav. Genet. 27 (4), 325–351.
Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium, 2015Network and Pathway Analysis Subgroup of Psychiatric Genomi. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. Nat. Neurosci. 18 (2), 199–209.
Newcomer, J.W., 2007. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. J. Clin. Psychiatry 68 (Suppl. 1), 20–27.
Qi, L., Cho, Y.A., 2008. Gene-environment interaction and obesity. Nutr. Rev. 66 (12), 684–694.
Quteineh, L., Vandenberghe, F., Saigi Morgui, N., Delacretaz, A., Choong, E., Gholam-Rezaee, M., et al., 2015. Impact of HSD11B1 polymorphisms on BMI and components of the metabolic syndrome in patients receiving psychotropic treatments. Pharmacogenet. Genomics 25 (5), 246–258.
Ren, D., Zhou, Y., Morris, D., Li, M., Li, Z., Rui, L., 2007. Neuronal SH2B1 is essential for controlling energy and glucose homeostasis. J. Clin. Invest. 117 (2), 397–406.
Rui, L., 2014. SH2B1 regulation of energy balance, body weight, and glucose metabolism. World J. Diabetes 5 (4), 511–526.
Ryu, S., Cho, E.Y., Park, T., Oh, S., Jang, W.S., Kim, S.K., et al., 2007. 759 C/T polymorphism of 5-HT2C receptor gene and early phase weight gain associated with antipsychotic drug treatment. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 31 (3), 673–677.
Saigi-Morgui, N., Vandenberghe, F., Delacretaz, A., Quteineh, L., Choong, E., Gholamrezaee, M., et al., 2015. Association of PCK1 with body mass index and other metabolic features in patients with psychotropic treatments. J. Clin. Psychopharmacol. 35 (5), 544–552.
Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014Schizophrenia Working Group of the Psychiatric Genomics Con. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511 (7510), 421–427.
Sernyak, M.J., Leslie, D.L., Alarcon, R.D., Losonczy, M.F., Rosenheck, R., 2002. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am. J. Psychiatry 159 (4), 561–566.
Sheng, L., Liu, Y., Jiang, L., Chen, Z., Zhou, Y., Cho, K.W., et al., 2013. Hepatic SH2B1 and SH2B2 regulate liver lipid metabolism and VLDL secretion in mice. PLoS One 8 (12), e83269.
Stahl, S.M., 2008. Stahl's Essential Psychopharmacology - Neuroscientific Basis and Practical Applications. Cambridge University Press, New York, pp. 1–1057.
Tessneer, K.L., Jackson, R.M., Griesel, B.A., Olson, A.L., 2014. Rab5 activity regulates GLUT4 sorting into insulin-responsive and non-insulin-responsive endosomal compartments: a potential mechanism for development of insulin resistance. Endocrinology 155 (9), 3315–3328.
Third Report of the National Cholesterol Education Program (NCEP), 2002Third Report of the National Cholesterol Education Program. Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. Circulation 106 (25), 3143–3421.
Vandenberghe, F., Gholam-Rezaee, M., Saigi-Morgui, N., Delacretaz, A., Choong, E., Solida-Tozzi, A., et al., 2015. Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment. J. Clin. Psychiatry 76 (11), e1417–e1423.
Visscher, P.M., Brown, M.A., McCarthy, M.I., Yang, J., 2012. Five years of GWAS discovery. Am. J. Hum. Genet. 90 (1), 7–24.
Voight, B.F., Kang, H.M., Ding, J., Palmer, C.D., Sidore, C., Chines, P.S., et al., 2012. The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. PLoS Genet. 8 (8), e1002793.
Voisin, S., Almen, M.S., Zheleznyakova, G.Y., Lundberg, L., Zarei, S., Castillo, S., et al., 2015. Many obesity-associated SNPs strongly associate with DNA methylation changes at proximal promoters and enhancers. Genome Med. 7 (1), 103.
Yamauchi, T., Oike, Y., Kamon, J., Waki, H., Komeda, K., Tsuchida, A., et al., 2002. Increased insulin sensitivity despite lipodystrophy in Crebbp heterozygous mice. Nat. Genet. 30 (2), 221–226.
Yang, R., Trevillyan, J.M., 2008. c-Jun N-terminal kinase pathways in diabetes. Int. J. Biochem. Cell Biol. 40 (12), 2702–2706.
Zaitlen, N., Kraft, P., Patterson, N., Pasaniuc, B., Bhatia, G., Pollack, S., et al., 2013. Using extended genealogy to estimate components of heritability for 23 quantitative and dichotomous traits. PLoS Genet. 9 (5), e1003520.
Zeigerer, A., Bogorad, R.L., Sharma, K., Gilleron, J., Seifert, S., Sales, S., et al., 2015. Regulation of liver metabolism by the endosomal GTPase Rab5. Cell Rep. 11 (6), 884–892.

S1 Table. Lipid-lowering drugs, antidiabetic drugs and antihypertensive drugs considered to characterize dyslipidemia, type 2 diabetes and/or hypertension.

Lipid-lowering drugs	Antidiabetic drugs	Antihypertensive drugs
Atorvastatin	Desmopressin	Aliskiren
Ezetimibe	Glibenclamid	Amiloride hydrochlorothiazide
Fenofibrate	Gliclazide	Amlodipin
Fluvastatin	Glimepiride	Atenolol
Pravastatin	Insulin	Bisoprolol
Rosuvastatin	Metformin	Bosentan
Simvastatin	Pioglitazone	Candesartan
	Rosiglitazone	Captopril
	Sitagliptin	Carvedilol
	Vildagliptin	Celiprolol
		Dilitiazem
		Enalapril
		Eplerenone
		Felodipine
		Furosemide
		Hydrochlorothiazide
		Irbesartan
		Lercanidipine
		Lisinopril
		Losartan
		Metolazone
		Metoprolol
		Midodrine
		Molsidomine
		Nebivolol
		Nifedipine
		Nitroglycerin
		Olmesartan
		Perindopril
		Propranolol
		Ramipril
		Spironolactone
		Telmisartan
		Torasemide
		Trandolapril
		Valsartan
		Verapamil

The list was extracted from (1)

S2 Table. Characteristics of psychiatric samples: discovery and replication samples

Characteristics	Discovery sample		Replication sample		p-value[7]
	n	median (range)	n	median (range)	
Male (%)	356	156 (43.8)	140	58 (41.4)	0.63
Age, years	356	47 (12-96)	140	52 (15-97)	**0.04**
Medication, n(%)	356		140		0.74
Amisulpride		28 (7.9)		13 (9.3)	
Aripiprazole		32 (9)		10 (7.2)	
Clozapine		25 (7.0)		11 (7.9)	
Lithium		31 (8.6)		8 (5.7)	
Mirtazapine		15 (4.2)		8 (5.7)	
Olanzapine		41 (11.5)		12 (8.6)	
Quetiapine		115 (32.4)		47 (33.8)	
Risperidone		52(14.6)		26 (18.7)	
Valproate		17 (4.8)		4 (2.9)	
Main diagnosis, n(%)	269		90		0.42
Organic mental disorders		10 (3.7)		8 (8.9)	
Psychotic disorders		107 (39.8)		25 (27.8)	
Schizoaffective disorders		21 (7.8)		10 (11.1)	
Bipolar disorders		65 (24.2)		21 (23.3)	
Depressive disorder		66 (24.5)		26 (28.9)	
Treatment duration, months	356	3 (1-12)	140	3 (1-12)	0.63
Treatment duration[1]: 0					
Total cholesterol, *mmol/l*	355	4.6 (2.1-8.4)			
Hypercholesterolemia (≥ 5 *mmol/l)*, n(%) [2]		166 (46.8)			
High-density lipoprotein, *mmol/l*	348	1.4 (0.6-3.3)			
Hypocholesterolemia (≤ 1 *mmol/l)*, n(%) [2]		77 (22.1)			
Low-density lipoprotein, *mmol/l*	338	2.6 (0.6-6.1)			
Hypercholesterolemia (≥ 3 *mmol/l)*, n(%) [2]		148 (43.8)			
Triglycerides, *mmol/l* [3]	279	1.1 (0.4-8.5)			
Hypertriglyceridemia (≥ 2 *mmol/l)*, n(%) [2,3]		51 (18.3)			
Glucose, *mmol/l*	272	5.1 (3.5-10.3)			
Hyperglycemia (≥ 5.6 *mmol/l)*, n(%) [4]		71 (26.1)			
Body mass index, *kg/m²*	343	23.0 (13.3-42.5)			
Obesity (≥30 *kg/m²)*, n(%)		45 (13.1)			
Waist circumference, *cm*	310	86 (54-136)			
Obesity in women (≥80 *cm)* ,n(%) [5]		112 (64)			
Obesity in men (≥94 *cm)* ,n(%) [5]		52 (38.5)			
Systolic blood pressure, *mm Hg*	320	123 (70-214)			
Hypertension (≥140 *mm Hg)* ,n(%) [6]		102 (31.9)			
Diastolic blood pressure, *mm Hg*	320	75 (47-150)			
Hypertension (≥90 *mm Hg)* ,n(%) [6]		90 (28.1)			

Treatment duration[1]: 1					
Total cholesterol, *mmol/l*	207	4.8 (2.4-8.6)	86	5.1 (2.8-7.7)	0.21
Hypercholesterolemia (≥ 5 *mmol/l)*, n(%) [2]		109 (52.7)		54 (62.8)	0.11
High-density lipoprotein, *mmol/l*	206	1.4 (0.6-3.2)	87	1.4 (0.7-2.8)	0.19
Hypocholesterolemia (≤ 1 *mmol/l)*, n(%) [2]		55 (26.7)		20 (23.0)	0.5
Low-density lipoprotein, *mmol/l*	199	2.8 (0.5-6.3)	81	3.0 (0.8-5.3)	0.25
Hypercholesterolemia (≥ 3 *mmol/l)*, n(%) [2]		96 (48.2)		47 (58)	0.13
Triglycerides, *mmol/l* [3]	177	1.1 (0.3-6.5)	65	1.2 (0.4-4.6)	0.68
Hypertriglyceridemia (≥ 2 *mmol/l)*, n(%) [2,3]		41 (23.1)		18 (27.7)	0.46
Glucose, *mmol/l*	115	4.9 (2.9-18.7)	44	5.0 (4.1-20.8)	0.06
Hyperglycemia (≥ 5.6 *mmol/l)*, n(%) [4]		20 (17.4)		11 (25.0)	0.28
Body mass index, *kg/m²*	200	23.6 (13.4-43.5)	77	24.3 (14.7-40.6)	0.57
Obesity (≥30 *kg/m²)*, n(%)		27 (13.5)		14 (18.2)	0.32
Waist circumference, *cm*	187	88 (62-142)	69	88 (58-126)	0.47
Obesity in women (≥80 *cm)* ,n(%) [5]		65 (67)		29 (70.7)	0.67
Obesity in men (≥94 *cm)* ,n(%) [5]		33 (36.7)		28 (46.4)	0.35
Systolic blood pressure, *mm Hg*	38	119.5 (98-155)	20	122 (100-170)	0.47
Hypertension (≥140 *mm Hg)* ,n(%) [6]		8 (21)		7 (35)	0.25
Diastolic blood pressure, *mm Hg*	38	75.5 (54-103)	20	75 (60-115)	0.92
Hypertension (≥90 *mm Hg)* ,n(%) [6]		9 (23.7)		7 (35)	0.36
Treatment duration[1]: 2					
Total cholesterol, *mmol/l*	233	4.9 (2.1-8.9)	103	5 (2.7-8.6)	0.29
Hypercholesterolemia (≥ 5 *mmol/l)*, n(%) [2]		134 (57.5)		58 (56.3)	0.84
High-density lipoprotein, *mmol/l*	232	1.3 (0.6-2.8)	103	1.4 (0.6-2.7)	0.53
Hypocholesterolemia (≤ 1 *mmol/l)*, n(%) [2]		61 (26.3)		24 (23.3)	0.56
Low-density lipoprotein, *mmol/l*	219	2.8 (0.6-6)	99	3 (1.4-6.2)	0.19
Hypercholesterolemia (≥ 3 *mmol/l)*, n(%) [2]		114 (52)		55 (55.5)	0.56
Triglycerides, *mmol/l* [3]	178	1.2 (0.3-6.8)	73	1.2 (0.4-4.1)	0.74
Hypertriglyceridemia (≥ 2 *mmol/l)*, n(%) [2,3]		45 (25.3)		19 (26)	0.9
Glucose, *mmol/l*	147	4.9 (3.5-7.9)	69	5.1 (2.7-11.2)	0.32
Hyperglycemia (≥ 5.6 *mmol/l)*, n(%) [4]		29 (19.7)		13 (18.8)	0.88
Body mass index, *kg/m²*	229	23.7 (16.1-44.1)	98	25.5 (14.3-50.2)	**0.04**
Obesity (≥30 *kg/m²)*, n(%)		36 (15.7)		29 (29.6)	**0.004**
Waist circumference, *cm*	201	91 (67-147)	95	95 (66-162)	**0.03**
Obesity in women (≥80 *cm)* ,n(%) [5]		77 (78.6)		42 (77.8)	0.91
Obesity in men (≥94 *cm)* ,n(%) [5]		51 (49.5)		26 63.4)	0.13
Systolic blood pressure, *mm Hg*	145	120 (85-180)	76	120 (84-162)	0.77
Hypertension (≥140 *mm Hg)* ,n(%) [6]		27 (18.6)		18 (23.7)	0.37
Diastolic blood pressure, *mm Hg*	144	76 (48-120)	76	77.5 (56-110)	0.36

Hypertension (≥90 *mm Hg)* ,n(%) [6]		34 (23.6)		22 (28.9)	0.38
Treatment duration[1]: 3					
Total cholesterol, *mmol/l*	166	5.1 (2.3-8.7)	73	5.2 (3.3-8.2)	0.25
Hypercholesterolemia (≥ 5 *mmol/l)*, n(%) [2]		103 (62)		50 (68.5)	0.34
High-density lipoprotein, *mmol/l*	161	1.3 (0.6-2.7)	71	1.3 (0.7-4.8)	0.29
Hypocholesterolemia (≤ 1 *mmol/l)*, n(%) [2]		47 (29.2)		17 (23.9)	0.41
Low-density lipoprotein, *mmol/l*	147	3 (0.7-6)	69	3.1 (0.6-6.4)	0.75
Hypercholesterolemia (≥ 3 *mmol/l)*, n(%) [2]		85 (57.8)		39 (56.5)	0.86
Triglycerides, *mmol/l* [3]	125	1.2 (0.3-6.1)	56	1.2 (0.5-3.7)	0.69
Hypertriglyceridemia (≥ 2 *mmol/l)*, n(%) [2,3]		32 (25.6)		16 (28.6)	0.67
Glucose, *mmol/l*	122	5.2 (3.1-7.6)	54	5.2 (3.1-13.6)	0.9
Hyperglycemia (≥ 5.6 *mmol/l)*, n(%) [4]		33 (27.1)		15 (27.8)	0.92
Body mass index, *kg/m²*	160	24.9 (15.2-47.2)	62	25.5 (15.3-41.2)	0.77
Obesity (≥30 *kg/m²)*, n(%)		34 (21.2)		15 (24.2)	0.63
Waist circumference, *cm*	150	92 (64-155)	61	92 (48-137)	0.46
Obesity in women (≥80 *cm)* ,n(%) [5]		58 (71.6)		21 (65.6)	0.53
Obesity in men (≥94 *cm)* ,n(%) [5]		39 (56.5)		18 (62.1)	0.61
Systolic blood pressure, *mm Hg*	135	120 (91-182)	63	120 (88-177)	0.76
Hypertension (≥140 *mm Hg)* ,n(%) [6]		32 (23.7)		16 (25.4)	0.79
Diastolic blood pressure, *mm Hg*	135	76 (50-113)	63	77 (58-106)	0.5
Hypertension (≥90 *mm Hg)* ,n(%) [6]		35 (25.9)		18 (28.6)	0.69

[1] Treatment duration: period of the current psychotropic treatment. This variable was categorized into four categories according to the number of days of psychotropic treatment as follow: 0: 0 days i.e baseline before the prescription of the studied drug; 1: from ≥10 to <45 days; 2: from ≥45 to <135 days; 3: from ≥135 to <535 days.

[2] Lipid levels thresholds were defined according to ESH/ESC guidelines(2). Patients with treated dyslipidemia (S2 Table) were also included in the abnormal lipid levels category.

[3] Triglyceride levels were collected in fasting conditions.

[4] Threshold for fasting glucose levels (≥5.6 mmol/l) was defined according to IDF definition(3). Patients with treated diabetes (S2 Table) were also included in the abnormal glucose levels category.

[5] Waist circumference thresholds (≥80 cm for women and ≥94 cm for men) were defined according to IDF definition(3).

[6] Hypertension thresholds (≥140 mm Hg for systolic blood pressure and ≥ 90 mm Hg for diastolic blood pressure) were defined according to ESH/ESC guidelines(2). Patients with treated hypertension (S2 Table) were also included in the abnormal hypertension category.

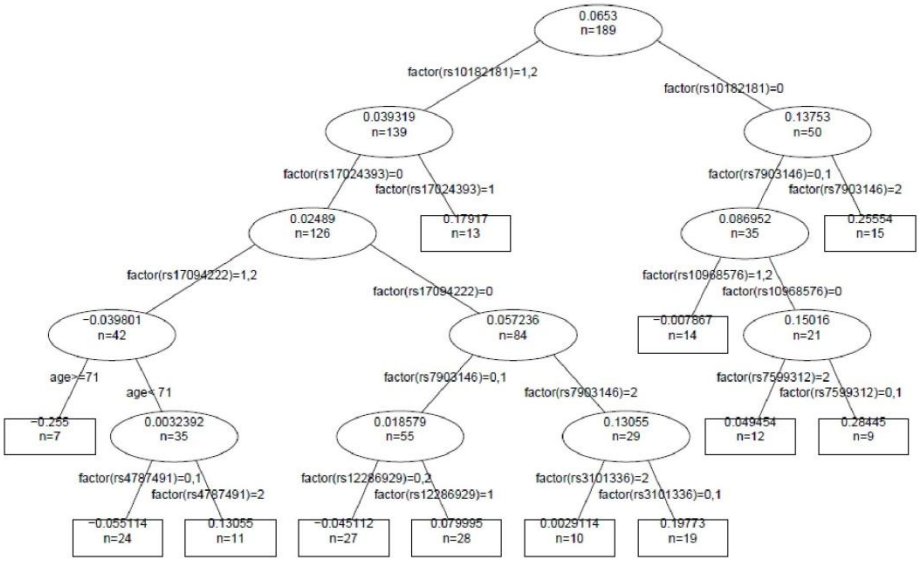
[7] P values were calculated using Wilcoxon-Mann-Whitney tests or Chi2 tests between the two psychiatric samples. Values in bold are significant.

Abbreviations: IDF: International Diabetes Federation.ESH/ESC: European Society of Hypertension/European Society of Cardiology.

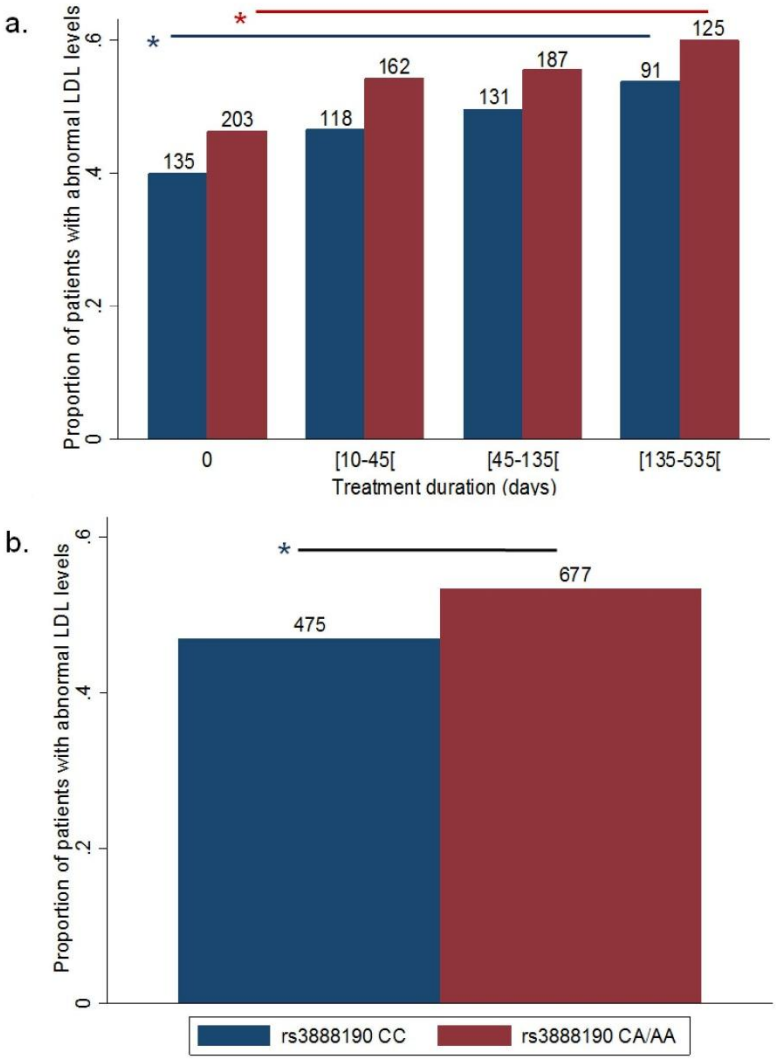
S3 Table. Genotype frequencies in two Caucasian psychiatric samples.

Psychiatric sample	Total (n)	n (%)			HWE	MAF	MAF Hap Map CEU
***SH2B1* rs3888190 C>A**		**CC**	**CA**	**AA**			**0.36**
Discovery sample	356	143 (40.3)	171 (47.9)	42 (11.7)	0.39	0.36	
Replication sample	140	66 (47.14)	57 (40.71)	17 (12.14)	0.39	0.32	
***RABEP1* rs1000940A>G**		**AA**	**AG**	**GG**			**0.35**
Discovery sample	356	185 (51.9)	141 (39.6)	30 (8.4)	0.67	0.28	
Replication sample	140	67 (48.2)	59 (42.4)	13 (9.3)	0.93	0.30	

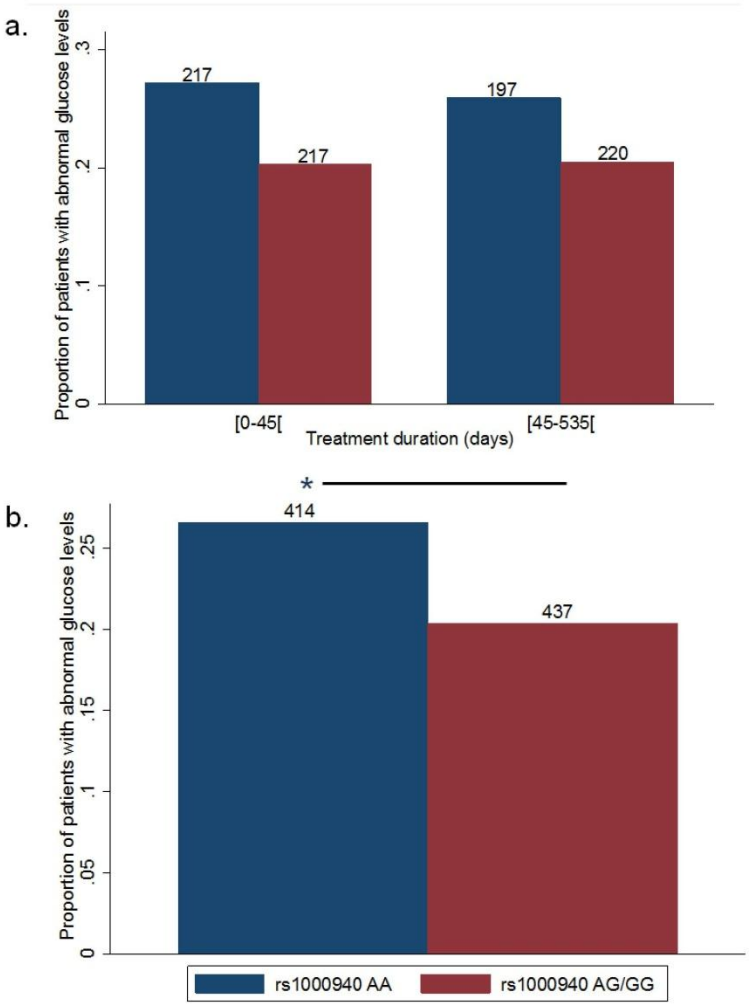
Deviation from Hardy Weinberg Equilibrium (HWE) and minor allele frequencies (MAF) observed in our samples and referred in HapMap are indicated.



S1 Fig. Tree structure of the classification and regression tree (CART) analysis for the evolution of TC levels within the first category of psychotropic treatment duration (i.e from 10 to 45 days of treatment). Each node indicates the mean of TC difference (within the current psychotropic treatment duration) and the number of observations.



S2 Fig. a. Evolution of the proportion of patients with abnormal LDL values (≥3mmol/l or prescription of a lipid-lowering medication) during psychotropic treatment according to rs3888190C>A genotype. b. Overall proportion of patients with abnormal LDL values (≥3mmol/l or prescription of a lipid-lowering medication) according to rs3888190C>A genotype. Numbers of observations are indicated above each category. *:p-value of Chi^2 test≤0.05.



S3 Fig. a. Evolution of the proportion of patients with abnormal fasting glucose values (≥5.6mmol/l or prescription of an antidiabetic medication) during psychotropic treatment according to rs1000940A>G genotype. The first two periods, as well as the last two periods of psychotropic treatment were pooled together for statistical power purposes. b. Overall proportion of patients with abnormal fasting glucose values (≥5.6mmol/l or prescription of an antidiabetic medication) according to rs1000940A>G genotype.
Numbers of observations are indicated above each category. *:p-value of Chi^2 test≤0.05.

TISSUE	CDC37P1			EIF3C			EIF3CL			SH2B1			SULT1A2			TUFM			IL27		
	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β
Adipose - Subcutaneous	rs3888190	2.00E-23	0.78	rs3888190	0.0000023	0.32	rs3888190	7.80E-10	0.39	rs3888190	7.70E-11	-0.2	rs3888190	1.10E-16	0.53	rs3888190	2.00E-10	0.31			
	rs62037371	1.90E-24	0.8	rs62037371	0.0000015	0.32	rs62037371	3.20E-10	0.4	rs62037371	4.20E-11	-0.2	rs62037371	3.10E-17	0.54	rs62037371	3.70E-10	0.31			
	rs8055138	1.60E-24	0.8	rs8055138	0.0000015	0.32	rs8055138	3.00E-10	0.4	rs8055138	4.30E-11	-0.2	rs8055138	2.90E-17	0.54	rs8055138	4.00E-10	0.31			
	rs7498555	6.70E-21	0.77	rs7498555	1.60E-07	0.36	rs7498555	1.30E-11	0.44	rs7498555	1.40E-09	-0.19	rs7498555	1.20E-17	0.57	rs7498555	1.00E-10	0.33			
	rs8061590	1.50E-24	0.81	rs8061590	7.80E-07	0.33	rs8061590	5.20E-11	0.42	rs8061590	1.20E-10	-0.2	rs8061590	1.70E-16	0.54	rs8061590	1.40E-09	0.3			
	rs62037369	1.10E-20	0.76	rs62037369	1.50E-07	0.36	rs62037369	1.90E-11	0.44	rs62037369	1.10E-09	-0.19	rs62037369	1.70E-17	0.56	rs62037369	5.50E-11	0.33			
	rs7498665	1.90E-24	0.8	rs7498665	0.0000015	0.32	rs7498665	3.20E-10	0.4	rs7498665	4.20E-11	-0.2	rs7498665	3.10E-17	0.54	rs7498665	3.70E-10	0.31			
	rs8055982	1.90E-24	0.8	rs8055982	0.0000015	0.32	rs8055982	3.20E-10	0.4	rs8055982	4.20E-11	-0.2	rs8055982	3.10E-17	0.54	rs8055982	3.70E-10	0.31			
	rs7198606	1.90E-24	0.8	rs7198606	0.0000015	0.32	rs7198606	3.20E-10	0.4	rs7198606	4.20E-11	-0.2	rs7198606	3.10E-17	0.54	rs7198606	3.70E-10	0.31			
	rs62037367	1.90E-24	0.8	rs62037367	0.0000015	0.32	rs62037367	3.20E-10	0.4	rs62037367	4.20E-11	-0.2	rs62037367	3.10E-17	0.54	rs62037367	3.70E-10	0.31			
	rs4788102	1.10E-23	0.79	rs4788102	0.0000012	0.33	rs4788102	2.00E-10	0.41	rs4788102	6.70E-11	-0.2	rs4788102	1.50E-17	0.55	rs4788102	4.00E-10	0.31			
	rs11861174	1.90E-24	0.8	rs11861174	0.0000015	0.32	rs11861174	3.20E-10	0.4	rs11861174	4.20E-11	-0.2	rs11861174	3.10E-17	0.54	rs11861174	3.70E-10	0.31			
	rs12446589	1.50E-21	0.77	rs12446589	1.10E-07	0.36	rs12446589	2.80E-11	0.43	rs12446589	1.90E-09	-0.19	rs12446589	1.50E-17	0.56	rs12446589	1.40E-10	0.32			
	rs62037365	1.90E-24	0.8	rs62037365	0.0000015	0.32	rs62037365	3.20E-10	0.4	rs62037365	4.20E-11	-0.2	rs62037365	3.10E-17	0.54	rs62037365	3.70E-10	0.31			
	rs62037364	8.90E-24	0.79	rs62037364	0.0000013	0.33	rs62037364	4.50E-10	0.4	rs62037364	1.80E-10	-0.19	rs62037364	5.40E-17	0.54	rs62037364	5.00E-10	0.31			
	rs4788101	1.90E-24	0.8	rs4788101	0.0000015	0.32	rs4788101	3.20E-10	0.4	rs4788101	4.20E-11	-0.2	rs4788101	3.10E-17	0.54	rs4788101	3.70E-10	0.31			
	rs7205323	1.30E-24	0.8	rs7205323	0.0000012	0.33	rs7205323	2.30E-10	0.4	rs7205323	3.30E-11	-0.2	rs7205323	8.60E-17	0.54	rs7205323	7.10E-10	0.3			
	rs80275162	1.50E-24	0.81	rs80275162	0.0000071	0.31	rs80275162	3.00E-09	0.39	rs80275162	6.10E-11	-0.2	rs80275162	2.50E-16	0.54	rs80275162	4.00E-10	0.31			
	rs9972693	1.90E-24	0.8	rs9972693	0.0000015	0.32	rs9972693	3.20E-10	0.4	rs9972693	4.20E-11	-0.2	rs9972693	3.10E-17	0.54	rs9972693	3.70E-10	0.31			
	rs7187776	1.60E-17	0.66	rs4788099	0.0000015	0.32	rs7187776	2.40E-08	0.34	rs7187776	2.10E-08	-0.17	rs7187776	6.80E-15	0.49	rs7187776	9.40E-16	0.37			
	rs4788099	1.90E-24	0.8	rs61737565	0.0000015	0.32	rs4788099	3.20E-10	0.4	rs4788099	4.20E-11	-0.2	rs4788099	3.10E-17	0.54	rs4788099	3.70E-10	0.31			
	rs61737565	1.90E-24	0.8	rs28403629	0.0000015	0.32	rs61737565	3.20E-10	0.4	rs61737565	4.20E-11	-0.2	rs61737565	3.10E-17	0.54	rs61737565	3.70E-10	0.31			
	rs28403629	1.90E-24	0.8	rs3088215	0.0000015	0.32	rs28403629	3.20E-10	0.4	rs28403629	4.20E-11	-0.2	rs28403629	3.10E-17	0.54	rs28403629	3.70E-10	0.31			
	rs3088215	1.90E-24	0.8	rs12325113	1.50E-07	0.36	rs3088215	3.20E-10	0.4	rs3088215	4.20E-11	-0.2	rs3088215	3.10E-17	0.54	rs3088215	3.70E-10	0.31			
	rs12325113	1.10E-20	0.76	rs55830740	0.0000015	0.32	rs12325113	1.90E-11	0.44	rs12325113	1.10E-09	-0.19	rs12325113	1.70E-17	0.56	rs12325113	5.50E-11	0.33			
	rs55830740	1.90E-24	0.8	rs55719896	0.0000015	0.32	rs55830740	3.20E-10	0.4	rs55830740	4.20E-11	-0.2	rs55830740	3.10E-17	0.54	rs55830740	3.70E-10	0.31			
	rs55719896	1.90E-24	0.8	rs56404918	0.0000015	0.32	rs55719896	3.20E-10	0.4	rs55719896	4.20E-11	-0.2	rs55719896	3.10E-17	0.54	rs55719896	3.70E-10	0.31			
	rs56404918	1.90E-24	0.8	rs12444171	0.0000015	0.32	rs56404918	3.20E-10	0.4	rs56404918	4.20E-11	-0.2	rs56404918	3.10E-17	0.54	rs56404918	3.70E-10	0.31			
	rs12444171	1.90E-24	0.8	rs62036657	0.0000015	0.32	rs12444171	3.20E-10	0.4	rs12444171	4.20E-11	-0.2	rs12444171	3.10E-17	0.54	rs12444171	3.70E-10	0.31			
	rs62036657	1.90E-24	0.8	rs62036626	0.0000015	0.32	rs62036657	3.20E-10	0.4	rs62036657	4.20E-11	-0.2	rs62036657	3.10E-17	0.54	rs62036657	3.70E-10	0.31			
	rs62036626	1.90E-24	0.8	rs56358680	0.0000015	0.32	rs62036626	3.20E-10	0.4	rs62036626	4.20E-11	-0.2	rs62036626	3.10E-17	0.54	rs62036626	3.70E-10	0.31			
	rs56358680	1.90E-24	0.8	rs55991577	0.0000015	0.32	rs56358680	3.20E-10	0.4	rs56358680	4.20E-11	-0.2	rs56358680	3.10E-17	0.54	rs56358680	3.70E-10	0.31			
	rs55991577	1.90E-24	0.8	rs12443881	1.60E-07	0.36	rs55991577	3.20E-10	0.4	rs55991577	4.20E-11	-0.2	rs55991577	3.10E-17	0.54	rs55991577	3.70E-10	0.31			
	rs12443881	5.00E-21	0.77	rs72793812	1.40E-07	0.36	rs12443881	2.30E-11	0.44	rs12443881	9.00E-10	-0.19	rs12443881	2.30E-17	0.56	rs12443881	5.10E-11	0.33			
	rs72793812	7.30E-21	0.77	rs62036624	0.0000014	0.33	rs72793812	1.80E-11	0.44	rs72793812	1.20E-09	-0.19	rs72793812	2.00E-17	0.56	rs72793812	5.90E-11	0.33			
	rs62036624	2.70E-24	0.8	rs72793811	1.50E-07	0.36	rs62036624	2.80E-10	0.4	rs62036624	4.60E-11	-0.2	rs62036624	2.40E-17	0.55	rs62036624	3.70E-10	0.31			
	rs72793811	1.10E-20	0.76	rs8062405	0.0000012	0.33	rs72793811	1.90E-11	0.44	rs72793811	1.10E-09	-0.19	rs72793811	1.70E-17	0.56	rs72793811	5.50E-11	0.33			
	rs8062405	8.80E-24	0.79	rs62036622	7.50E-08	0.37	rs8062405	2.20E-10	0.4	rs8062405	6.50E-11	-0.2	rs8062405	2.80E-17	0.54	rs8062405	1.10E-10	0.32			
	rs62036622	1.40E-21	0.78	rs4451951	0.0000012	0.32	rs62036622	6.70E-12	0.45	rs62036622	9.80E-10	-0.19	rs62036622	1.00E-17	0.57	rs62036622	1.30E-10	0.33			
	rs4451951	3.70E-26	0.8	rs62036621	8.20E-07	0.33	rs4451951	1.40E-10	0.4	rs4451951	4.50E-12	-0.2	rs4451951	6.70E-17	0.52	rs4451951	6.30E-10	0.3			
	rs62036621	1.80E-25	0.81	rs62036620	8.20E-07	0.33	rs62036621	1.30E-10	0.41	rs62036621	3.60E-11	-0.2	rs62036621	1.90E-17	0.55	rs62036621	8.20E-10	0.3			
	rs62036620	1.80E-25	0.81	rs4788095	8.20E-07	0.33	rs62036620	1.30E-10	0.41	rs62036620	3.60E-11	-0.2	rs62036620	1.90E-17	0.55	rs62036620	8.20E-10	0.3			
	rs4788095	1.80E-25	0.81	rs62036617	8.20E-07	0.33	rs4788095	1.30E-10	0.41	rs4788095	3.60E-11	-0.2	rs4788095	1.90E-17	0.55	rs4788095	8.20E-10	0.3			
	rs62036617	1.90E-25	0.81	rs62036616	3.30E-08	0.38	rs62036617	1.30E-10	0.41	rs62036617	3.60E-11	-0.2	rs62036617	1.90E-17	0.55	rs62036617	7.80E-10	0.3			
	rs62036616	3.10E-22	0.79	rs1987472	8.20E-07	0.33	rs62036616	2.10E-12	0.46	rs62036616	8.90E-10	-0.19	rs62036616	5.10E-17	0.56	rs62036616	1.30E-10	0.33			
	rs1987472	1.90E-25	0.81	rs2008514	8.20E-07	0.33	rs1987472	1.30E-10	0.41	rs1987472	3.60E-11	-0.2	rs1987472	1.90E-17	0.55	rs1987472	8.20E-10	0.3			
	rs2008514	1.80E-25	0.81	rs7359397	1.50E-07	0.36	rs2008514	1.30E-10	0.41	rs2008514	3.60E-11	-0.2	rs2008514	2.00E-17	0.55	rs2008514	8.20E-10	0.3			
	rs7359397	1.10E-20	0.76	rs62037363	0.0000012	0.33	rs7359397	1.90E-11	0.44	rs7359397	1.10E-09	-0.19	rs7359397	1.70E-17	0.56	rs7359397	5.50E-11	0.33			
	rs62037363	7.70E-25	0.8	rs56040780	0.0000015	0.32	rs62037363	2.20E-10	0.4	rs62037363	3.50E-11	-0.2	rs62037363	1.10E-16	0.53	rs62037363	7.40E-10	0.3			
	rs56040780	1.90E-24	0.8	rs11864107	0.0000018	0.32	rs56040780	3.20E-10	0.4	rs56040780	4.20E-11	-0.2	rs56040780	3.10E-17	0.54	rs56040780	3.60E-10	0.31			
	rs8049439	2.40E-18	0.67	rs7193733	0.0000015	0.32	rs8049439	9.60E-09	0.35	rs8049439	1.80E-08	-0.17	rs8049439	1.30E-15	0.5	rs8049439	2.10E-15	0.37			
	rs11864107	4.80E-24	0.79	rs12448902	3.30E-07	0.35	rs11864107	5.60E-10	0.39	rs11864107	1.40E-10	-0.19	rs11864107	1.60E-16	0.53	rs11864107	4.30E-10	0.31			
	rs7193733	4.40E-25	0.81	rs7187333	1.60E-07	0.36	rs7193733	2.70E-10	0.4	rs7193733	6.10E-11	-0.2	rs7193733	5.10E-18	0.55	rs7193733	8.40E-10	0.3			
	rs12448902	1.40E-20	0.76	rs9972768	0.0000015	0.32	rs12448902	1.10E-10	0.42	rs12448902	1.90E-09	-0.19	rs12448902	1.10E-16	0.55	rs12448902	2.00E-11	0.34			
	rs7187333	1.70E-21	0.77	rs78613234	0.0000014	0.33	rs7187333	2.40E-11	0.43	rs7187333	6.00E-10	-0.19	rs7187333	1.20E-16	0.55	rs7187333	1.10E-10	0.33			
	rs9972768	1.90E-24	0.8	rs72793809	8.20E-07	0.33	rs9972768	3.20E-10	0.4	rs9972768	4.20E-11	-0.2	rs9972768	3.10E-17	0.54	rs9972768	3.70E-10	0.31			
	rs78613234	2.50E-24	0.8	rs11860513	6.90E-07	0.33	rs78613234	2.90E-10	0.4	rs78613234	4.50E-11	-0.2	rs78613234	2.60E-17	0.54	rs78613234	3.70E-10	0.31			
	rs72793809	1.80E-25	0.81	rs62036614	2.20E-08	0.39	rs72793809	1.30E-10	0.41	rs72793809	3.60E-11	-0.2	rs72793809	1.90E-17	0.55	rs72793809	8.20E-10	0.3			
	rs11860513	4.60E-25	0.81	rs12928404	0.000014	0.27	rs11860513	1.20E-10	0.41	rs11860513	3.70E-11	-0.2	rs11860513	1.30E-17	0.55	rs11860513	5.30E-10	0.31			
	rs62036614	5.50E-22	0.79	rs11864750	0.000002	0.32	rs62036614	3.90E-12	0.46	rs62036614	1.70E-09	-0.19	rs62036614	2.50E-17	0.56	rs62036614	2.30E-10	0.33			
	rs12928404	4.70E-16	0.61	rs11150609	0.0000015	0.32	rs12928404	7.10E-09	0.35	rs12928404	1.40E-07	-0.15	rs12928404	4.90E-15	0.47	rs12928404	9.30E-15	0.35			
	rs11864750	7.00E-24	0.79	rs62036658	3.60E-07	0.35	rs11864750	3.30E-10	0.4	rs11864750	8.50E-11	-0.2	rs11864750	9.40E-17	0.54	rs11864750	1.20E-09	0.3			
	rs11150609	1.90E-24	0.8	rs56186137	8.20E-07	0.33	rs11150609	3.20E-10	0.4	rs11150609	4.20E-11	-0.2	rs11150609	3.10E-17	0.54	rs11150609	3.70E-10	0.31			
	rs62036658	4.00E-19	0.74				rs62036658	3.60E-11	0.44	rs62036658	2.60E-09	-0.19	rs62036658	3.50E-17	0.56	rs62036658	6.80E-10	0.32			
	rs56186137	1.90E-25	0.81				rs56186137	1.30E-10	0.41	rs56186137	3.60E-11	-0.2	rs56186137	1.90E-17	0.55	rs56186137	8.10E-10	0.3			
	rs7191618	3.80E-19	0.71				rs7191618	0.0000024	0.3	rs7191618	1.40E-08	-0.17	rs7191618	1.20E-24	0.63	rs7191618	4.60E-08	0.27			
	rs4788083	2.40E-19	0.72				rs4788083	0.0000022	0.31	rs4788083	2.70E-09	-0.18	rs4788083	1.80E-24	0.63	rs4788083	3.00E-08	0.28			
	rs4788084	5.90E-21	0.75				rs4788084	6.30E-07	0.33	rs4788084	2.30E-09	-0.18	rs4788084	3.00E-23	0.63	rs4788084	3.10E-09	0.3			
	rs62034326	7.60E-21	0.75				rs62034326	7.20E-07	0.32	rs62034326	2.60E-09	-0.18	rs62034326	3.50E-23	0.63	rs62034326	3.30E-09	0.3			
	rs62034324	6.40E-20	0.75				rs62034324	3.50E-07	0.34	rs62034324	3.10E-09	-0.19	rs62034324	1.00E-22	0.63	rs62034324	9.00E-09	0.29			
	rs28772958	1.00E-19	0.73				rs28772958	7.60E-07	0.32	rs28772958	4.40E-09	-0.18	rs28772958	5.00E-23	0.62	rs28772958	5.50E-08	0.27			
	rs4788085	1.00E-19	0.72				rs4788085	7.40E-07	0.32	rs4788085	4.80E-09	-0.18	rs4788085	4.90E-23	0.62	rs4788085	6.10E-08	0.27			
	rs28698667	7.50E-21	0.75				rs28698667	7.00E-07	0.32	rs28698667	2.50E-09	-0.18	rs28698667	3.20E-23	0.63	rs28698667	3.30E-09	0.3			
	rs62034319	1.60E-21	0.75				rs62034319	6.50E-07	0.32	rs62034319	8.10E-09	-0.18	rs62034319	4.10E-24	0.63	rs62034319	2.90E-08	0.28			
	rs240702	2.50E-21	0.75				rs240702	6.80E-07	0.32	rs240702	9.40E-09	-0.17	rs240702	1.30E-24	0.63	rs240702	5.00E-08	0.27			
	rs153106	5.00E-21	0.75				rs153106	7.20E-07	0.32	rs153106	1.00E-08	-0.18	rs153106	2.00E-25	0.65	rs153106	3.60E-08	0.27			
	rs7202948	4.50E-20	0.72				rs7202948	0.000001	0.31	rs7202948	1.70E-08	-0.17	rs7202948	9.40E-25	0.63	rs7202948	1.90E-08	0.28			

TISSUE	CDC37P1			EIF3C			EIF3CL			SH2B1			SULT1A2			TUFM			IL27		
	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β
Adipose - Visceral (Omentum)	rs3888190	1.10E-11	0.67							rs3888190	0.0000012	-0.15	rs3888190	8.50E-11	0.51	rs12928404	0.0000052	0.21			
	rs62037371	1.10E-11	0.67							rs62037371	0.0000012	-0.15	rs62037371	8.50E-11	0.51						
	rs8055138	1.10E-11	0.67							rs8055138	0.0000014	-0.15	rs8055138	9.90E-11	0.51						
	rs7498555	6.30E-07	0.54							rs8061590	0.0000041	-0.14	rs7498555	1.70E-10	0.53						
	rs8061590	4.30E-11	0.66							rs7498665	0.0000012	-0.15	rs8061590	3.60E-10	0.5						
	rs62037369	6.60E-07	0.53							rs8055982	0.0000012	-0.15	rs62037369	6.70E-11	0.54						
	rs7498665	1.10E-11	0.67							rs7198606	0.0000012	-0.15	rs7498665	8.50E-11	0.51						
	rs8055982	1.10E-11	0.67							rs62037367	0.0000012	-0.15	rs8055982	8.50E-11	0.51						
	rs7198606	1.10E-11	0.67							rs4788102	0.0000015	-0.14	rs7198606	8.50E-11	0.51						
	rs62037367	1.10E-11	0.67							rs11861174	0.0000012	-0.15	rs62037367	8.50E-11	0.51						
	rs4788102	8.10E-11	0.65							rs62037365	0.0000012	-0.15	rs4788102	1.00E-10	0.51						
	rs11861174	1.10E-11	0.67							rs62037364	0.0000019	-0.14	rs11861174	8.50E-11	0.51						
	rs12446589	1.10E-07	0.57							rs4788101	0.0000012	-0.15	rs12446589	5.40E-11	0.54						
	rs62037365	1.10E-11	0.67							rs7205323	0.0000012	-0.15	rs62037365	8.50E-11	0.51						
	rs62037364	1.60E-11	0.67							rs80275162	0.0000012	-0.15	rs62037364	1.10E-10	0.51						
	rs4788101	1.10E-11	0.67							rs9972693	0.0000012	-0.15	rs4788101	8.50E-11	0.51						
	rs7205323	1.20E-11	0.67							rs7187776	0.0000012	-0.15	rs7205323	8.40E-11	0.51						
	rs80275162	5.90E-10	0.63							rs4788099	0.0000012	-0.15	rs80275162	2.00E-11	0.53						
	rs9972693	1.10E-11	0.67							rs61737565	0.0000012	-0.15	rs9972693	8.50E-11	0.51						
	rs7187776	2.30E-09	0.6							rs28403629	0.0000012	-0.15	rs7187776	8.00E-11	0.51						
	rs4788099	1.10E-11	0.67							rs3088215	0.0000012	-0.15	rs4788099	8.50E-11	0.51						
	rs61737565	1.10E-11	0.67							rs55830740	0.0000012	-0.15	rs61737565	8.50E-11	0.51						
	rs28403629	1.10E-11	0.67							rs55719896	0.0000012	-0.15	rs28403629	8.50E-11	0.51						
	rs3088215	1.10E-11	0.67							rs56404918	0.0000012	-0.15	rs3088215	8.50E-11	0.51						
	rs12325113	6.60E-07	0.53							rs12444171	0.0000012	-0.15	rs12325113	7.00E-11	0.54						
	rs55830740	1.10E-11	0.67							rs62036657	0.0000012	-0.15	rs55830740	8.50E-11	0.51						
	rs55719896	1.10E-11	0.67							rs62036626	0.0000012	-0.15	rs55719896	8.50E-11	0.51						
	rs56404918	1.10E-11	0.67							rs56358680	0.0000012	-0.15	rs56404918	8.50E-11	0.51						
	rs12444171	1.10E-11	0.67							rs55991577	0.0000012	-0.15	rs12444171	8.50E-11	0.51						
	rs62036657	1.10E-11	0.67							rs62036624	0.0000012	-0.15	rs62036657	8.50E-11	0.51						
	rs62036626	1.10E-11	0.67							rs8062405	9.60E-07	-0.15	rs62036626	8.50E-11	0.51						
	rs56358680	1.10E-11	0.67							rs62036621	0.0000012	-0.15	rs56358680	8.50E-11	0.51						
	rs55991577	1.10E-11	0.67							rs62036620	0.0000012	-0.15	rs55991577	8.50E-11	0.51						
	rs12443881	3.80E-07	0.55							rs4788095	0.0000013	-0.14	rs12443881	3.50E-11	0.55						
	rs72793812	5.20E-07	0.54							rs62036617	0.0000014	-0.14	rs72793812	4.20E-11	0.54						
	rs62036624	1.80E-11	0.67							rs1987472	0.0000014	-0.14	rs62036624	8.50E-11	0.51						
	rs72793811	6.80E-07	0.54							rs2008514	0.0000015	-0.14	rs72793811	4.30E-11	0.54						
	rs8062405	2.10E-11	0.67							rs62037363	0.0000012	-0.15	rs8062405	7.40E-11	0.51						
	rs62036622	7.10E-07	0.54							rs56040780	0.0000012	-0.15	rs62036622	3.60E-11	0.55						
	rs4451951	1.30E-11	0.65							rs8049439	0.0000011	-0.15	rs4451951	4.10E-11	0.5						
	rs62036621	7.20E-12	0.68							rs11864107	0.0000012	-0.15	rs62036621	8.00E-11	0.51						
	rs62036620	7.00E-12	0.68							rs7193733	0.0000012	-0.15	rs62036620	8.00E-11	0.51						
	rs4788095	5.30E-12	0.68							rs9972768	0.0000012	-0.15	rs4788095	7.80E-11	0.51						
	rs62036617	2.90E-12	0.68							rs78613234	0.0000012	-0.15	rs62036617	7.90E-11	0.51						
	rs62036616	6.90E-07	0.54							rs72793809	0.0000012	-0.15	rs62036616	4.40E-11	0.54						
	rs1987472	2.30E-12	0.68							rs11860513	0.0000011	-0.14	rs1987472	8.20E-11	0.51						
	rs2008514	2.20E-12	0.68							rs11864750	0.0000022	-0.14	rs2008514	8.20E-11	0.51						
	rs7359397	6.60E-07	0.53							rs11150609	0.0000012	-0.15	rs7359397	6.70E-11	0.54						
	rs62037363	8.00E-12	0.68							rs56186137	0.0000014	-0.14	rs62037363	8.10E-11	0.51						
	rs56040780	1.10E-11	0.67							rs7191618	3.20E-08	-0.16	rs56040780	8.40E-11	0.51						
	rs8049439	1.30E-09	0.61							rs4788083	4.30E-08	-0.16	rs8049439	2.40E-11	0.52						
	rs11864107	1.10E-11	0.67							rs4788084	4.20E-08	-0.16	rs11864107	8.50E-11	0.51						
	rs7193733	8.00E-12	0.68							rs62034326	4.20E-08	-0.16	rs7193733	4.50E-11	0.52						
	rs12448902	2.10E-07	0.56							rs62034324	2.80E-08	-0.16	rs12448902	3.70E-11	0.54						
	rs7187333	2.20E-07	0.55							rs28772958	4.30E-08	-0.16	rs7187333	3.00E-11	0.54						
	rs9972768	1.10E-11	0.67							rs4788085	4.30E-08	-0.16	rs9972768	8.50E-11	0.51						
	rs78613234	1.60E-11	0.67							rs28698667	4.20E-08	-0.16	rs78613234	8.50E-11	0.51						
	rs72793809	6.20E-12	0.68							rs62034319	4.50E-08	-0.16	rs72793809	7.90E-11	0.51						
	rs11860513	2.30E-12	0.68							rs240702	4.70E-08	-0.16	rs11860513	7.70E-11	0.5						
	rs62036614	6.70E-07	0.53							rs153106	1.70E-07	-0.15	rs62036614	3.30E-11	0.55						
	rs12928404	3.80E-09	0.57							rs7202948	8.00E-08	-0.16	rs12928404	5.50E-11	0.49						
	rs11864750	5.60E-12	0.67										rs11864750	3.70E-11	0.51						
	rs11150609	1.10E-11	0.67										rs11150609	8.50E-11	0.51						
	rs62036658	0.0000015	0.53										rs62036658	9.70E-11	0.55						
	rs56186137	2.30E-12	0.68										rs56186137	8.20E-11	0.51						
	rs7191618	2.00E-09	0.6										rs7191618	4.00E-16	0.61						
	rs4788083	4.40E-09	0.58										rs4788083	1.40E-16	0.61						
	rs4788084	3.10E-10	0.62										rs4788084	6.40E-17	0.62						
	rs62034326	3.10E-10	0.62										rs62034326	6.60E-17	0.62						
	rs62034324	8.50E-10	0.61										rs62034324	3.10E-17	0.63						
	rs28772958	4.40E-09	0.58										rs28772958	1.40E-16	0.61						
	rs4788085	4.40E-09	0.58										rs4788085	1.40E-16	0.61						
	rs28698667	3.10E-10	0.62										rs28698667	6.50E-17	0.62						
	rs62034319	2.60E-09	0.58										rs62034319	2.50E-17	0.62						
	rs240702	4.20E-09	0.58										rs240702	4.00E-17	0.62						
	rs153106	6.60E-10	0.61										rs153106	2.70E-17	0.62						
	rs7202948	2.70E-09	0.6										rs7202948	3.00E-16	0.62						

TISSUE	CDC37P1			EIF3C			EIF3CL			SH2B1			SULT1A2			TUFM			IL27		
	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β
Liver																			rs3888190	2.70E-08	0.39
																			rs62037371	2.70E-08	0.39
																			rs8055138	2.70E-08	0.39
																			rs7496555	3.60E-07	0.38
																			rs8061690	3.00E-08	0.38
																			rs62037369	3.60E-07	0.38
																			rs7496665	2.70E-08	0.39
																			rs8055982	2.70E-08	0.39
																			rs7196606	2.70E-08	0.39
																			rs62037367	2.70E-08	0.39
																			rs4788102	2.70E-08	0.39
																			rs11961174	2.70E-08	0.39
																			rs12446589	3.60E-07	0.38
																			rs62037365	2.70E-08	0.39
																			rs62037364	2.40E-08	0.39
																			rs4788101	2.70E-08	0.39
																			rs7205323	4.30E-08	0.38
																			rs80275162	1.40E-08	0.39
																			rs9972693	2.70E-08	0.39
																			rs7187776	0.0000027	0.33
																			rs4788099	2.70E-08	0.39
																			rs61737565	2.70E-08	0.39
																			rs28403629	2.70E-08	0.39
																			rs3088215	2.70E-08	0.39
																			rs12325113	3.60E-07	0.38
																			rs56830740	2.70E-08	0.39
																			rs55719896	2.70E-08	0.39
																			rs56404918	2.70E-08	0.39
																			rs12444171	2.70E-08	0.39
																			rs62036657	2.70E-08	0.39
																			rs62036626	2.70E-08	0.39
																			rs56358680	2.70E-08	0.39
																			rs55991577	2.70E-08	0.39
																			rs12443881	3.60E-07	0.38
																			rs72793812	5.60E-07	0.37
																			rs62036624	2.70E-08	0.39
																			rs72793811	3.60E-07	0.38
																			rs8062405	5.10E-08	0.38
																			rs62036622	3.60E-07	0.38
																			rs445195	2.00E-08	0.38
																			rs62036621	2.70E-08	0.39
																			rs62036620	2.70E-08	0.39
																			rs4788096	2.70E-08	0.39
																			rs62036617	2.60E-08	0.39
																			rs62036616	3.60E-07	0.38
																			rs1987472	2.70E-08	0.39
																			rs2006514	2.70E-08	0.39
																			rs7359397	3.60E-07	0.38
																			rs62037363	4.20E-08	0.38
																			rs56040780	2.70E-08	0.39
																			rs8049439	0.0000027	0.33
																			rs11854107	2.70E-08	0.39
																			rs7193733	2.70E-08	0.39
																			rs12448902	3.90E-07	0.37
																			rs7187333	5.50E-07	0.37
																			rs9972768	2.70E-08	0.39
																			rs78613234	2.70E-08	0.39
																			rs72793809	2.70E-08	0.39
																			rs11860513	2.60E-08	0.39
																			rs62036614	3.60E-07	0.38
																			rs11864750	8.40E-08	0.37
																			rs11150609	2.70E-08	0.39
																			rs62036656	5.30E-07	0.37
																			rs56186137	2.70E-08	0.39
																			rs7191618	5.20E-11	0.45
																			rs4788083	5.20E-11	0.45
																			rs4788084	6.30E-10	0.42
																			rs62034326	6.30E-10	0.42
																			rs62034324	7.30E-09	0.41
																			rs28772958	5.20E-11	0.45
																			rs4788085	5.20E-11	0.45
																			rs28698667	6.30E-10	0.42
																			rs62034319	6.30E-10	0.42
																			rs240702	6.50E-10	0.42
																			rs153106	1.20E-09	0.42
																			rs7202948	1.20E-10	0.44

S4 Fig. eQTL data of rs3888190 and its proxies (r2≥0.8) Cis-association data of significant SNPs influence on the expression of nearby genes were extracted from the Genotype-Tissue Expression (GTEx) project, a public source (http://www.gtexportal.org/home/) with available expression Quantative Trait Loci (eQTL) data of 7051 samples from 44 different tissues and for genome-wide genetic variations (Illumina OMNI 5M SNP Array)(4)

TISSUE	DHX33			RPAIN			NUP88			RABEP1		
	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β	SNP	P-value	β
Adipose - Subcutaneous	rs3026101	0.0000069	-0.17	rs1000940	1.40E-08	-0.24						
	rs58351927	0.0000061	-0.17	rs3026101	4.70E-09	-0.25						
	rs12600578	0.0000061	-0.17	rs16954604	2.80E-08	-0.23						
	rs1806263	0.00001	-0.17	rs58351927	1.80E-08	-0.24						
	rs1806246	0.0000051	-0.18	rs12600578	1.80E-08	-0.24						
				rs1806263	3.90E-08	-0.23						
				rs1806246	1.60E-08	-0.24						
Adrenal Gland												
Brain							rs3026101	0.0000031	0.51			
Pituitary										rs1000940	4.50E-07	-0.7
										rs3026101	1.00E-07	-0.73
										rs16954604	1.00E-07	-0.73
										rs58351927	1.00E-07	-0.73
										rs12600578	1.00E-07	-0.73
										rs1806263	9.60E-08	-0.74
										rs1806246	9.70E-08	-0.74
Thyroid	rs1000940	0.0000028	-0.22							rs1000940	2.00E-16	-0.41
	rs3026101	0.000005	-0.22							rs3026101	1.50E-16	-0.41
	rs16954604	0.0000027	-0.22							rs16954604	3.00E-16	-0.4
	rs58351927	0.0000027	-0.22							rs58351927	3.00E-16	-0.4
	rs12600578	0.0000027	-0.22							rs12600578	3.00E-16	-0.4
	rs1806263	0.0000057	-0.22							rs1806263	4.50E-16	-0.4
	rs1806246	0.0000036	-0.22							rs1806246	9.20E-17	-0.41

S5 Fig. eQTL data of rs1000940 and its proxies r2≥0.8 Cis-association data of significant SNPs influence on the expression of nearby genes were extracted from the Genotype-Tissue Expression (GTEx) project, a public source (http://www.gtexportal.org/home/) with available expression Quantative Trait Loci (eQTL) data of 7051 samples from 44 different tissues and for genome-wide genetic variations (Illumina OMNI 5M SNP Array)(4)

REFERENCES

1. Compendium Suisse des Medicaments Bern, Switzerland: Institut Suisse des produits thérapeutiques; 2014 [Available from: http://www.swissmedicinfo.ch.
2. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 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). Journal of hypertension. 2013;31(7):1281-357.
3. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabetic medicine : a journal of the British Diabetic Association. 2006;23(5):469-80.
4. GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. Nature genetics. 2013;45(6):580-5.

Project III: Influence of polygenic risk scores on lipid levels and dyslipidemia in a psychiatric population receiving weight gain-inducing psychotropic drugs

Influence of polygenic risk scores on lipid levels and dyslipidemia in a psychiatric population receiving weight gain-inducing psychotropic drugs

Aurélie Delacrétaz[a], Patricia Lagares Santos[a], Nuria Saigi Morgui[a], Frederik Vandenberghe[a], Anaïs Glatard[a], Mehdi Gholam-Rezaee[b], Armin von Gunten[c], Philippe Conus[d] and Chin B. Eap[a,e]

Objectives **Dyslipidemia represents a major health issue in psychiatry. We determined whether weighted polygenic risk scores (wPRSs) combining multiple single-nucleotide polymorphisms (SNPs) associated with lipid levels in the general population are associated with lipid levels [high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides] and/or dyslipidemia in patients receiving weight gain-inducing psychotropic drugs. We also determined whether genetics improve the predictive power of dyslipidemia.**

Patients and methods **The influence of wPRS on lipid levels was firstly assessed in a discovery psychiatric sample ($n = 332$) and was then tested for replication in an independent psychiatric sample ($n = 140$). The contribution of genetic markers to predict dyslipidemia was evaluated in the combined psychiatric sample.**

Results **wPRSs were significantly associated with the four lipid traits in the discovery ($P \leq 0.02$) and in the replication sample ($P \leq 0.03$). Patients whose wPRS was higher than the median wPRS had significantly higher LDL, TC, and triglyceride levels (0.20, 0.32 and 0.26 mmol/l, respectively; $P \leq 0.004$) and significantly lower HDL levels (0.13 mmol/l; $P < 0.0001$) compared with others. Adding wPRS to clinical data significantly improved dyslipidemia prediction of HDL ($P = 0.03$) and a trend for improvement was observed for the prediction of TC dyslipidemia ($P = 0.08$).**

Conclusion **Population-based wPRSs have thus significant effects on lipid levels in the psychiatric population. As genetics improved the predictive power of dyslipidemia development, only 24 patients need to be genotyped to prevent the development of one case of HDL hypocholesterolemia. If confirmed by further prospective investigations, the present results could be used for individualizing psychotropic treatment.** ***Pharmacogenetics and Genomics*** **00:000–000** **Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.**

Pharmacogenetics and Genomics 2017, **00**:000–000

Keywords: lipid traits, polygenic risk score, psychiatry, psychotropic drugs

[a]Unit of Pharmacogenetics and Clinical Psychopharmacology, Department of Psychiatry, Centre for Psychiatric Neuroscience, [b]Department of Psychiatry, Centre of Psychiatric Epidemiology and Psychopathology, [c]Department of Psychiatry, Service of Old Age Psychiatry, [d]Department of Psychiatry, Service of General Psychiatry, Lausanne University Hospital, Prilly and [e]School of Pharmaceutical Sciences, University of Geneva–Lausanne, Geneva, Switzerland

Correspondence to Chin B. Eap, PhD, Hôpital de Cery, 1008 Prilly, Lausanne, Switzerland
Tel: +41 21 314 26 04; fax: +41 21 314 24 44; e-mail: chin.eap@chuv.ch

Received 19 May 2017 **Accepted** 24 August 2017

Introduction

Cardiovascular diseases have become a major public health burden, with their prevalence increasing considerably over the past decades [1,2]. Dyslipidemia, in particular abnormal plasma levels of circulating lipoproteins, is a clinical condition contributing to the development of atherosclerosis and cardiovascular diseases, for example, coronary artery diseases, strokes, and peripheral artery diseases [3–8]. In addition to being influenced by environmental factors such as diet, lifestyle, and other environmental factors, plasma lipid levels are determined by the genetic background as well [9]. Although several forms of monogenic dyslipidemia associated with critical lipid level changes have been described, the most prevalent form of dyslipidemia has polygenic causes, resulting from the combination of many common, rare, and copy number genetic variants with a substantial contribution of environmental factors [9].

In the psychiatric population, the use of psychotropic medications such as antipsychotics (most atypical but also some typical), mood stabilizers (e.g. lithium and valproate), and some antidepressants (e.g. mirtazapine) worsen patients' metabolic condition (e.g. weight gain and/or alteration of lipid and glucose metabolism) [10,11]. Dyslipidemia, defined as high total cholesterol (TC), low-density lipoprotein (LDL)-cholesterol, triglyceride (TG), and/or low high-density lipoprotein (HDL)-cholesterol levels, constitutes a considerable risk factor for cardiovascular diseases in the psychiatric population as its prevalence was shown to increase as much as 60% [12]. Some factors were associated with psychotropic

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (*www.pharmacogeneticsandgenomics.com*).

1744-6872 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/FPC.0000000000000313

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

drug-induced metabolic complications, including female sex, low baseline BMI, young age, or non-Caucasian ethnicities [13]. In addition, many genetic susceptibilities as variations in pharmacodynamic receptors or in energy homeostasis regulating genes were associated with metabolic adverse effects [14–18]. For instance, previous studies demonstrated the influence of $5HT_{2C}$ serotonin and H_1 histamine receptors on weight gain induced by psychotropic drugs [19,20]. Although mechanisms underlying psychotropic-induced dyslipidemia are only partially understood, recent studies suggested a role of the sterol regulatory element-binding protein pathway [21]. Thus, olanzapine, clozapine, and risperidone were shown to promote the up-regulation of sterol regulatory element-binding protein, leading to enhanced lipid and cholesterol synthesis in mice [22,23].

With the rapid emergence of genome-wide association studies (GWAS), many genetic variants in association with metabolic phenotypes were discovered in the last decade [24–26]. Two recent GWAS meta-analyses from the Global Lipids Genetics Consortium and the Engage Consortium were conducted to reveal associations between abnormal lipid levels and single-nucleotide polymorphisms (SNPs) in the general population [27,28]. When considered individually, these genetic variants have shown minor effects on lipid phenotypes. As an alternative method of testing individual SNP effect, integrating data from numerous SNPs in the construction of a polygenic risk score (PRS) allows to better integrate the global information of these numerous little effects [29], with small effects increasing the consistency and power to determine genetic risk in polygenic diseases such as dyslipidemia [30]. Although several PRSs were determined as significant predictors of obesity, diabetes, and dyslipidemia [31–33], associations between PRS and dyslipidemia among the psychiatric population have never been established.

The aim of the present study was to investigate whether PRSs combining multiple risk-associated SNPs from two lipid meta-analyses were associated with dyslipidemia-related traits (HDL, LDL, TC, and TG) in patients from Lausanne University Hospital receiving psychotropic drugs known to induce worsening of metabolic parameters. Furthermore, the predictive power of models containing only clinical data was compared with models including both clinical and genetic data to examine whether models including genetics could be useful enough to be applied in clinical settings.

Patients and methods

Psychiatric samples

A prospective cohort study approved by the local ethics committee is ongoing in Lausanne Psychiatric University Hospital since 2007. In total, 472 patients of European ancestry who started treatment with atypical antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, paliperidone, and risperidone), mood stabilizers (lithium and valproate), and/or antidepressants (mirtazapine) were included in the present analysis. Patients without available prospective lipid values were excluded from the analyses. Further description of the psychiatric samples was published elsewhere [15] and in Supplementary Material (Supplemental digital content 1, *http://links.lww.com/FPC/B279*). All individuals or their legal representatives signed a written informed consent for genetic analyses. Low HDL-cholesterol, high LDL-cholesterol, high TG, and high TC levels were defined by HDL hypocholesterolemia ($\leq$ 1 mmol/l), LDL hypercholesterolemia ($\geq$3 mmol/l), hypertriglyceridemia ($\geq$2 mmol/l), and hypercholesterolemia ($\geq$5 mmol/l), respectively, and/or by the prescription of a lipid-lowering agent [34], according to European Society of Hypertension/European Society of Cardiology guidelines [35].

The discovery sample consisted of 332 patients from the aforementioned cohort with psychotropic treatments starting between 2007 and 31 December 2010. The replication sample was composed of 140 patients of the same cohort with treatments starting between 1 January 2011 and 2014. Only patients of European ancestry were included in the analysis. More details are present in Supplementary Material (Supplemental digital content 1, *http://links.lww.com/FPC/B279*).

Single-nucleotide polymorphism selection, genotyping, and construction of the polygenic risk score

Single-nucleotide polymorphism selection

A meta-analysis of 60 studies was performed by The Global Lipids Genetics Consortium with data from 188 577 individuals of European, East Asian, South Asian, and African ancestry using both GWAS and MetaboChip array genotyping data [28]. In addition, a second meta-analysis was conducted by the Engage Consortium with a set of 62 166 individuals of European ancestry from 22 GWAS [27]. Both population-based samples were used to select genetic variants associated with lipid levels. In the present study, β-coefficients (i.e. allele effects) were used to assign weights to each variant for the calculation of PRS in the psychiatric samples. More details in Supplementary Fig. S1 (Supplemental digital content 1, *http://links.lww.com/FPC/B279*) describes SNP selection.

Genotyping

CardioMetabochip genotyping of European ancestry patients from the Lausanne Psychiatric University Hospital study was performed using the Illumina 200K CardioMetabochip (Illumina, San Diego, California, USA) at the iGE3 genomics platform of the University of Geneva (*http://www.ige3.unige.ch/genomics-platform.php*). More details are present in Supplementary Material (Supplemental digital content 1, *http://links.lww.com/FPC/B279*).

Construction of the polygenic risk scores

One PRS was calculated by taking into account SNPs from each GWAS meta-analysis (i.e. PRS_{Willer} and $PRS_{Surakka}$) in association with each lipid phenotype,

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

namely HDL, LDL, TC, and TG. In addition, according to their respective inclusion criteria (Supplementary Fig. S1, Supplemental digital content 1, *http://links.lww.com/FPC/B279*), one PRS was calculated for each lipid phenotype by considering SNPs from both meta-analyses (i.e. $PRS_{combined}$; $n = 73$, 60, 72, and 47 SNPs for HDL, LDL, TC, and TG, respectively). More details are present in Supplementary Material (Supplemental digital content 1, *http://links.lww.com/FPC/B279*).

Statistical analyses

For the assessment of the influence of genetic parameters on dyslipidemia among psychiatric patients throughout the psychotropic treatment duration, generalized additive mixed models (GAMMs) were used, adjusting for covariates possibly associated with lipid parameters, that is, BMI, age, sex, smoking status, and psychotropic drug class. GAMMs were implemented using the mgcv and the nlme packages in R (settings were fixed at package defaults) [36], in which parameter uncertainties (confidence intervals and *P* values) were computed using up to 100 000 bootstrap replicates with replacement, performed on patient level. The explained variance of weighted polygenic risk score (wPRS) on the four lipid variables was calculated by running GAMM with and without polygenic scores. All the statistical analyses were performed using Stata 14 (StataCorp., College Station Texas, USA) and R software (version 3.2.3; Teddington, Middlesex, UK). *P* values less than or equal to 0.05 of these two-sided models were considered as statistically significant.

Receiver operating characteristic (ROC) curves were used to compare the predictive power of models including only clinical data with models containing both clinical and genetic data using pROC and predictABEL R packages [37,38]. More details about area under the curve (AUC) construction and interpretation are available in Supplementary Material (Supplemental digital content 1, *http://links.lww.com/FPC/B279*).

Evaluation of pharmacogenetic screening benefit

The clinical value of pharmacogenetic testing could be assessed by calculating the number needed to genotype (NNG). NNG defines the number of patients who would need to be genotyped to prevent dyslipidemia for one patient under psychotropic treatment [39]. Sensitivity for the calculation of the NNG was chosen according to best threshold coordinates for specificity and sensitivity of the ROC curve including genetics and clinical data.

Results

Characteristics of psychiatric samples

Demographic and clinical characteristics of the discovery ($n = 332$), replication ($n = 140$), and combined sample ($n = 472$) are presented in Supplementary Table S1 (Supplemental digital content 1, *http://links.lww.com/FPC/B279*). The combined sample included individuals of European ancestry with a median age of 48 years (ranging from 12 to 97 years), of whom 53, 24, 50, and 17% had TC, HDL, LDL, and TG dyslipidemia at baseline, respectively. Psychotic disorders (F20: schizophrenia; F21: schizotypal disorder; F22: delusional disorder; F23: brief psychotic disorder; F24: shared psychotic disorder; F28: other psychotic disorder not due to a substance or known physiological condition; and F29: unspecified psychosis not due to a substance or known physiological condition) were the most frequent diagnosis (33%), quetiapine was the most frequently prescribed psychotropic drug (34%), 35% of patients were smokers, and 44% were men. There was no significant difference regarding demographic or clinical characteristics between the two psychiatric samples, except lower baseline levels of TC and LDL in the discovery sample compared with the replication sample (4.7 vs. 5.2 mmol/l, $P = 0.002$, and 2.6 vs. 3.0 mmol/l, $P = 0.005$, respectively). Between baseline and current psychotropic treatment, the incidence of dyslipidemia (i.e. abnormal lipid levels or treated dyslipidemia) development under the current psychotropic treatment reached 8.6, 6, 5.8, and 10.7% for TC, HDL, LDL, and TG, respectively. Supplementary Figs S2–S6 (Supplemental digital content 1, *http://links.lww.com/FPC/B279*) show the evolution of lipid levels during psychotropic treatment stratified by covariates taken into account in GAMM analyses, that is, BMI, age, sex, smoking status, and psychotropic drug class. More details are available in Supplementary Material (Supplemental digital content 1, *http://links.lww.com/FPC/B279*).

Influence of polygenic risk score on lipid phenotype worsening during psychotropic treatment

SNPs considered for the construction of the wPRS for each lipid trait and each meta-analysis (from Global Lipids Genetics Consortium and from Engage Consortium, namely $wPRS_{Willer}$ and $wPRS_{Surakka}$, respectively) are listed in Supplementary Tables S2–S13 (Supplemental digital content 1, *http://links.lww.com/FPC/B279*). In the discovery sample, $wPRS_{Willer}$ and $wPRS_{Surakka}$ calculated for each phenotype were significantly associated with HDL, LDL, TC, and TG ($P \leq 0.02$) (Supplementary Table S14, Supplemental digital content 1, *http://links.lww.com/FPC/B279*). In the discovery sample, $wPRS_{combined}$ were also significantly associated with lipid levels ($P \leq 0.01$) and replicated in the independent psychiatric replication sample ($P \leq 0.01$) (Table 1). In the combined psychiatric sample using $wPRS_{combined}$, each additional risk allele significantly increased LDL, TC, and TG by 0.03, 0.04, and 0.04 mmol/l, respectively, and decreased HDL by 0.02 mmol/l (Table 1; $P < 0.001$, <0.00001, <0.0001 and <0.00001, respectively). As analyses on $wPRS_{combined}$ in the combined psychiatric sample showed significant associations and because estimates between the discovery and replication psychiatric samples were almost similar, further analyses were conducted using only $wPRS_{combined}$ in the combined psychiatric sample. Details for further analyses

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 1 Association of weighted polygenic risk score groups (single-nucleotide polymorphisms selected from both meta-analyses) with lipid traits in generalized additive mixed model adjusted with age, sex, BMI, medication, and smoking status in the discovery, replication, and combined sample

	Phenotype	Number of SNPs	Number of patients	Estimate [95% CI] (mmol/l)	Explained variability (%)	Explained variability by PRS (%)	*P*-value
Discovery sample	HDL	73	233	0.01 [0.01–0.02]	18.32	3.44	< 0.001
	LDL	60	211	0.03 [0.01–0.05]	15.05	1.85	0.004
	TC	72	234	0.03 [0.02–0.05]	16.12	2.48	< 0.001
	TG	47	213	0.05 [0.03–0.06]	25.08	5.25	< 0.01
Replication sample	HDL	73	98	0.02 [0.01–0.03]	41.88	7.16	< 0.01
	LDL	60	92	0.04 [0.02–0.07]	14.5	8.86	< 0.001
	TC	72	102	0.06 [0.03–0.08]	17.53	6.63	< 0.01
	TG	47	86	0.03 [0.00–0.06]	26.87	3.93	< 0.01
Combined sample	HDL	73	331	0.02 [0.01–0.02]	22.79	4.33	< 0.00001
	LDL	60	303	0.03 [0.02–0.05]	13.61	3.4	< 0.001
	TC	72	336	0.04 [0.02–0.06]	15.91	3.25	< 0.00001
	TG	47	299	0.04 [0.03–0.06]	24.97	4.86	< 0.0001

Explained variability (%) refers to models including all variables.
Caucasian patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.
Estimates indicate the influence of each additional risk allele on lipid levels (mmol/l). For instance, each additional risk allele significantly increases LDL by 0.03 mmol/l [0.01–0.05].
CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PRS, polygenic risk score; SNP, single-nucleotide polymorphism; TC, total cholesterol; TG, triglyceride.

are available in Supplementary Material (Supplementary Figs S7–S16 and Supplementary Table S15, Supplemental digital content 1, *http://links.lww.com/FPC/B279*).

In accordance with previous results, significant differences of the four lipid phenotype levels were observed between percentile groups ($P \leq 0.004$) (Table 2 and Fig. 1). Thus, patients whose wPRS was lower than the median value of all patients had significantly lower levels of LDL, TC, and TG [0.20 mmol/l (0.04–0.36); 0.32 mmol/l (0.15–0.49); 0.26 mmol/l (0.13–0.38), respectively] and higher levels of HDL [0.13 mmol/l (0.07–0.19)] compared with the others.

Predictive power of models containing clinical and genetic variables

Predictive powers of models including genetics were not improved compared with models including only clinical variables for any of the four lipid traits, in neither the discovery sample (Supplementary Fig. S17a, Supplemental digital content 1, *http://links.lww.com/FPC/B279*) nor the replication sample (Supplementary Fig. S17b, Supplemental digital content 1, *http://links.lww.com/FPC/B279*). In the combined sample (Fig. 2), adding genetics to models did not increase AUC for hypertriglyceridemia (AUC = 0.75 vs. 0.74; $P = 0.57$) and for LDL hypercholesterolemia (AUC = 0.68 vs. 0.66; $P = 0.41$). However, for HDL hypocholesterolemia, AUC was significantly increased when adding genetics to the clinical model (AUC = 0.76 vs. 0.73; $P = 0.03$), and for TC hypercholesterolemia, a trend of AUC increase was observed by adding genetics to the clinical model (AUC = 0.73 vs. 0.70; $P = 0.08$). More details are available in Supplementary Table S16 (Supplemental digital content 1, *http://links.lww.com/FPC/B279*). As fasting TG levels may vary considerably following a high-fat diet, more stringent analyses were also conducted considering hypertriglyceridemia only if patients had at least two abnormal TG values during the psychotropic treatment. This new criterion slightly improved AUC (0.82 vs. 0.79; $P = 0.29$) but did not reveal any significant AUC increase by adding genetics (data not shown).

Supplementary Table S17 (Supplemental digital content 1, *http://links.lww.com/FPC/B279*) displays interaction results between wPRS and age, sex, and BMI on the four lipid phenotypes. A significant interaction was observed between wPRS and BMI on LDL ($P = 0.02$), and between wPRS and sex on TC ($P = 0.04$). Details of further analyses are available in Supplementary Material (Supplementary Figs S18–S20 and Supplementary Table S18, Supplemental digital content 1, *http://links.lww.com/FPC/B279*).

Explained variability

In the combined psychiatric sample, total variability explained by GAMMs including clinical and genetic components reached 22.8, 13.6, 15.9, and 23.0% for HDL, LDL, TC, and TG, respectively (Supplementary Table S19, Supplemental digital content 1, *http://links.lww.com/FPC/B279*). Interestingly, wPRS was among the variables having increased effect on the total explained variability for each lipid trait. Indeed, genetics alone explained 4.3, 3.4, 3.3, and 4.8% of HDL, LDL, TC, and TG variability, respectively. Further analyses showed that only a small fraction (i.e. 5%) of SNPs drove the total variability explained by genetics. Thus, SNPs whose β values were higher than the percentile 95 of all β values explained 3.5, 3.1, 2.5, and 3.3% of the total lipid variability for HDL, LDL, TC, and TG, respectively (Supplementary Table S20, Supplemental digital content 1, *http://links.lww.com/FPC/B279*). Strikingly, the variability explained by genetics was drastically decreased (1.58, 0.04, 1.15, and 2.61% of HDL, LDL, TC, and TG, respectively) when considering unweighted PRS (i.e. PRS with β value of 1 for each individual SNPs (Supplementary Table S20, Supplemental digital content 1, *http://links.lww.com/FPC/B279*),

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 2 Association of weighted polygenic risk score groups (single-nucleotide polymorphisms selected from both meta-analyses) with lipid traits in generalized additive mixed model adjusted with age, sex, BMI, medication, and smoking status in the combined sample

	Number of SNPs	Number of patients	wPRS groups	Estimates [95% CI] (mmol/l)	*P*-value
HDL	73	331	wPRS < p50	0.13 [0.07–0.19]	< 0.0001
			wPRS ≥ p50	Ref	
		167	wPRS < p25	0.28 [0.19–0.36]	< 0.0001
			wPRS > p75	Ref	
		68	wPRS < p10	0.35 [0.22–0.49]	< 0.0001
			wPRS > p90	Ref	
LDL	60	303	wPRS < p50	Ref	0.004
			wPRS ≥ p50	0.20 [0.04–0.36]	
		158	wPRS < p25	Ref	0.003
			wPRS > p75	0.31 [0.11–0.53]	
		68	wPRS < p10	Ref	0.0004
			wPRS > p90	0.63 [0.27–1.00]	
TC	72	336	wPRS < p50	Ref	< 0.0001
			wPRS ≥ p50	0.32 [0.15–0.49]	
		171	wPRS < p25	Ref	< 0.0001
			wPRS > p75	0.50 [0.28–0.74]	
		76	wPRS < p10	Ref	0.0002
			wPRS > p90	0.66 [0.30–1.07]	
TG	47	299	wPRS < p50	Ref	< 0.0001
			wPRS ≥ p50	0.26 [0.13–0.38]	
		146	wPRS < p25	Ref	< 0.0001
			wPRS > p75	0.47 [0.30–0.64]	
		56	wPRS < p10	Ref	0.002
			wPRS > p90	0.60 [0.19–0.91]	

Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.
Estimates indicate the difference of lipid levels between wPRS percentile groups (i.e. between median percentile groups, between percentile 25 and percentile 75 groups or between percentile 10 and percentile 90 groups).
Generalized additive mixed models were performed with polygenic risk score as a categorical variable with two groups.
CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SNP, single-nucleotide polymorphism; TC, total cholesterol; TG, triglyceride; wPRS, weighted polygenic risk score; wPRS < p50, group of patients whose wPRS was lower than the median of all patients wPRS; wPRS ≥ p50, group of patients whose wPRS was higher or equal to the median of all patients wPRS; wPRS < p25, group of patients whose wPRS was lower than the percentile 25 of all patients wPRS; wPRS > p75, group of patients whose wPRS was higher than the percentile 75 of all patients wPRS; wPRS < p10, group of patients whose wPRS was lower than the percentile 10 of all patients wPRS; wPRS > p90, group of patients whose wPRS was higher than the percentile 90 of all patients wPRS.

showing the importance to consider allele effects in a weighted approach. SNPs whose β values were higher than the percentile 95 of all β values are lying in well-known genes involved in the regulation of lipid homeostasis, as for instance in the lipoprotein lipase, in the LDL receptor, or in the apolipoprotein E (Supplementary Table S21, Supplemental digital content 1, *http://links.lww.com/FPC/B279*).

Number needed to genotype

To detect whether genotyping would be useful as a routine test, the NNG for HDL was calculated (Table 3). In the combined psychiatric sample, 24 patients would be needed to be genotyped to avoid HDL hypocholesterolemia for one patient.

Discussion

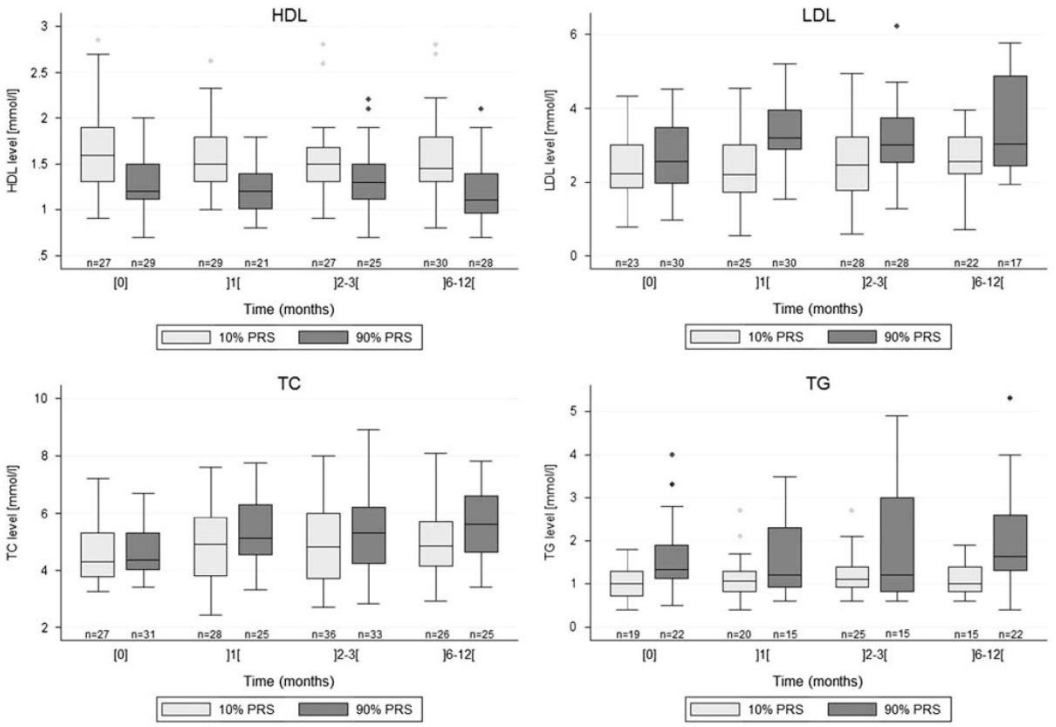
The present study shows that wPRS constructed with lipid-associated SNPs from population-based samples had a significant influence on HDL, LDL, TC, and TG levels in the psychiatric population receiving psychotropic treatment inducing metabolic disturbances. Moreover, adding genetics to clinical models significantly improved HDL hypocholesterolemia prediction and a trend for improvement was observed for the prediction of TC dyslipidemia.

In the present psychiatric sample, dyslipidemia prevalence for TC, LDL, HDL, and TG was higher than reported in the Recovery After an Initial Schizophrenia Episode study [12], possibly because of the shorter lifetime exposure to psychotropic treatment in the latter (<6 months) than in the present psychiatric sample (~8 years). In contrast, in accordance with the latter study [12], only a small proportion of patients (<7%) received lipid-lowering agent(s), corresponding to 14% of patients with hypercholesterolemia. A significant increase in the incidence of dyslipidemia was observed over time despite the worrisome prevalence already observed at baseline. This emphasizes the importance to prospectively monitor metabolic (including lipid) parameters during psychotropic treatment in each patient starting psychotropic medication [40]. Although most patients were not drug naive before starting the current psychotropic treatment, our results within this observational psychiatric sample reflected real medical conditions in clinical practice. In addition, the present psychiatric sample was clinically heterogeneous in terms of drug classes (i.e. antipsychotics, mood stabilizers, and antidepressants) and of diagnoses (i.e. bipolar disorder, major depression, and schizophrenia). However, diagnosis was not identified as a moderator of psychotropic drug-induced metabolic disturbances [41,42]. Moreover, although antipsychotic drugs are known to be associated with different degrees of weight gain, larger studies and meta-analyses are needed to determine how these drugs alter the lipid profile and whether their rank of risks is similar to weight gain. Thus, further studies are warranted to determine whether the alteration of the lipid profile depends on the drug class. In contrast, the clinical heterogeneity of the present sample also constitutes strength, reflecting real clinical conditions.

To date, a large number of lipid-associated SNPs discovered among general population accounted for 6.6, 5.7, 8.2, and 5.0% for HDL, LDL, TC, and TG, respectively, of the variance explained by wPRS [43]. Results obtained from our psychiatric samples showed a slightly smaller explained variability for lipid phenotypes (4.3, 3.4, 3.3, and 4.8%, respectively). As the explained variability by genetics was strongly decreased in unweighted PRS, our results are in accordance with the importance of weighted approaches in PRS analyses. The difference between our results compared with population-based wPRS on lipids may be not only because of a lower number of patients in our psychiatric sample but also to the use of nonappropriate allele estimates. Thus, population-based estimates could

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Fig. 1

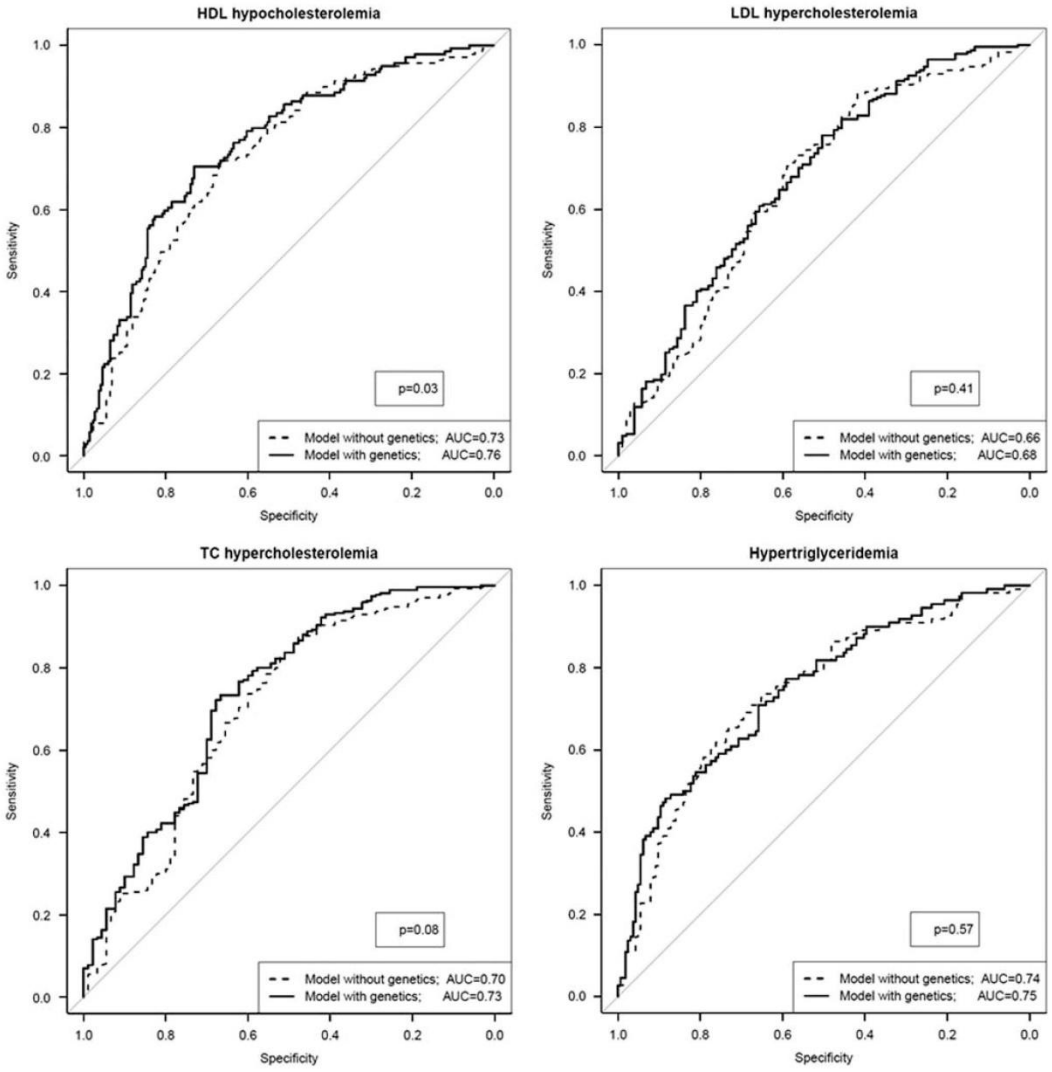


Evolution of lipid variables during psychotropic treatment, according to extreme groups of PRS. Median, interquartile, and number of observations are indicated for each box. Months were defined as follows: month [0]: day 0, month [1]: ≥ 10 and <45 days, month [2–3]: ≥ 45 and <135 days, and month [6–12]: ≥ 135 and <535 days. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses. HDL, high-density lipoprotein; LDL, low-density lipoprotein; PRS, polygenic risk score; 10% PRS, PRS lower than the 10th percentile; 90% PRS, PRS higher than the 90th percentile; TC, total cholesterol; TG, triglyceride.

either under-represent or over-represent the influence of some SNPs in the psychiatric population, which may flatten the explained variability. As a matter of fact, the psychiatric population displays a greater influence of some genetic variants on metabolic features than does the general population, possibly because of an intricate interaction between the psychiatric illness and metabolic regulation [16,44] as well as a higher prevalence of metabolic abnormalities in this specific population [45]. As a consequence, a wPRS constructed with estimates from psychiatric samples would be more pertinent and would certainly enhance the explained variability of genetics in this high-risk population. Of note, it is very likely that the consideration of additional genetic variants (e.g. SNPs associated with psychotropic drug-induced weight gain and metabolic abnormalities in genes such as *FTO*, *LEP*, *LEPR*, or *HTR2C* [46,47]) in the weighted polygenic risk score may help to improve the predictive power of weighted polygenic risk score on dyslipidemia. Unfortunately, such promising variants could not be included in PRSs because no allele effect (β-coefficient from GWAS) for these SNPs was available in the literature. In addition, SNPs from candidate gene studies arose from heterogeneous studies in terms of drugs and of treatment durations, and these studies were limited by a lack of replication and a poor sample size. Unfortunately, no GWAS on lipid traits has been yet performed in either drug-free psychiatric population or patients receiving psychotropic drugs inducing metabolic disturbances. Such studies and meta-analyses conducted on lipid levels would help to provide more accurate allelic estimates. In the present study, most of the lipid variance explained by genetics was driven by a very low number of SNPs with large effects, localized in well-known genes involved in lipid homeostasis and/or associated with cardiovascular risk [48]. Copy number variants, insertions or deletions, not taken into account in this study, might further increase explained variability. Moreover, whether selecting more than one single SNP per gene would increase the explained variability remains unknown. Finally, the

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Fig. 2



Receiver operating characteristic curves for abnormal lipid levels in the combined sample, defined by abnormal levels and/or by the prescription of a lipid-lowering comedication. Solid curves correspond to the model including clinical and genetics components, whereas the dashed curves include only clinical values. Only fasting patients were included for TG analyses. Low HDL-cholesterol level, that is, HDL hypocholesterolemia was defined as less than 1 mmol/l and/or prescription of a lipid-lowering agent; high LDL-cholesterol level, that is, LDL hypercholesterolemia was defined as at least 3 mmol/l and/or prescription of a lipid-lowering agent; high TG level, that is, hypertriglyceridemia was defined as at least 2 mmol/l and/or prescription of a lipid-lowering agent; and high TC level, that is, hypercholesterolemia was defined as at least 5 mmol/l and/or prescription of a lipid-lowering agent [34], according to European Society of Hypertension/European Society of Cardiology guidelines [35]. AUC, area under the curve; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.

explained variability could be increased by adding new additional common variants (probably with modest effects), rare variants (probably with large effects), methylation profile as well as more clinical lipid-related characteristics.

Several reports recently described the use of predictive models containing genetics in cardiovascular disease to prevent long-term health consequences [49–51]. Although wPRSs were highly associated with lipid levels in the present

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 3 High-density lipoprotein dyslipidemia incidence and number needed to genotype for the discovery, replication, and combined samples

	Dyslipidemia incidence (%)	Sensitivity	Number needed to genotype
Discovery sample	7.1	0.63	22
Replication sample	2.9	0.49	70
Combined sample	6.0	0.70	24

Number needed to genotype calculations were done using sensitivity of the best threshold coordinates in each sample for high-density lipoprotein dyslipidemia development.

study, models containing both clinical and genetic components in the discovery and replication samples did not show a significant increase in the power to predict lipid phenotypes compared with models containing clinical variables only. However, in the combined sample, AUCs were significantly increased for HDL and a trend of increase was observed for TC, suggesting that statistical power could be improved by increasing population samples. In addition, adding more dyslipidemia-associated genetic markers as well as covariate risk factors for dyslipidemia development could also improve the prediction. Of note, AUC for HDL model including both genetics and clinical variables in the combined sample was higher than 0.75 and sensitivity, specificity, and accuracy were higher than 70%, indicating that the prediction was informative and useful enough [52]. On the basis of the present results, 24 patients would be needed to be genotyped to avoid HDL hypocholesterolemia for one patient [53]. Thus, additional studies with larger sample sizes are needed to replicate the present findings and to identify new lipid-associated variants before the additive value of including genetic information in predictive models is transposable to routine clinical practice. In addition, larger studies are warranted to investigate the influence of wPRS on lipid levels in specific subgroups of patients (e.g. drug-stratified and/or diagnosis-stratified samples).

Results of the present study should be considered with the following limitations. First, the study was restricted to European patients, which impedes extrapolation to other ethnicities. Second, effects of environmental changes such as physical exercise or diet habits throughout the treatment, which could have influenced the evolution of lipid levels, were not taken into account. The strength of our study is the use of a weighted approach for the PRS. In addition, therapeutic drug monitoring was performed to ascertain compliance to exclude false negative, that is, patients who did not develop dylipidemia because they did not take the drug, an important factor to consider in the psychiatric population.

Conclusion

We showed an influence of PRS built from variants related to lipid traits in population-based samples on lipid levels in the psychiatric population. Moreover, adding genetic information to clinical variables may improve the prediction of HDL hypocholesterolemia in psychiatric patients treated with weight gain-inducing psychotropic drugs. Forthcoming work is needed to examine whether predictive models are accurate and useful enough for the clinical purpose of individualizing psychiatric treatment.

Acknowledgements

The authors thank C. Brogli, V. Hodel (logistical assistance), E. Ponce (bibliographical help), A. C. Aubert, M. Brocard, N. Cochard, M. Delessert, A. Vuilloud, M. Brawand, K. Powell Golay, S. Jacquet, C. Darbellay, and A. Chevalley (sample analysis). The authors are grateful to all participating medical (Jacques Thonney, Alessandra Solida-Tozzi, Stéphane Kolly, Sylfa Fassassi Gallo, Philipp Baumann, Sylvie Berney, Sandrine Valloton Zulauff, Jean-Michel Aubry, Roland Hasler, and Karsten Ebbing) and nursing (Jacques Herrgott, Daniel Ducraux, Didier Wrobel, Marco di Camillo, Yoann Levet, Charlotte Leon, Sabrina Kormann, Hugo Correia Da Rocha Capela, Justine Brea, Olivier Lafoy, Valentin Monnier, Boris Pourre, and Mélanie Lenzi) staff who were involved in the metabolic monitoring program. The authors are also grateful to the patients who gave their consent for the present study.

This work has been funded in part by the Swiss National Research Foundation (C.B.E. and P.C.: 320030-120686, 324730-144064 and 320030-173211).

Conflicts of interest

C.B.E. received honoraria for conferences or teaching CME courses from Astra Zeneca, Forum für Medizinische Fortbildung, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Mepha, Otsuka, Servier and Vifor-Pharma in the past 3 years, and for writing a review article for the journal 'Dialogues in clinical neurosciences' (Servier). He received an unrestricted educational research grant from Takeda in the past 3 years. A.v.G. received honoraria for a conference or workshop participation unrelated to this study from Vifor and Schwabe in the previous 3 years. For the remaining authors there are no conflicts of interest.

References

1 Al-Mawali A. Non-communicable diseases: shining a light on cardiovascular disease, Oman's biggest killer. *Oman Med J* 2015; **30**:227–228.
2 Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**:e442.
3 Strong A, Rader DJ. Clinical implications of lipid genetics for cardiovascular disease. *Curr Cardiovasc Risk Rep* 2010; **4**:461–468.
4 Manjunath CN, Rawal JR, Irani PM, Madhu K. Atherogenic dyslipidemia. *Indian J Endocrinol Metab* 2013; **17**:969–976.
5 Kuo PT. Dyslipidemia and coronary artery disease. *Clin Cardiol* 1994; **17**:519–527.
6 Hirsch AT, Gotto AM Jr. Undertreatment of dyslipidemia in peripheral arterial disease and other high-risk populations: an opportunity for cardiovascular disease reduction. *Vasc Med* 2002; **7**:323–331.
7 Choy PC, Siow YL, Mymin D, O K. Lipids and atherosclerosis. *Biochem Cell Biol* 2004; **82**:212–224.
8 Graham I, Cooney MT, Bradley D, Dudina A, Reiner Z. Dyslipidemias in the prevention of cardiovascular disease: risks and causality. *Curr Cardiol Rep* 2012; **14**:709–720.
9 Ramasamy I. Update on the molecular biology of dyslipidemias. *Clin Chim Acta* 2016; **454**:143–185.

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

10 Wofford MR, King DS, Harrell TK. Drug-induced metabolic syndrome. *J Clin Hypertens* 2006; **8**:114–119.
11 Correll CU, Detraux J, de Lepeleire J, de Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry* 2015; **14**:119–136.
12 Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, *et al.* Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry* 2014; **71**:1350–1363.
13 De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* 2012; **8**:114–126.
14 Vehof J, Risselada AJ, Al Hadithy AF, Burger H, Snieder H, Wilffert B, *et al.* Association of genetic variants of the histamine H1 and muscarinic M3 receptors with BMI and HbA1c values in patients on antipsychotic medication. *Psychopharmacology (Berl)* 2011; **216**:257–265.
15 Choong E, Quteineh L, Cardinaux JR, Gholam-Rezaee M, Vandenberghe F, Dobrinas M, *et al.* Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and the general adult population. *JAMA Psychiatry* 2013; **70**:1011–1019.
16 Delacretaz A, Preisig M, Vandenberghe F, Saigi Morgui N, Quteineh L, Choong E, *et al.* Influence of MCHR2 and MCHR2-AS1 genetic polymorphisms on body mass index in psychiatric patients and in population-based subjects with present or past atypical depression. *PloS One* 2015; **10**:e0139155.
17 Balt SL, Galloway GP, Baggott MJ, Schwartz Z, Mendelson J. Mechanisms and genetics of antipsychotic-associated weight gain. *Clin Pharmacol Ther* 2011; **90**:179–183.
18 Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Muller DJ. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Mol Psychiatry* 2012; **17**:242–266.
19 Reynolds GP, Hill MJ, Kirk SL. The 5-HT2C receptor and antipsychoticinduced weight gain – mechanisms and genetics. *J Psychopharmacol* 2006; **20** (**Suppl**): 15–18.
20 Kim SF, Huang AS, Snowman AM, Teuscher C, Snyder SH. From the Cover: Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. *Proc Natl Acad Sci USA* 2007; **104**:3456–3459.
21 Cai HL, Tan QY, Jiang P, Dang RL, Xue Y, Tang MM, *et al.* A potential mechanism underlying atypical antipsychotics-induced lipid disturbances. *Transl Psychiatry* 2015; **5**:e661.
22 Lauressergues E, Staels B, Valeille K, Majd Z, Hum DW, Duriez P, *et al.* Antipsychotic drug action on SREBPs-related lipogenesis and cholesterogenesis in primary rat hepatocytes. *Naunyn Schmiedebergs Arch Pharmacol* 2010; **381**:427–439.
23 Ferno J, Raeder MB, Vik-Mo AO, Skrede S, Glambek M, Tronstad KJ, *et al.* Antipsychotic drugs activate SREBP-regulated expression of lipid biosynthetic genes in cultured human glioma cells: a novel mechanism of action? *Pharmacogenomics J* 2005; **5**:298–304.
24 Wang K, Li WD, Zhang CK, Wang Z, Glessner JT, Grant SF, *et al.* A genome-wide association study on obesity and obesity-related traits. *PloS One* 2011; **6**:e18939.
25 Warrington NM, Howe LD, Paternoster L, Kaakinen M, Herrala S, Huikari V, *et al.* A genome-wide association study of body mass index across early life and childhood. *Int J Epidemiol* 2015; **44**:700–712.
26 Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, *et al.* Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015; **518**:197–206.
27 Surakka I, Horikoshi M, Magi R, Sarin AP, Mahajan A, Lagou V, *et al.* The impact of low-frequency and rare variants on lipid levels. *Nat Genet* 2015; **47**:589–597.
28 Global Lipids Genetics C, Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, *et al.* Discovery and refinement of loci associated with lipid levels. *Nat Genet* 2013; **45**:1274–1283.
29 Belsky DW, Moffitt TE, Sugden K, Williams B, Houts R, McCarthy J, *et al.* Development and evaluation of a genetic risk score for obesity. *Biodemography Soc Biol* 2013; **59**:85–100.
30 Buscot MJ, Magnussen CG, Juonala M, Pitkanen N, Lehtimaki T, Viikari JS, *et al.* The combined effect of common genetic risk variants on circulating lipoproteins is evident in childhood: a longitudinal analysis of the Cardiovascular Risk in Young Finns Study. *PloS One* 2016; **11**:e0146081.
31 Hung CF, Breen G, Czamara D, Corre T, Wolf C, Kloiber S, *et al.* A genetic risk score combining 32 SNPs is associated with body mass index and improves obesity prediction in people with major depressive disorder. *BMC Med* 2015; **13**:86.
32 Lin X, Song K, Lim N, Yuan X, Johnson T, Abderrahmani A, *et al.* Risk prediction of prevalent diabetes in a Swiss population using a weighted genetic score – the CoLaus Study. *Diabetologia* 2009; **52**:600–608.
33 Saigi-Morgui N, Vandenberghe F, Delacretaz A, Quteineh L, Gholamrezaee M, Aubry JM, *et al.* Association of genetic risk scores with body mass index in Swiss psychiatric cohorts. *Pharmacogenet Genomics* 2016; **26**:208–217.
34 Compendium Suisse des Medicaments. Bern, Switzerland: Institut Suisse des produits thérapeutiques. Available at: *http://www.swissmedicinfo.ch*. [Accessed 15 June 2016].
35 Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, *et al.* 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**:1281–1357.
36 R Development Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2013.
37 Tse L, Procyshyn RM, Fredrikson DH, Boyda HN, Honer WG, Barr AM. Pharmacological treatment of antipsychotic-induced dyslipidemia and hypertension. *Int Clin Psychopharmacol* 2014; **29**:125–137.
38 Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, *et al.* pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC bioinformatics* 2011; **12**:77.
39 De Graaff LC, van Schaik RH, van Gelder T. A clinical approach to pharmacogenetics. *Neth J Med* 2013; **71**:145–152.
40 Choong E, Solida A, Lechaire C, Conus P, Eap CB. Follow-up of the metabolic syndrome induced by atypical antipsychotics: recommendations and pharmacogenetics perspectives. *Rev Med Suisse* 2008; **4**:1994–1999.
41 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**:3143–3421.
42 Vandenberghe F, Gholam-Rezaee M, Saigi-Morgui N, Delacretaz A, Choong E, Solida-Tozzi A, *et al.* Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment. *J Clin Psychiatry* 2015; **76**:e1417–e1423.
43 Justesen JM, Allin KH, Sandholt CH, Borglykke A, Krarup NT, Grarup N, *et al.* Interactions of lipid genetic risk scores with estimates of metabolic health in a Danish population. *Circ Cardiovasc Genet* 2015; **8**:465–472.
44 Quteineh L, Preisig M, Rivera M, Milaneschi Y, Castelao E, Gholam-Rezaee M, *et al.* Association of CRTC1 polymorphisms with obesity markers in subjects from the general population with lifetime depression. *J Affect Disord* 2016; **198**:43–49.
45 Toalson P, Ahmed S, Hardy T, Kabinoff G. The metabolic syndrome in patients with severe mental illnesses. *Prim Care Companion J Clin Psychiatry* 2004; **6**:152–158.
46 MacNeil RR, Muller DJ. Genetics of common antipsychotic-induced adverse effects. *Mol Neuropsychiatry* 2016; **2**:61–78.
47 Roffeei SN, Mohamed Z, Reynolds GP, Said MA, Hatim A, Mohamed EH, *et al.* Association of FTO, LEPR and MTHFR gene polymorphisms with metabolic syndrome in schizophrenia patients receiving antipsychotics. *Pharmacogenomics* 2014; **15**:477–485.
48 Helgadottir A, Gretarsdottir S, Thorleifsson G, Hjartarson E, Sigurdsson A, Magnusdottir A, *et al.* Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease. *Nat Genet* 2016; **48**:634–639.
49 Damen JA, Hooft L, Schuit E, Debray TP, Collins GS, Tzoulaki I, *et al.* Prediction models for cardiovascular disease risk in the general population: systematic review. *BMJ* 2016; **353**:i2416.
50 Thanassoulis G, Peloso GM, Pencina MJ, Hoffmann U, Fox CS, Cupples LA, *et al.* A genetic risk score is associated with incident cardiovascular disease and coronary artery calcium: the Framingham Heart Study. *Circ Cardiovasc Genet* 2012; **5**:113–121.
51 Wang CJ, Li YQ, Wang L, Li LL, Guo YR, Zhang LY, *et al.* Development and evaluation of a simple and effective prediction approach for identifying those at high risk of dyslipidemia in rural adult residents. *PloS One* 2012; **7**:e43834.
52 Janssens AC, Moonesinghe R, Yang Q, Steyerberg EW, van Duijn CM, Khoury MJ. The impact of genotype frequencies on the clinical validity of genomic profiling for predicting common chronic diseases. *Genet Med* 2007; **9**:528–535.
53 Muller B, Wilcke A, Boulesteix AL, Brauer J, Passarge E, Boltze J, *et al.* Improved prediction of complex diseases by common genetic markers: state of the art and further perspectives. *Hum Genet* 2016; **135**:259–272.

Copyright © 2017 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

SUPPLEMENTARY DATA

Material and methods

Psychiatric samples

Anthropometric measurements (weight and height), demographic variables (sex and age), history of treatments (treatment duration and psychotropic treatment), co-medications and lipid variables (i.e. HDL, LDL, TC and TG) were collected at baseline (i.e. before psychotropic treatment) and 1, 3 and 12 months after initiating a treatment with weight gain – inducing psychotropic drug. Patients having switched to such medication (i.e. non treatment-naive patients) were also included. Most blood samples were drawn in the morning in fasting conditions. Non-fasting blood samples (i.e. within six hours following last meal) were excluded for triglyceride analysis (1) and not for total, HDL- and LDL-cholesterol (1). Most clinical chemistry assays were conducted by the clinical laboratory, Department of Biomedicine, Lausanne University Hospital, which is ISO 15189:2012 certified. LDL-cholesterol was calculated using the Friedewald formula only if triglyceride levels were lower than 4.6 mmol/l (2).

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 aripiprazole, amisulpride, clozapine, haloperidol, olanzapine, risperidone, OH-risperidone (paliperidone), quetiapine or plasma levels as previously described (3-5) and/or as recommended in our unit (Eap et al., unpublished data, available on request). Mirtazapine was measured by gas-chromatography-nitrogen detector (Eap et al., unpublished data, available on request), valproate 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 in our accredited laboratory (ISO 15189

and 17025). Patients were considered compliant when drug plasma concentrations were higher than 10% of the lower value of the recommended therapeutic range (6). Of note, the sum of plasma concentrations risperidone and of its metabolite OH-risperidone was used.

Genotyping

The iSelect genotyping array was designed to test DNA variations of 200'000 SNPs from regions associated with metabolic and cardiovascular characteristics (7). All genotyped SNPs underwent quality control tests: when sex was inconsistent with genetic data from X-linked markers and genotype call rate was < 0.8, samples were excluded from the analyses. The results were extracted using the software GenomeStudio Data Analysis.

From the reviewed variants, SNPs (or proxies with $r^2 \geq 0.8$ and a MAF≥5%) that were not available in the CardioMetabochip in the psychiatric sample were genotyped by the KBioscience Institute in the United Kingdom using the novel fluorescence-based competitive allele-specific PCR technology (KASP™) as described by the manufacturer. Genotyping of one SNP (rs1047891) with missing values for a subset of patients was performed using TaqMan SNP Genotyping Assays on ViiA™ 7 Real-Time PCR System as described by the manufacturer's instructions.

Ethnicity was assessed by patient's reported ethnicity and confirmed by genotyping using principal component analysis with the EIGENSTRAT algorithm implemented in GCTA software (8). The majority of the variance was explained by the two first vectors, and Caucasian ethnicity was arbitrarily selected when pca1<0.0025 and pca2>-0.0125, values which gave the highest concordance with the patient's reported ethnicity.

Construction of the PRSs

Among the different PRS model approaches (e.g. simple count or odds ratio weighted PRS), a weighted PRS (wPRS) is a more adequate option than unweighted PRS since allele effects (β-coefficients) vary among SNPs (9). In the present study, PRS were constructed as a weighted sum of all SNPs. Each patient received for each SNP the coding value of 0, 1 or 2 according to the number of risk alleles. For instance, for a given SNP, a score of 1 was assigned for a carrier of one risk allele, whereas a value of 0 was attributed to non-carriers of this risk allele. Weighted PRS were subsequently obtained by the summation of the lipid-associated risk alleles multiplied by their effect size reported for each SNP in corresponding meta-analyses, assuming that each SNP contributes to the PRS in an additive way (10,11). In order to facilitate interpretation of the results, wPRS were then rescaled according to a calculation described elsewhere (9). Of note, increasing the wPRS by one unit indicates one additional lipid-association risk allele (12).

Construction and interpretation of AUC

AUC of the models were compared using a bootstrap test as published previously (13). An AUC of 0.5 would indicate a random test with 50% chance of positive response, whereas an AUC of 1 suggests an ideal test where all patients are correctly classified (14). Tests having an AUC of 0.75 or higher are considered informative and useful (15).

Results

Influence of GAMM covariates on the evolution of lipid levels during psychotropic treatment

The evolution of lipid levels during psychotropic treatment according to covariates taken into account in GAMM analyses is presented in **S2-S6 Figures**. Because of their known influence on psychotropic-drug induced metabolic abnormalities (16), these variables were included in mixed models. Of note, although no study has been conducted yet to determine an influence of

psychotropic drug class on the deterioration of lipid profile, this variable was also considered in mixed models. The difference of lipid levels between patients whose BMI was above or below the BMI median was statistically significant for HDL, LDL, TC and TG levels (p=0.03, 0.0005, 0.003 and 0.001, respectively, **S2 Figure**). In addition, the difference of HDL, LDL and TC levels between patients younger or older than the median age was statistically significant (p=0.007, 0.01, 0.001, respectively, **S3 Figure**), but not for TG levels (p=0.82). Women had significantly higher levels of HDL, LDL and TC (p<0.0001, p=0.005, p<0.0001) but not of TG levels (p=0.32, **S4 Figure**). No difference of HDL, LDL and TC levels was observed between psychotropic drug classes. However, patients receiving mood stabilizers had significantly higher TG levels compared to those receiving antipsychotics (**S5 Figure**). Finally, although smoking status was not associated with lipid levels (p>0.05, **S6 Figure**), this variable was considered in GAMM because non smokers were observed to have a more favourable lipid profile compared to smokers in a recent systematic review and meta-analysis (17).

Influence of polygenic risk scores on lipid phenotype worsening during psychotropic treatment

The evolution of lipid levels during psychotropic treatment according to high- and low- wPRS groups is presented in **S7-S8 Figures**. The more extreme the groups were, the higher the differences of each lipid level were measured between the groups. Overall, HDL was the only lipid trait that did not significantly change along the psychotropic treatment (p=0.62), whereas LDL, TC and TG levels significantly increased over time (p=0.01, 0.001 and 0.03 respectively, **S9 Figure)**. The difference of lipid levels between high- and low- risk wPRS were statistically significant for HDL and TG levels (p=0.002), but not for LDL and TC levels (p=0.25 and 0.31, respectively; **S9 Figure)**. **S10 Figure** represents the evolution of dyslipidemia prevalence according to the two groups of p50-classified wPRS. The same patterns of evolution were observed as described previously (i.e. influence of p50-classified wPRS groups on HDL and TG levels, but no clear effect on LDL and TC levels). Comparison of extreme wPRS percentiles (i.e.

p25-p75 and p10-p90) in **S11 and S12 Figures,** respectively, allowed to better illustrate the evolution of lipid variables in function of the wPRS.

To date, many publications showed that the influence of genetic susceptibilities is greater among young patients (18-21). For exploratory purposes, and despite the fact that there was no significant interaction between age and wPRS on lipid levels in the present study, GAMMs were performed by stratifying the combined psychiatric sample according to the median of age (**S15 Table**). In young patients, weighted PRSs were significantly associated with each lipid trait ($p \leq 0.006$) apart from LDL ($p=0.08$), whereas they were significant for all lipid traits in old patients ($p \leq 0.03$). Among statistical analyses not adjusted for covariates, in young patients (**S13 and S14 Figures**), a significant influence of low- and high- risk wPRS groups was observed on HDL ($p=0.02$) and a similar trend was observed for TG ($p=0.07$). In patients older than the median of age, low- and high- risk wPRSs were also significantly associated with HDL and TG (**S15 and S16 Figures**; $p=0.002$ and 0.009 respectively), but along the treatment, HDL and TG levels of the two wPRS groups tended to converge. Interestingly, it seemed that low-risk wPRS patients tended to reach the same lipid levels than high-risk wPRS patients for HDL and TG after several months of psychotropic treatment.

Interaction between polygenic risk scores and covariates on lipid phenotypes

S17 Table displays results of interaction between wPRSs and age, sex and BMI on the four lipid phenotypes. A significant interaction was observed between wPRSs and BMI on LDL ($p=0.02$), and between wPRS and sex on TC ($p=0.04$). These results suggest that the influence of wPRS on LDL may be tested in BMI-stratified subsamples, and that the influence of wPRS on TC may be tested in men and women separately. GAMM performed in BMI-stratified samples showed a significant association between p50-classified wPRS groups and LDL only in patients having a BMI higher than the median value (**S18 Table**; 0.46 mmol/l; $p<0.0001$). In analyses not adjusted for covariates, no influence of wPRS on LDL within both BMI subgroups was observed (**S18**

Figure). Moreover, AUC of the model including genetics compared to the model with only clinical data was not significantly increased in both BMI subgroups (**S19 Figure**), possibly because of a poor statistical power. With regard to analyses of association between p50-classified wPRS groups and TC levels performed in men and women separately, significant influences were observed in both sexes (**S18 Table**; p≤0.01). **S20 Figure** shows that the prevalence of hypercholesterolemia seemed higher in women than in men, and that the influence of p50-classified wPRS groups on total hypercholesterolemia was greater in the former group compared to the latter (p=0.009 for women and p=0.98 for men). ROC curves suggest a higher increase of AUC with the model incorporating genetic data compared to the model with clinical data only, in women (AUC = 0.74 versus 0.67; p=0.11), compared to men (AUC = 0.78 versus 0.77; p=0.43), although none reached statistical significance in both gender.

S1 Table. Characteristics of psychiatric Caucasian samples: discovery, replication and combined samples

Characteristics	n	Discovery sample	n	Replication sample	p-value[7]	n	Combined sample
Male, n (%)	332	142 (42.8)	140	65 (46.4)	0.46	472	207 (43.8)
Age, median (IQ range), *years*	332	48 (29-73)	140	49.5 (33-68)	0.87	472	48 (30-71)
BMI							
Inital BMI, median (IQ range), *kg/m²* [1]	332	23.3 (20.6-26.9)	140	24.9 (21.4-28.2)	0.06	472	23.7 (20.9-27.5)
Initial BMI ≤25 *kg/m²*, n (%) [1,2]		211 (63.5)		75 (53.6)			286 (60.6)
Initial BMI 25-30 *kg/m²*, n (%) [1,2]		69 (20.8)		42 (30.0)	0.07		111 (23.5)
Initial BMI ≥30 *kg/m²*,n (%) [1,2]		52 (15.7)		23 (16.4)			75 (15.9)
Current BMI, median (IQ range), *kg/m²* [2,3]	332	24.4 (21.7-28.1)	140	25.1 (21.6-29.5)	0.31	472	24.5 (21.7-28.4)
Current BMI ≤25 *kg/m²*,n (%) [2,3]		184 (55.4)		70 (50.0)			254 (53.8)
Current BMI 25-30 *kg/m²*,n (%) [2,3]		90 (27.1)		38 (27.1)	0.36		128 (27.1)
Current BMI≥30 *kg/m²*,n (%) [2,3]		58 (17.5)		32 (22.9)			90 (19.1)
Lipids levels							
Lipids levels at baseline [4]							
Total cholesterol, median (IQ range), *mmol/l*	331	4.7 (3.9-5.6)	140	5.2 (4.3-5.9)	**0.002**	471	4.8 (4-5.7)
Total cholesterol < 5 mmol/l, n (%) [5]		189 (57.1)		62 (44.3)	**0.01**		251 (53.3)
Total cholesterol ≥ 5 mmol/l, n (%) [5]		142 (42.9)		78 (55.7)			220 (46.7)
Total cholesterol < 5 mmol/l, n (%) [5] **without hypolipemiant**		167 (50.5)		55 (39.3)	**0.02**		222 (47.3)
Total cholesterol ≥ 5 mmol/l, n (%) [5] **or treated dyslipidemia**		164 (49.6)		85 (60.7)			249 (52.7)
HDL, median (IQ range), *mmol/l*	325	1.4 (1.1-1.6)	139	1.4 (1.1-1.7)	0.41	464	1.4 (1.1-1.7)
HDL > 1 mmol/l, n (%) [5]		272 (83.7)		111 (79.9)	0.32		383 (82.5)
HDL ≤ 1 mmol/l, n (%) [5]		53 (16.3)		28 (20.1)			81 (17.5)
HDL > 1 mmol/l, n (%) [5] **without hypolipemiant**		251 (77.2)		104 (74.8)	0.57		355 (76.5)
HDL ≤ 1 mmol/l, n (%) [5] **or treated dyslipidemia**		74 (22.8)		35 (25.2)			109 (23.5)
LDL, median (IQ range), *mmol/l*	314	2.6 (2.1-3.5)	133	3.0 (2.4-3.6)	**0.005**	447	2.7 (2.1-3.5)
LDL < 3 mmol/l, n (%) [5]		187 (59.6)		66 (49.6)	**0.05**		253 (56.6)
LDL ≥ 3 mmol/l, n (%) [5]		127 (40.5)		67 (50.4)			194 (43.4)
LDL < 3 mmol/l, n (%) [5] **without hypolipemiant**		164 (52.2)		60 (45.1)	0.15		224 (50.1)
LDL ≥ 3 mmol/l, n (%) [5] **or treated dyslipidemia**		150 (47.7)		73 (54.9)			223 (49.9)
Triglycerides, median (IQ range), *mmol/l*	168	1.0 (0.8-1.3)	59	1.1 (0.8-1.6)	0.5	227	1.0 (0.8-1.4)
Triglycerides < 2 mmol/l, n (%) [5,8]		153 (91.1)		48 (81.4)	0.54		201 (88.6)
Triglycerides ≥ 2 mmol/l, n (%) [5,8]		15 (8.9)		11 (18.6)			26 (11.5)
Triglycerides < 2 mmol/l, n (%) [5,8] **without hypolipemiant**		142 (84.5)		46 (77.9)	0.97		188 (82.8)
Triglycerides ≥ 2 mmol/l, n (%) [5,8] **or treated dyslipidemia**		26 (15.5)		13 (22.1)			39 (17.2)
Treatment with hypolipemiant, n (%)	332	28 (8.4)	140	9 (6.4)	0.29	472	37 (7.8)
Lipids levels at current state [6]							
Total cholesterol, median (IQ range), *mmol/l*	328	5.0 (4.1-5.8)	140	5.2 (4.4-5.8)		468	5.0 (4.2-5.8)
Total cholesterol < 5 mmol/l, n (%) [5]		164 (50.0)		59 (42.1)	0.06		223 (47.6)
Total cholesterol ≥ 5 mmol/l, n (%) [5]		164 (50.0)		81 (57.9)			245 (52.3)
Total cholesterol < 5 mmol/l, n (%) [5] **without hypolipemiant**		134 (40.9)		50 (35.7)	0.30		181 (38.7)
Total cholesterol ≥ 5 mmol/l, n (%) [5] **or treated dyslipidemia**		194 (59.2)		90 (64.3)			287 (61.3)
HDL, median (IQ range), *mmol/l*	325	1.3 (1.1-1.6)	139	1.4 (1.1-1.7)	0.23	464	1.3 (1.1-1.6)
HDL > 1 mmol/l, n (%) [5]		256 (78.8)		110 (79.1)	0.93		366 (78.9)
HDL ≤ 1 mmol/l, n (%) [5]		69 (21.2)		29 (20.9)			98 (21.1)
HDL > 1 mmol/l, n (%) [5] **without hypolipemiant**		228 (70.2)		100 (71.9)	0.69		327 (70.5)
HDL ≤ 1 mmol/l, n (%) [5] **or treated dyslipidemia**		97 (29.9)		39 (28.1)			137 (29.5)
LDL, median (IQ range),*mmol/l*	305	2.8 (2.2-3.5)	131	3.1 (2.4-3.7)	0.13	436	2.9 (2.3-3.5)
LDL < 3 mmol/l, n (%) [5]		174 (57.1)		60 (45.8)	**0.03**		234 (53.7)
LDL ≥ 3 mmol/l, n (%) [5]		131 (43.0)		71 (54.2)			202 (46.3)
LDL < 3 mmol/l, n (%) [5] **without hypolipemiant**		143 (46.9)		52 (39.7)	0.16		193 (44.3)
LDL ≥ 3 mmol/l, n (%) [5] **or treated dyslipidemia**		162 (53.1)		79 (60.3)			243 (55.7)

Characteristics	n	Discovery sample	n	Replication sample	p-value[7]	n	Combined sample
Male, n (%)	332	142 (42.8)	140	65 (46.4)	0.46	472	207 (43.8)
Age, median (IQ range), *years*	332	48 (29-73)	140	49.5 (33-68)	0.87	472	48 (30-71)
Lipids levels at current state [6]							
Triglycerides, median (IQ range), *mmol/l*	241	1.2 (0.8-1.6)	96	1.3 (0.6-1.9)	0.06	337	1.2 (0.9-1.7)
Triglycerides < 2 mmol/l, n (%) [5,8]		198 (82.2)		74 (77.1)	0.38		272 (80.7)
Triglycerides ≥ 2 mmol/l, n (%) [5,8]		43 (17.8)		22 (22.9)			65 (19.3)
Triglycerides < 2 mmol/l, n (%) [5,8] without hypolipemiant		176 (73.0)		67 (69.8)	0.65		243 (72.1)
Triglycerides ≥ 2 mmol/l, n (%) [5,8] or treated dyslipidemia		65 (27.0)		29 (30.2)			94 (27.9)
Treatment with hypolipemiant, n (%)	332	38 (11.4)	140	13 (9.3)	0.44	472	51 (10.8)
Medication, n (%)							
Amisulpride	331	27 (8.2)	140	10 (7.1)		471	37 (7.9)
Aripiprazole		24 (7.3)		15 (10.7)			39 (8.3)
Clozapine		25 (7.6)		9 (6.4)			34 (7.2)
Lithium		23 (7.0)		13 (9.3)			36 (7.6)
Mirtazapine		13 (3.9)		9 (6.4)	0.15		22 (4.7)
Olanzapine		43 (13.0)		8 (5.7)			51 (10.8)
Paliperidone		1 (0.3)		3 (2.1)			4 (0.8)
Quetiapine		109 (32.9)		49 (35.0)			158 (33.5)
Risperidone		50 (15.1)		17 (12.1)			67 (14.2)
Valproate		16 (4.8)		7 (5.0)			23 (4.9)
Main diagnosis, n (%)							
Organic mental disorders	276	30 (10.9)	94	11 (11.7)		370	41 (11.1)
Psychotic disorders		90 (32.6)		31 (32.9)			121 (32.7)
Schizoaffective disorders		22 (7.9)		13 (13.8)	0.49		35 (9.5)
Bipolar disorders		66 (23.9)		20 (21.3)			86 (23.2)
Depressive disorder		68 (24.6)		19 (20.2)			87 (23.5)
Smoker, n (%)	332	108 (32.5)	140	57 (40.7)	0.51	472	165 (34.9)
Treatment duration, median (IQ range), *days*	332	146.5 (67-370)	140	110 (51-372)	0.12	472	134 (59-370)

[1] Initial BMI represents BMI before the current psychotropic treatment.

[2] BMI from >25 to <30 kg/m^2 refers to overweight, BMI ≥ 30 kg/m^2 refers to obesity.

[3] Current BMI represents BMI at the end of the follow-up.

[4] Lipid levels at baseline represent lipid values before the current psychotropic treatment.

[5] Lipid level thresholds were defined according to ESH/ESC guidelines (22).

[6] Lipid levels at current state represent lipid values at the end of the follow-up.

[7] P-values were calculated using Wilcoxon-Mann-Whitney tests for Chi^2 tests between the two psychiatric samples. Values in bold are significant.

[8] Triglyceride levels were collected in fasting conditions.

S2 Table. List of SNPs from the Global Lipids Genetics Consortium meta-analysis with their β-effect on HDL and HWE p-value

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	GWAS p-value	HWE p-value
1	rs1883025	ABCA1	rs1883025		C/T	0.75	0.070	2E-65	0.463
2	rs4148008	ABCA8	rs4148005	1.000	C/G	0.67	0.028	1E-12	0.546
3	rs13076253	ACAD11	rs13076253		G/T	0.86	0.028	5E-09	0.060
4	rs2602836	ADH5	rs2602836		A/G	0.44	0.019	5E-08	0.129
5	rs2923084	AMPD3	rs2923084		A/G	0.82	0.026	5E-08	0.062
6	rs7255436	ANGPTL4	rs2278236	0.965	A/C	0.53	0.032	2E-08	0.788
7	rs737337	ANGPTL8	rs737337		T/C	0.89	0.056	5E-17	0.511
8	rs964184	APOA1	rs964184		C/G	0.84	0.106	6E-48	0.482
9	rs6450176	ARL15	rs6450176		G/A	0.74	0.025	7E-10	0.287
10	rs2606736	ATG7	rs2606736		C/T	0.39	0.025	5E-08	0.734
11	rs10019888	C4orf52	rs10019888		A/G	0.82	0.027	5E-08	0.461
12	rs3764261	CETP	rs3764261		A/C	0.32	0.241	1E-769	0.432
13	rs605066	CITED2	rs651837	1.000	T/C	0.58	0.028	3E-08	0.756
14	rs2925979	CMIP	rs2925979		C/T	0.69	0.035	1E-19	0.479
15	rs12328675	COBLL1	rs12328675		C/T	0.13	0.045	2E-15	0.542
16	rs1047891	CPS1	rs1047891		C/A	0.67	0.027	9E-10	0.737
17	rs702485	DAGLB	rs702485		G/A	0.45	0.024	6E-12	0.905
18	rs174546	FADS1-2-3	rs174546		C/T	0.64	0.039	8E-28	0.450
19	rs3822072	FAM13A	rs3822072		G/A	0.54	0.025	4E-12	0.237
20	rs1121980	FTO	rs1121980		G/A	0.57	0.020	7E-09	0.812
21	rs4846914	GALNT2	rs4846914		A/G	0.59	0.048	4E-41	0.441
22	rs6805251	GSK3B	rs6805251		T/C	0.39	0.020	1E-08	0.593
23	rs17695224	HAS1	rs17695224		G/A	0.74	0.029	2E-13	0.916
24	rs12145743	HDGF-PMVK	rs12145743		G/T	0.34	0.020	2E-08	0.946
25	rs1800961	HNF4A	rs1800961		C/T	0.95	0.127	2E-34	0.647
26	rs4917014	IKZF1	rs4917014		G/T	0.32	0.022	1E-08	0.201
27	rs2972146	IRS1	rs1515100	0.891	G/T	0.37	0.032	2E-17	0.082
28	rs4731702	KLF14	rs4731702		T/C	0.49	0.029	5E-17	0.965
29	rs2652834	LACTB	rs2652834		G/A	0.79	0.028	4E-11	0.346
30	rs16942887	LCAT	rs16942887		A/G	0.14	0.083	8E-54	0.117
31	rs386000	LILRA3	rs386000		C/G	0.26	0.048	3E-23	0.818
32	rs1532085	LIPC	rs1532085		A/G	0.40	0.107	1E-188	0.688
33	rs7241918	LIPG	rs10438978	1.000	T/G	0.81	0.090	1E-44	0.064
34	rs12678919	LPL	rs12678919		G/A	0.13	0.155	1E-149	0.411
35	rs11613352	LRP1	rs11613352		T/C	0.26	0.028	2E-13	0.165
36	rs3136441	LRP4	rs3136441		C/T	0.18	0.054	7E-29	0.380
37	rs970548	MARCH8-ALOX5	rs970548		C/A	0.26	0.026	2E-10	0.787
38	rs12967135	MC4R	rs523288	1.000	G/A	0.75	0.026	4E-08	0.327
39	rs499974	MOGAT2-DGAT2	rs499974		C/A	0.81	0.026	1E-08	0.472
40	rs7134594	MVK	rs7134594		T/C	0.52	0.035	2E-13	0.128

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	GWAS p-value	HWE p-value
41	rs11246602	OR4C46	rs11246602		C/T	0.15	0.034	2E-10	0.140
42	rs4660293	PABPC4	rs4660293		A/G	0.76	0.035	3E-18	0.201
43	rs7134375	PDE3A	rs7134375		A/C	0.43	0.021	1E-08	0.526
44	rs731839	PEPD	rs731839		A/G	0.65	0.022	3E-09	0.109
45	rs4129767	PGS1	rs4129767		A/G	0.52	0.024	2E-11	0.359
46	rs12748152	PIGV-NROB2	rs12748152		C/T	0.91	0.051	1E-15	0.672
47	rs6065906	PLTP	rs6065906		T/C	0.81	0.059	5E-40	0.093
48	rs9987289	PPP1R3B	rs9987289		G/A	0.90	0.082	2E-41	0.352
49	rs2013208	RBM5	rs2013208		T/C	0.50	0.025	9E-12	0.374
50	rs1936800	RSPO3	rs1936800		C/T	0.49	0.020	3E-10	0.858
51	rs4759375	SBNO1	rs4759377	1.000	T/C	0.08	0.056	3E-08	0.380
52	rs838880	SCARB1	rs838880		C/T	0.34	0.048	6E-32	0.645
53	rs13107325	SLC39A8	rs13107325		C/T	0.92	0.071	1E-15	0.345
54	rs4142995	SNX13	rs4142995		G/T	0.62	0.026	9E-12	0.869
55	rs13326165	STAB1	rs13326165		A/G	0.21	0.029	9E-11	0.099
56	rs11869286	STARD3	chr17:35067382		C/G	0.65	0.032	3E-17	0.142
57	rs17173637	TMEM176A	rs17173637		T/C	0.88	0.036	2E-08	0.830
58	rs2954029	TRIB1	rs2954029		T/A	0.47	0.040	3E-29	0.592
59	rs581080	TTC39B	chr9:15295378		C/G	0.79	0.042	1E-19	0.156
60	rs7941030	UBASH3B	rs7941030		C/T	0.39	0.027	1E-14	0.349
61	rs181362	UBE2L3	rs181362		C/T	0.77	0.038	4E-18	0.514
62	rs998584	VEGFA	rs1358980	0.837	C/A	0.51	0.026	2E-11	0.786
63	rs4983559	ZBTB42-AKT1	rs4983559		G/A	0.40	0.020	1E-08	0.297
64	rs1689800	ZNF648	rs1689800		A/G	0.65	0.034	5E-20	0.757
65	rs4765127	ZNF664	rs11057408	1.000	T/G	0.35	0.032	8E-10	0.834

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error. CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S3 Table. List of the selected SNPs from the Engage Consortium meta-analysis with their β-effect on HDL and HWE p-value

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
1	rs1883025	ABCA1	rs1883025		C/T	0.76	0.085	0.007	6.9E-31	0.463
2	rs4148008	ABCA6/8	rs4148005	1.000	C/G	0.68	0.020	0.007	3.0E-03	0.546
3	rs2602836	ADH5	rs2602836		A/G	0.44	0.023	0.006	2.9E-04	0.129
4	rs7255436	ANGPTL4	rs2278236	0.965	A/C	0.55	0.027	0.006	1.1E-05	0.788
5	rs2678379	APOB	rs1042034	1.000	A/G	0.24	0.065	0.007	7.2E-21	0.192
6	rs964184	APO-cluster	rs964184		C/G	0.87	0.102	0.009	9.7E-29	0.482
7	rs2606736	ATG7	rs2606736		C/T	0.38	0.034	0.006	3.7E-08	0.734
8	rs6657811	CELSR2-SORT1	rs6657811		T/A	0.12	0.057	0.009	1.9E-09	0.637
9	rs17231506	CETP	rs3764261	1.000	T/C	0.31	0.243	0.006	6.9E-316	0.432
10	rs605066	CITED2	rs651837	1.000	T/C	0.56	0.026	0.006	1.3E-05	0.756
11	rs56823429	CMIP	rs2925979	0.885	A/C	0.71	0.037	0.007	1.7E-08	0.479
12	rs174601	FADS1-2-3	rs174546	0.895	C/T	0.60	0.036	0.006	1.1E-08	0.450
13	rs4846914	GALNT2	rs4846914		A/G	0.59	0.048	0.006	3.3E-14	0.441
14	rs77147124	GPAM	rs1129555	1.000	A/G	0.28	0.039	0.007	7.4E-09	0.418
15	rs116569761	HLA-area	rs9275052		A/G	0.53	0.036	0.006	3.5E-08	0.182
16	rs1800961	HNF4A	rs1800961		C/T	0.96	0.149	0.016	5.1E-20	0.647
17	rs2713536	IRS1	rs1515100	1.000	C/T	0.38	0.038	0.006	3.4E-10	0.082
18	rs13241165	KLF14	rs4731702	1.000	T/A	0.51	0.037	0.006	8.4E-10	0.965
19	rs386000	LILRA3/5	rs386000		C/G	0.26	0.043	0.007	5.6E-09	0.818
20	rs1532085	LIPC	rs1532085		A/G	0.40	0.121	0.006	4.2E-86	0.688
21	rs10438978	LIPG	rs10438978		C/T	0.81	0.095	0.008	7.7E-36	0.064
22	rs12678919	LPL	rs12678919		G/A	0.09	0.167	0.011	5.7E-54	0.411
23	rs3741414	LRP1	rs11613352	0.959	T/C	0.27	0.028	0.007	9.4E-05	0.165
24	rs4660293	MACF1, PABPC4	rs4660293		A/G	0.77	0.039	0.007	2.2E-08	0.201
25	rs10838692	MADD	rs10838692		C/T	0.36	0.060	0.006	8.2E-21	0.704
26	rs970548	MARCH8	rs970548		C/A	0.25	0.028	0.007	3.8E-05	0.787
27	rs7134594	MMAB-MVK	rs7134594		T/C	0.52	0.036	0.006	1.7E-09	0.128
28	rs483465	MSL2L1	rs1279840	1.000	A/G	0.21	0.045	0.007	3.7E-10	0.226
29	rs12948394	PGS1	rs4129767	0.904	C/T	0.55	0.034	0.006	3.9E-08	0.359
30	rs12748152	PIGV-NROB2	rs12748152		C/T	0.91	0.050	0.010	1.3E-06	0.672
31	rs6073972	PLTP	rs6065906	1.000	C/G	0.81	0.065	0.008	9.2E-18	0.093
32	rs9987289	PPP1R3B	rs9987289		G/A	0.90	0.094	0.010	5.7E-20	0.352
33	rs78058190	PRKAG3	rs78058190		G/A	0.95	0.141	0.020	5.7E-12	0.811
34	rs73591976	RANBP10, LCAT	rs16942887	1.000	A/C	0.12	0.096	0.009	8.6E-26	0.117
35	rs7188861	RMI2	rs2867936	0.813	A/C	0.20	0.044	0.008	6.9E-09	0.734
36	rs1936800	RSPO3	rs1936800		C/T	0.47	0.021	0.006	4.8E-04	0.858
37	rs838880	SCARB1	rs838880		C/T	0.36	0.056	0.006	3.7E-18	0.645
38	rs13107325	SLC39A8	rs13107325		C/T	0.97	0.120	0.018	9.6E-12	0.345
39	rs2814944	SNRPC	rs2814944		G/A	0.84	0.048	0.008	1.7E-08	0.085
40	rs10808546	TRIB1	rs2954029	1.000	T/C	0.46	0.037	0.006	3.7E-09	0.592
41	rs540885	TTC39B	rs643531	1.000	A/G	0.87	0.055	0.009	5.2E-10	0.733
42	rs7115089	UBASH3B	rs7941030	0.871	G/C	0.39	0.019	0.006	2.2E-03	0.349
43	rs5754344	UBE2L3	rs181362	1.000	A/G	0.78	0.045	0.007	2.2E-10	0.514
44	rs998584	VEGFA	rs1358980	0.837	C/A	0.51	0.018	0.006	4.9E-03	0.786
45	rs4983559	ZBTB42-AKT1	rs4983559		G/A	0.38	0.039	0.007	1.9E-08	0.297
46	rs1689800	ZNF648	rs1689800		A/G	0.67	0.033	0.006	1.6E-07	0.757

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error. CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S4 Table. List of the selected SNPs from combined meta-analyses with their β-effect on HDL and HWE p-value

Number	Article	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
1	I	rs1883025	ABCA1	rs1883025		C/T	0.76	0.085	0.007	6.9E-31	0.463
2	D	rs4148008	ABCA8	rs4148005	1.000	C/G	0.67	0.028		1E-12	0.546
3	D	rs13076253	ACAD11	rs13076253		G/T	0.86	0.028		5E-09	0.060
4	D	rs2602836	ADH5	rs2602836		A/G	0.44	0.019		5E-08	0.129
5	D	rs2923084	AMPD3	rs2923084		A/G	0.82	0.026		5E-08	0.062
6	D	rs7255436	ANGPTL4	rs2278236	0.965	A/C	0.53	0.032		2E-08	0.788
7	D	rs737337	ANGPTL8	rs737337		T/C	0.89	0.056		5E-17	0.511
8	I	rs964184	APO-cluster	rs964184		C/G	0.87	0.102	0.009	9.7E-29	0.482
9	I	rs2678379	APOB	rs1042034	1.000	A/G	0.24	0.065	0.007	7.2E-21	0.192
10	D	rs6450176	ARL15	rs6450176		G/A	0.74	0.025		7E-10	0.287
11	I	rs2606736	ATG7	rs2606736		C/T	0.38	0.034	0.006	3.7E-08	0.734
12	D	rs10019888	C4orf52	rs10019888		A/G	0.82	0.027		5E-08	0.461
13	I	rs6657811	CELSR2-SORT1	rs6657811		T/A	0.12	0.057	0.009	1.9E-09	0.637
14	I	rs17231506	CETP	rs3764261	1.000	T/C	0.31	0.243	0.006	6.9E-316	0.432
15	D	rs605066	CITED2	rs651837	1.000	T/C	0.58	0.028		3E-08	0.756
16	D	rs2925979	CMIP	rs2925979		C/T	0.69	0.035		1E-19	0.479
17	D	rs12328675	COBLL1	rs12328675		C/T	0.13	0.045		2E-15	0.542
18	D	rs1047891	CPS1	rs1047891		C/A	0.67	0.027		9E-10	0.737
19	D	rs702485	DAGLB	rs702485		G/A	0.45	0.024		6E-12	0.905
20	D	rs174546	FADS1-2-3	rs174546		C/T	0.64	0.039		8E-28	0.450
21	D	rs3822072	FAM13A	rs3822072		G/A	0.54	0.025		4E-12	0.237
22	D	rs1121980	FTO	rs1121980		G/A	0.57	0.020		7E-09	0.812
23	I	rs4846914	GALNT2	rs4846914		A/G	0.59	0.048	0.006	3.3E-14	0.441
24	I	rs77147124	GPAM	rs1129555	1.000	A/G	0.28	0.039	0.007	7.4E-09	0.418
25	D	rs6805251	GSK3B	rs6805251		T/C	0.39	0.020		1E-08	0.593
26	D	rs17695224	HAS1	rs17695224		G/A	0.74	0.029		2E-13	0.916
27	D	rs12145743	HDGF-PMVK	rs12145743		G/T	0.34	0.020		2E-08	0.946
28	I	rs116569761	HLA-area	rs9275052		A/G	0.53	0.036	0.006	3.5E-08	0.182
29	I	rs1800961	HNF4A	rs1800961		C/T	0.96	0.149	0.016	5.1E-20	0.647
30	D	rs4917014	IKZF1	rs4917014		G/T	0.32	0.022		1E-08	0.201
31	I	rs2713536	IRS1	rs1515100	1.000	C/T	0.38	0.038	0.006	3.4E-10	0.082
32	I	rs13241165	KLF14	rs4731702	1.000	T/A	0.51	0.037	0.006	8.4E-10	0.965
33	D	rs2652834	LACTB	rs2652834		G/A	0.79	0.028		4E-11	0.346
34	I	rs386000	LILRA3/5	rs386000		C/G	0.26	0.043	0.007	5.6E-09	0.818
35	I	rs1532085	LIPC	rs1532085		A/G	0.40	0.121	0.006	4.2E-86	0.688
36	I	rs10438978	LIPG	rs10438978		C/T	0.81	0.095	0.008	7.7E-36	0.064
37	I	rs12678919	LPL	rs12678919		G/A	0.09	0.167	0.011	5.7E-54	0.411
38	D	rs11613352	LRP1	rs11613352		T/C	0.26	0.028		2E-13	0.165
39	I	rs4660293	MACF1, PABPC4	rs4660293		A/G	0.77	0.039	0.007	2.2E-08	0.201
40	I	rs10838692	MADD	rs10838692		C/T	0.36	0.060	0.006	8.2E-21	0.704

Number	Article	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
41	D	rs970548	MARCH8-ALOX5	rs970548		C/A	0.26	0.026		2E-10	0.787
42	D	rs12967135	MC4R	rs523288	1.000	G/A	0.75	0.026		4E-08	0.327
43	D	rs499974	MOGAT2-DGAT2	rs499974		C/A	0.81	0.026		1E-08	0.472
44	I	rs7134594	MMAB-MVK	rs7134594		T/C	0.52	0.036	0.006	1.7E-09	0.128
45	I	rs483465	MSL2L1	rs1279840	1.000	A/G	0.21	0.045	0.007	3.7E-10	0.226
46	D	rs11246602	OR4C46	rs11246602		C/T	0.15	0.034		2E-10	0.140
47	D	rs7134375	PDE3A	rs7134375		A/C	0.43	0.021		1E-08	0.526
48	D	rs731839	PEPD	rs731839		A/G	0.65	0.022		3E-09	0.109
49	I	rs12948394	PGS1	rs4129767	0.904	C/T	0.55	0.034	0.006	3.9E-08	0.359
50	D	rs12748152	PIGV-NROB2	rs12748152		C/T	0.91	0.051		1E-15	0.672
51	I	rs6073972	PLTP	rs6065906	1.000	C/G	0.81	0.065	0.008	9.2E-18	0.093
52	I	rs9987289	PPP1R3B	rs9987289		G/A	0.90	0.094	0.010	5.7E-20	0.352
53	I	rs78058190	PRKAG3	rs78058190		G/A	0.95	0.141	0.020	5.7E-12	0.811
54	I	rs73591976	RANBP10, LCAT	rs16942887	1.000	A/C	0.12	0.096	0.009	8.6E-26	0.117
55	D	rs2013208	RBM5	rs2013208		T/C	0.50	0.025		9E-12	0.374
56	I	rs7188861	RMI2	rs2867936	0.813	A/C	0.20	0.044	0.008	6.9E-09	0.734
57	D	rs1936800	RSPO3	rs1936800		C/T	0.49	0.020		3E-10	0.858
58	D	rs4759375	SBNO1	rs4759377	1.000	T/C	0.08	0.056		3E-08	0.380
59	I	rs838880	SCARB1	rs838880		C/T	0.36	0.056	0.006	3.7E-18	0.645
60	I	rs13107325	SLC39A8	rs13107325		C/T	0.97	0.120	0.018	9.6E-12	0.345
61	I	rs2814944	SNRPC	rs2814944		G/A	0.84	0.048	0.008	1.7E-08	0.085
62	D	rs4142995	SNX13	rs4142995		G/T	0.62	0.026		9E-12	0.869
63	D	rs13326165	STAB1	rs13326165		A/G	0.21	0.029		9E-11	0.099
64	D	rs11869286	STARD3	chr17:35067382		C/G	0.65	0.032		3E-17	0.142
65	D	rs17173637	TMEM176A	rs17173637		T/C	0.88	0.036		2E-08	0.830
66	I	rs10808546	TRIB1	rs2954029	1.000	T/C	0.46	0.037	0.006	3.7E-09	0.592
67	I	rs540885	TTC39B	rs643531	1.000	A/G	0.87	0.055	0.009	5.2E-10	0.733
68	D	rs7941030	UBASH3B	rs7941030		C/T	0.39	0.027		1E-14	0.349
69	I	rs5754344	UBE2L3	rs181362	1.000	A/G	0.78	0.045	0.007	2.2E-10	0.514
70	D	rs998584	VEGFA	rs1358980	0.837	C/A	0.51	0.026		2E-11	0.786
71	I	rs4983559	ZBTB42-AKT1	rs4983559		G/A	0.38	0.039	0.007	1.9E-08	0.297
72	D	rs1689800	ZNF648	rs1689800		A/G	0.65	0.034		5E-20	0.757
73	D	rs4765127	ZNF664	rs11057408	1.000	T/G	0.35	0.032		8E-10	0.834

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error, I: meta-analysis from Engage Consortium (from Surakka and al.), D: meta-analysis from the Global Lipids Genetics Consortium (from Willer and al.). CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S5 Table. List of SNPs from the Global Lipids Genetics Consortium meta-analysis with their β-effect on LDL and HWE p-value

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	GWAS p-value	HWE p-value
1	rs4299376	ABCG5/8	rs4299376		G/T	0.31	0.081	4E-72	0.598
2	rs9411489	ABO	rs507666		T/C	0.21	0.077	2E-41	0.934
3	rs17404153	ACAD11	rs17404153		G/T	0.86	0.034	2E-09	0.198
4	rs2131925	ANGPTL3	rs3850634	0.965	T/G	0.66	0.049	3E-32	0.937
5	rs267733	ANXA9-CERS2	rs267733		A/G	0.84	0.033	5E-09	0.761
6	rs964184	APOA1	rs964184		G/C	0.16	0.086	2E-26	0.482
7	rs1367117	APOB	rs1367117		A/G	0.32	0.119	1E-182	0.053
8	rs1801689	APOH-PRXCA	rs1801689		C/A	0.04	0.103	1E-11	0.403
9	rs11065987	BRAP	rs11065987		A/G	0.59	0.027	1E-11	0.509
10	rs4942486	BRCA2	rs4942486		T/C	0.48	0.024	2E-11	0.474
11	rs3764261	CETP	rs3764261		C/A	0.68	0.053	2E-34	0.432
12	rs10401969	CILP2	rs10401969		T/C	0.91	0.118	3E-54	0.595
13	rs7640978	CMTM6	rs7640978		C/T	0.91	0.039	1E-08	0.297
14	rs4530754	CSNK1G3	rs4530754		A/G	0.54	0.028	4E-12	0.121
15	rs2081687	CYP7A1	rs1030431	0.845	T/C	0.36	0.031	1E-07	0.084
16	rs314253	DLG4	rs314253		T/C	0.63	0.024	3E-10	0.412
17	rs12670798	DNAH11	rs12670798		C/T	0.25	0.034	5E-14	0.168
18	rs2710642	EHBP1	rs2710642		A/G	0.65	0.024	6E-09	0.368
19	rs174546	FADS1-2-3	rs174546		C/T	0.64	0.051	2E-39	0.450
20	rs1250229	FN1	rs1250229		C/T	0.73	0.024	3E-08	0.093
21	rs9488822	FRK	rs3798236	1.000	T/A	0.36	0.031	2E-07	0.593
22	rs2255141	GPAM	rs2255141		A/G	0.30	0.030	1E-13	0.380
23	rs1800562	HFE	rs1800562		G/A	0.93	0.062	8E-14	0.778
24	rs3177928	HLA	rs3177928		A/G	0.17	0.045	3E-17	0.786
25	rs12916	HMGCR	rs12916		C/T	0.40	0.073	8E-78	0.900
26	rs1169288	HNF1A	rs1169288		C/A	0.34	0.038	6E-21	0.639
27	rs2000999	HPR	rs2000999		A/G	0.20	0.065	4E-41	0.716
28	rs10490626	INSIG2	rs10490626		G/A	0.92	0.051	2E-12	0.291
29	rs514230	IRF2BP2	rs514230		T/A	0.52	0.036	9E-12	0.167
30	rs6511720	LDLR	rs6511720		G/T	0.88	0.221	4E-262	0.346
31	rs12027135	LDLRAP1	rs12027135		T/A	0.54	0.030	2E-14	0.721
32	rs2030746	LOC84931	rs2030746		T/C	0.40	0.021	9E-09	0.393
33	rs1564348	LPA	rs1564348		C/T	0.18	0.048	3E-21	0.133
34	rs6818397	LRPAP1	rs6818397		G/A	0.42	0.022	2E-08	0.783
35	rs4722551	MIR148A	rs4722551		C/T	0.20	0.039	4E-14	0.633
36	rs2642442	MOSC1	rs2642442		T/C	0.67	0.036	5E-11	0.555
37	rs5763662	MTMR3	rs5763662		T/C	0.04	0.077	1E-08	0.664
38	rs3757354	MYLIP	rs3757354		C/T	0.76	0.038	2E-17	0.142
39	rs2072183	NPC1L1	rs2072183		C/G	0.29	0.039	7E-16	0.100
40	rs8017377	NYNRIN	rs8017377		A/G	0.46	0.030	3E-15	0.497

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	GWAS p-value	HWE p-value
41	rs7206971	OSBPL7	rs6504872	0.935	A/G	0.49	0.029	3E-07	0.328
42	rs2479409	PCSK9	rs2479409		G/A	0.32	0.064	3E-50	0.597
43	rs12748152	PIGV-NROB2	rs12748152		T/C	0.09	0.050	3E-12	0.672
44	rs11136341	PLEC1	rs11785060	1.000	G/A	0.40	0.045	7E-12	0.231
45	rs4253776	PPARA	rs4253776		T/C	0.11	0.031	3E-08	0.319
46	rs9987289	PPP1R3B	rs9987289		G/A	0.90	0.071	9E-24	0.352
47	rs2328223	SNX5	rs2328223		C/A	0.21	0.030	6E-09	0.559
48	rs629301	SORT1	rs646776	1.000	T/G	0.76	0.167	5E-241	0.568
49	rs10102164	SOX17	rs10102164		A/G	0.21	0.032	4E-11	0.666
50	rs364585	SPTLC3	rs364585		G/A	0.62	0.025	4E-10	0.730
51	rs11220462	ST3GAL4	rs11220462		A/G	0.14	0.059	7E-21	0.642
52	rs6882076	TIMD4	rs6882076		C/T	0.64	0.046	3E-31	0.199
53	rs6029526	TOP1	rs6072249	1.000	A/T	0.47	0.044	5E-18	0.999
54	rs2954029	TRIB1	rs2954029		A/T	0.53	0.056	2E-50	0.592
55	rs3780181	VLDLR	rs3780181		A/G	0.92	0.044	2E-09	0.371

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error. CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S6 Table. List of the selected SNPs from the Engage Consortium meta-analysis with their β-effect on LDL and HWE p-value

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
1	rs4299376	ABCG8	rs4299376		G/T	0.27	0.074	0.007	8.3E-28	0.598
2	rs649129	ABO	rs507666	0.955	T/C	0.20	0.064	0.008	1.3E-17	0.934
3	rs3850634	ANGPTL3, DOCK7	rs3850634		T/G	0.68	0.042	0.006	4.7E-11	0.937
4	rs1367117	APOB	rs1367117		A/G	0.32	0.108	0.007	7.1E-58	0.053
5	rs964184	APO-cluster	rs964184		G/C	0.13	0.080	0.009	3.6E-18	0.482
6	rs1065853	APOE	rs1065853		G/T	0.93	0.603	0.013	<5E-324	0.515
7	rs646776	CELSR2-SORT1	rs646776		T/C	0.22	0.146	0.007	2.0E-91	0.568
8	rs247617	CETP	rs3764261	1.000	C/A	0.69	0.069	0.007	1.7E-24	0.432
9	rs10401969	CILP2	rs10401969		T/C	0.92	0.111	0.012	1.0E-21	0.595
10	rs1030431	CYP7A1	rs1030431		A/G	0.31	0.037	0.007	2.5E-08	0.084
11	rs314253	DLG4	rs314253		T/C	0.63	0.040	0.007	1.6E-09	0.412
12	rs12670798	DNAH11	rs12670798		C/T	0.24	0.050	0.007	7.3E-12	0.168
13	rs174583	FADS1-2-3	rs174546	1.000	C/T	0.62	0.063	0.006	1.1E-22	0.450
14	rs79588679	GATA6	rs79588679		C/T	0.83	0.049	0.009	3.6E-08	0.454
15	rs1129555	GPAM	rs2255141	0.959	A/G	0.27	0.035	0.007	5.4E-07	0.380
16	rs11136341	GRINA, PLECI	rs11785060	1.000	G/A	0.34	0.038	0.007	9.8E-09	0.231
17	rs3177928	HLA-area	rs3177928		A/G	0.17	0.050	0.009	1.3E-08	0.786
18	rs12916	HMGCR	rs12916		C/T	0.41	0.089	0.006	7.0E-45	0.900
19	rs1169314	HNF1A	rs2464196	1.000	G/A	0.30	0.037	0.007	2.3E-08	0.411
20	rs11648003	HP-HPR-DHX38	chr16:70609849		G/A	0.22	0.067	0.007	2.0E-20	0.976
21	rs514230	IRF2BP2	rs514230		T/A	0.54	0.041	0.006	1.1E-11	0.167
22	rs112374545	LDLR	chr19:11049899		C/T	0.89	0.250	0.010	7.2E-142	0.369
23	rs12027135	LDLRAP1	rs12027135		T/A	0.54	0.032	0.006	6.9E-08	0.721
24	rs2297374	LPA	rs9295125	0.865	C/T	0.64	0.029	0.006	4.7E-06	0.056
25	rs6818397	LRPAP1	rs6818397		T/G	0.36	0.025	0.007	1.4E-04	0.783
26	rs2902941	MAFB	rs2902941		A/G	0.66	0.022	0.006	6.0E-04	0.223
27	rs3757354	MYLIP	rs3757354		C/T	0.75	0.043	0.007	2.0E-09	0.142
28	rs41279633	NPC1L1	chr7:44547401		T/G	0.18	0.054	0.008	1.0E-10	0.432
29	rs11621792	NYNRIN, CBLN3	rs6573778	0.934	T/C	0.42	0.037	0.007	1.7E-08	0.806
30	rs7206971	OSBPL7	rs6504872	0.935	A/G	0.51	0.038	0.006	3.5E-10	0.328
31	rs2479409	PCSK9	rs2479409		G/A	0.31	0.071	0.007	3.5E-23	0.597
32	rs12748152	PIGV-NROB2	rs12748152		T/C	0.09	0.047	0.010	5.2E-06	0.672
33	rs2920503	PPARG	rs2920502	0.959	T/C	0.30	0.041	0.007	2.9E-10	0.280
34	rs2126259	PPP1R3B	rs9987289	0.803	C/T	0.89	0.078	0.010	3.8E-15	0.352
35	rs2618568	SNX5	rs2618568		C/A	0.37	0.049	0.006	6.9E-15	0.613
36	rs11220462	ST3GAL4	rs11220462		A/G	0.14	0.053	0.009	3.0E-09	0.642
37	rs6882076	TIMD4-HAVCR1	rs6882076		C/T	0.65	0.042	0.006	1.7E-11	0.199
38	rs2954022	TRIB1	rs2954029	0.966	C/A	0.52	0.054	0.006	2.8E-19	0.592
39	rs117492019	ZNF274	rs117492019		G/T	0.81	0.047	0.008	1.2E-08	0.072

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error. CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S7 Table. List of the selected SNPs from combined meta-analyses with their β-effect on LDL and HWE p-value

Number	Article	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
1	I	rs4299376	ABCG8	rs4299376		G/T	0.27	0.074	0.007	8.3E-28	0.598
2	I	rs649129	ABO	rs507666	0.955	T/C	0.20	0.064	0.008	1.3E-17	0.934
3	D	rs17404153	ACAD11	rs17404153		G/T	0.86	0.034		2.0E-09	0.198
4	I	rs3850634	ANGPTL3, DOCK7	rs3850634		T/G	0.68	0.042	0.006	4.7E-11	0.937
5	D	rs267733	ANXA9-CERS2	rs267733		A/G	0.84	0.033		5.0E-09	0.761
6	I	rs964184	APO-cluster	rs964184		G/C	0.13	0.080	0.009	3.6E-18	0.482
7	I	rs1367117	APOB	rs1367117		A/G	0.32	0.108	0.007	7.1E-58	0.053
8	I	rs1065853	APOE	rs1065853		G/T	0.93	0.603	0.013	<5E-324	0.515
9	D	rs1801689	APOH-PRXCA	rs1801689		C/A	0.04	0.103		1.0E-11	0.403
10	D	rs11065987	BRAP	rs11065987		A/G	0.59	0.027		1.0E-11	0.509
11	D	rs4942486	BRCA2	rs4942486		T/C	0.48	0.024		2.0E-11	0.474
12	I	rs646776	CELSR2-SORT1	rs646776		T/C	0.22	0.146	0.007	2.0E-91	0.568
13	I	rs247617	CETP	rs3764261	1.000	C/A	0.69	0.069	0.007	1.7E-24	0.432
14	I	rs10401969	CILP2	rs10401969		T/C	0.92	0.111	0.012	1.0E-21	0.595
15	D	rs7640978	CMTM6	rs7640978		C/T	0.91	0.039		1.0E-08	0.297
16	D	rs4530754	CSNK1G3	rs4530754		A/G	0.54	0.028		4.0E-12	0.121
17	I	rs1030431	CYP7A1	rs1030431		A/G	0.31	0.037	0.007	2.5E-08	0.084
18	I	rs314253	DLG4	rs314253		T/C	0.63	0.040	0.007	1.6E-09	0.412
19	I	rs12670798	DNAH11	rs12670798		C/T	0.24	0.050	0.007	7.3E-12	0.168
20	D	rs2710642	EHBP1	rs2710642		A/G	0.65	0.024		6.0E-09	0.368
21	I	rs174583	FADS1-2-3	rs174546	1.000	C/T	0.62	0.063	0.006	1.1E-22	0.450
22	D	rs1250229	FN1	rs1250229		C/T	0.73	0.024		3.0E-08	0.093
23	D	rs9488822	FRK	rs3798236	1.000	T/A	0.36	0.031		2.0E-07	0.593
24	I	rs79588679	GATA6	rs79588679		C/T	0.83	0.049	0.009	3.6E-08	0.454
25	D	rs2255141	GPAM	rs2255141		A/G	0.30	0.030		1.0E-13	0.380
26	I	rs11136341	GRINA, PLECI	rs11785060	1.000	G/A	0.34	0.038	0.007	9.8E-09	0.231
27	D	rs1800562	HFE	rs1800562		G/A	0.93	0.062		8.0E-14	0.778
28	I	rs3177928	HLA-area	rs3177928		A/G	0.17	0.050	0.009	1.3E-08	0.786
29	I	rs12916	HMGCR	rs12916		C/T	0.41	0.089	0.006	7.0E-45	0.900
30	I	rs1169314	HNF1A	rs2464196	1.000	G/A	0.30	0.037	0.007	2.3E-08	0.411
31	I	rs11648003	HP-HPR-DHX38	chr16:70609849		G/A	0.22	0.067	0.007	2.0E-20	0.976
32	D	rs10490626	INSIG2	rs10490626		G/A	0.92	0.051		2.0E-12	0.291
33	I	rs514230	IRF2BP2	rs514230		T/A	0.54	0.041	0.006	1.1E-11	0.167
34	I	rs112374545	LDLR	chr19:11049899		C/T	0.89	0.250	0.010	7.2E-142	0.369
35	D	rs12027135	LDLRAP1	rs12027135		T/A	0.54	0.030		2.0E-14	0.721
36	D	rs2030746	LOC84931	rs2030746		T/C	0.40	0.021		9.0E-09	0.393
37	D	rs1564348	LPA	rs1564348		C/T	0.18	0.048		3.0E-21	0.133
38	D	rs6818397	LRPAP1	rs6818397		G/A	0.42	0.022		2.0E-08	0.783
39	I	rs2902941	MAFB	rs2902941		A/G	0.66	0.022	0.006	6.0E-04	0.223
40	D	rs4722551	MIR148A	rs4722551		C/T	0.20	0.039		4.0E-14	0.633

Number	Article	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
41	D	rs2642442	MOSC1	rs2642442		T/C	0.67	0.036		5.0E-11	0.555
42	D	rs5763662	MTMR3	rs5763662		T/C	0.04	0.077		1.0E-08	0.664
43	I	rs3757354	MYLIP	rs3757354		C/T	0.75	0.043	0.007	2.0E-09	0.142
44	I	rs41279633	NPC1L1	chr7:44547401		T/G	0.18	0.054	0.008	1.0E-10	0.432
45	D	rs8017377	NYNRIN	rs8017377		A/G	0.46	0.030		3.0E-15	0.497
46	I	rs7206971	OSBPL7	rs6504872	0.935	A/G	0.51	0.038	0.006	3.5E-10	0.328
47	I	rs2479409	PCSK9	rs2479409		G/A	0.31	0.071	0.007	3.5E-23	0.597
48	D	rs12748152	PIGV-NROB2	rs12748152		T/C	0.09	0.050		3.0E-12	0.672
49	D	rs4253776	PPARA	rs4253776		T/C	0.11	0.031		3.0E-08	0.319
50	I	rs2920503	PPARG	rs2920502	0.959	T/C	0.30	0.041	0.007	2.9E-10	0.280
51	D	rs9987289	PPP1R3B	rs9987289		G/A	0.90	0.071		9.0E-24	0.352
52	I	rs2618568	SNX5	rs2618568		C/A	0.37	0.049	0.006	6.9E-15	0.613
53	D	rs10102164	SOX17	rs10102164		A/G	0.21	0.032		4.0E-11	0.666
54	D	rs364585	SPTLC3	rs364585		G/A	0.62	0.025		4.0E-10	0.730
55	I	rs11220462	ST3GAL4	rs11220462		A/G	0.14	0.053	0.009	3.0E-09	0.642
56	I	rs6882076	TIMD4-HAVCR1	rs6882076		C/T	0.65	0.042	0.006	1.7E-11	0.199
57	D	rs6029526	TOP1	rs6072249	1.000	A/T	0.47	0.044		5.0E-18	0.999
58	I	rs2954022	TRIB1	rs2954029	0.966	C/A	0.52	0.054	0.006	2.8E-19	0.592
59	D	rs3780181	VLDLR	rs3780181		A/G	0.92	0.044		2.0E-09	0.371
60	I	rs117492019	ZNF274	rs117492019		G/T	0.81	0.047	0.008	1.2E-08	0.072

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error, I: meta-analysis from Engage Consortium (from Surakka and al.), D: meta-analysis from the Global Lipids Genetics Consortium (from Willer and al.). CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S8 Table. List of SNPs from the Global Lipids Genetics Consortium meta-analysis with their β-effect on TC and HWE p-value

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	GWAS p-value	HWE p-value
1	rs1883025	ABCA1	rs1883025		C/T	0.75	0.067	6.E-53	0.463
2	rs2287623	ABCB11	rs2287623		G/A	0.41	0.027	4.E-12	0.319
3	rs4299376	ABCG5/8	rs4299376		G/T	0.31	0.079	3.E-73	0.598
4	rs9411489	ABO	rs507666	0.955	T/C	0.21	0.069	3.E-35	0.934
5	rs2131925	ANGPTL3	rs3850634	0.965	T/G	0.66	0.075	4.E-80	0.937
6	rs964184	APOA1	rs964184		G/C	0.16	0.121	3.0.E-55	0.482
7	rs1367117	APOB	rs1367117		A/G	0.32	0.100	3.E-139	0.053
8	rs1077514	ASAP3	rs1077514		T/C	0.85	0.030	6.E-09	0.718
9	rs11065987	BRAP	rs11065987		A/G	0.59	0.031	2.E-16	0.509
10	rs2814982	C6orf106	rs2814982		C/T	0.88	0.044	4.E-15	0.589
11	rs3764261	CETP	rs3764261		A/C	0.32	0.050	4.E-31	0.432
12	rs10401969	CILP2	rs10401969		T/C	0.91	0.137	4.E-77	0.595
13	rs7640978	CMTM6	rs7640978		C/T	0.91	0.038	2.E-08	0.297
14	rs4530754	CSNK1G3	rs4530754		A/G	0.54	0.023	2.E-09	0.121
15	rs2081687	CYP7A1	rs1030431	0.845	T/C	0.36	0.038	9.E-12	0.084
16	rs314253	DLG4	rs314253		T/C	0.63	0.023	3.E-10	0.412
17	rs12670798	DNAH11	rs12670798		C/T	0.25	0.036	1.E-16	0.168
18	rs2277862	ERGIC3	rs2277862		C/T	0.85	0.035	5.E-11	0.287
19	rs7515577	EVI5	rs6603981	1.000	A/C	0.77	0.037	2.E-08	0.704
20	rs174546	FADS1-2-3	rs174546		C/T	0.64	0.048	3.E-37	0.450
21	rs11694172	FAM117B	rs11694172		G/A	0.25	0.028	2.E-09	0.136
22	rs492602	FLJ36070	rs492602		G/A	0.47	0.031	1.E-16	0.125
23	rs9488822	FRK	rs3798236	1.000	T/A	0.36	0.034	1.E-09	0.593
24	rs1260326	GCKR	rs1260326		T/C	0.39	0.051	3.E-42	0.633
25	rs2255141	GPAM	rs2255141		A/G	0.3	0.031	7.E-16	0.380
26	rs1997243	GPR146	rs1997243		G/A	0.16	0.033	3.E-10	0.596
27	rs1800562	HFE	rs1800562		G/A	0.93	0.056	2.E-12	0.778
28	rs3177928	HLA	rs3177928		A/G	0.17	0.048	1.E-21	0.786
29	rs12916	HMGCR	rs12916		C/T	0.4	0.068	5.E-74	0.900
30	rs1169288	HNF1A	rs1169288		C/A	0.34	0.032	4.E-17	0.639
31	rs1800961	HNF4A	rs1800961		C/T	0.95	0.106	1.E-24	0.647
32	rs2000999	HPR	rs2000999		A/G	0.2	0.062	7.E-41	0.716
33	rs17526895	INSIG2	rs17526895		G/A	0.92	0.042	6.E-09	0.212
34	rs514230	IRF2BP2	rs514230		T/A	0.52	0.039	5.E-14	0.167
35	rs2758886	KCNK17	rs2758886		A/G	0.3	0.023	3.E-08	0.707
36	rs6511720	LDLR	rs6511720		G/T	0.88	0.185	5.E-202	0.346
37	rs12027135	LDLRAP1	rs12027135		T/A	0.54	0.027	5.E-12	0.721
38	rs1532085	LIPC	rs1532085		A/G	0.4	0.054	7.E-47	0.688
39	rs7241918	LIPG	rs10438978	1.000	T/G	0.81	0.058	4.E-18	0.064
40	rs2030746	LOC84931	rs2030746		T/C	0.4	0.020	4.E-08	0.393

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	GWAS p-value	HWE p-value
41	rs1564348	LPA	rs1564348		C/T	0.18	0.049	3.E-23	0.133
42	rs6818397	LRPAP1	rs6818397		G/A	0.42	0.025	1.E-10	0.783
43	rs970548	MARCH8-ALOX5	rs970548		C/A	0.26	0.025	8.E-09	0.787
44	rs4722551	MIR148A	rs4722551		C/T	0.2	0.029	7.E-09	0.633
45	rs2642442	MOSC1	rs2642442		T/C	0.67	0.035	3.E-11	0.555
46	rs3757354	MYLIP	rs3757354		C/T	0.76	0.035	2.E-15	0.142
47	rs1495741	NAT2	rs1495741		G/A	0.26	0.032	3.E-08	0.835
48	rs2072183	NPC1L1	rs2072183		C/G	0.29	0.036	4.E-15	0.100
49	rs7206971	OSBPL7	rs6504872	0.935	A/G	0.49	0.030	1.E-07	0.328
50	rs2479409	PCSK9	rs2479409		G/A	0.32	0.054	2.E-39	0.597
51	rs4883201	PHC1-A2ML1	rs4883201		A/G	0.88	0.035	2.E-09	0.581
52	rs11603023	PHLDB1	rs11603023		T/C	0.42	0.022	1.E-08	0.418
53	rs11136341	PLEC1	rs11785060	1.000	G/A	0.4	0.038	6.E-09	0.231
54	rs4253772	PPARA	rs4253772		T/C	0.11	0.032	1.E-08	0.833
55	rs9987289	PPP1R3B	rs9987289		G/A	0.9	0.084	2.E-36	0.352
56	rs13315871	PXK	rs13315871		G/A	0.9	0.036	4.E-08	0.213
57	rs7570971	RAB3GAP1	rs7570971		A/C	0.35	0.030	1.E-13	0.334
58	rs629301	SORT1	rs646776	1.000	T/G	0.76	0.134	2.E-170	0.568
59	rs10102164	SOX17	rs10102164		A/G	0.21	0.030	5.E-11	0.666
60	rs10128711	SPTY2D1	rs10128711		C/T	0.7	0.031	1.E-11	0.844
61	rs11220462	ST3GAL4	rs11220462		A/G	0.14	0.047	6.E-15	0.642
62	rs6882076	TIMD4	rs6882076		C/T	0.64	0.051	5.E-41	0.199
63	rs138777	TOM1	rs138777		A/G	0.36	0.021	5.E-08	0.072
64	rs6029526	TOP1	rs6072249	1.000	A/T	0.47	0.040	1.E-16	0.999
65	rs2954029	TRIB1	rs2954029		A/T	0.53	0.062	2.E-65	0.592
66	rs581080	TTC39B	chr9:15295378		C/G	0.79	0.038	1.E-13	0.156
67	rs7941030	UBASH3B	rs7941030		C/T	0.39	0.028	2.E-14	0.349
68	rs10904908	VIM-CUBN	rs10904908		G/A	0.43	0.025	3.E-11	0.869
69	rs3780181	VLDLR	rs3780181		A/G	0.92	0.044	7.E-10	0.371

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error. CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S9 Table. List of the selected SNPs from the Engage Consortium meta-analysis with their β-effect on TC and HWE p-value

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
1	rs1883025	ABCA1	rs1883025		C/T	0.76	0.068	0.007	6.0E-21	0.463
2	rs4299376	ABCG8	rs4299376		G/T	0.27	0.069	0.007	1.5E-25	0.598
3	rs507666	ABO	rs507666		A/G	0.18	0.067	0.008	2.0E-18	0.934
4	rs3850634	ANGPTL3, DOCK7	rs3850634		T/G	0.68	0.076	0.006	3.8E-34	0.937
5	rs1041968	APOB	rs952275	1.000	A/G	0.48	0.095	0.006	4.6E-54	0.123
6	rs964184	APO-cluster	rs964184		G/C	0.13	0.118	0.009	3.7E-39	0.482
7	rs7412	APOE	chr19:50103919		C/T	0.93	0.413	0.013	7.5E-239	0.964
8	rs646776	CELSR2-SORT1	rs646776		T/C	0.22	0.120	0.007	1.9E-64	0.568
9	rs10401969	CILP2	rs10401969		T/C	0.92	0.123	0.011	1.7E-27	0.595
10	rs1030431	CYP7A1	rs1030431		A/G	0.31	0.035	0.007	9.4E-08	0.084
11	rs314253	DLG4	rs314253		T/C	0.63	0.037	0.007	2.5E-08	0.412
12	rs55649657	DNAH11	rs12670798	0.853	G/C	0.21	0.052	0.007	4.1E-13	0.168
13	rs2277862	ERGIC3	rs2277862		C/T	0.89	0.052	0.009	2.7E-08	0.287
14	rs174554	FADS1-2-3	rs174546	1.000	A/G	0.63	0.062	0.006	5.1E-24	0.450
15	rs115400054	FAM117B	rs6705330	1.000	C/T	0.88	0.054	0.009	5.4E-09	0.055
16	rs1260326	GCKR	rs1260326		T/C	0.36	0.045	0.006	2.5E-13	0.633
17	rs2255141	GPAM	rs2255141		A/G	0.27	0.036	0.007	3.5E-08	0.380
18	rs7515577	GVI1-EVI5	rs6603981	1.000	A/C	0.80	0.042	0.007	4.2E-09	0.704
19	rs3177928	HLA-area	rs3177928		A/G	0.16	0.055	0.008	6.7E-11	0.786
20	rs12916	HMGCR	rs12916		C/T	0.40	0.082	0.006	2.9E-40	0.900
21	rs1169288	HNF1A	rs1169288		C/A	0.33	0.037	0.007	2.1E-08	0.639
22	rs11648003	HP-HPR-DHX38	chr16:70609849		G/A	0.22	0.070	0.007	2.8E-23	0.976
23	rs514230	IRF2BP2	rs514230		T/A	0.54	0.048	0.006	1.1E-15	0.167
24	rs112374545	LDLR	chr19:11049899		C/T	0.89	0.217	0.010	1.5E-113	0.369
25	rs12027135	LDLRAP1	rs12027135		T/A	0.54	0.032	0.006	7.1E-08	0.721
26	rs1532085	LIPC	rs1532085		A/G	0.40	0.049	0.006	4.6E-16	0.688
27	rs7239867	LIPG	rs7239867		G/A	0.82	0.047	0.008	2.3E-09	0.118
28	rs12208357	LPA	chr6:160463138		T/C	0.06	0.092	0.012	8.5E-14	0.567
29	rs6818397	LRPAP1	rs6818397		T/G	0.36	0.028	0.007	2.0E-05	0.783
30	rs970548	MARCH8	rs970548		C/A	0.25	0.035	0.007	1.5E-07	0.787
31	rs2807834	MOSC1	rs2642442	0.962	G/T	0.71	0.037	0.007	1.7E-08	0.555
32	rs2072183	NPC1L1	rs2072183		C/G	0.27	0.041	0.007	3.2E-08	0.100
33	rs7206971	OSBPL7	rs6504872	0.935	A/G	0.51	0.043	0.006	3.7E-13	0.328
34	rs2479409	PCSK9	rs2479409		G/A	0.31	0.066	0.007	4.9E-21	0.597
35	rs1699337	PPARG	rs1151996	1.000	G/A	0.65	0.043	0.006	9.3E-12	0.523
36	rs9987289	PPP1R3B	rs9987289		G/A	0.90	0.097	0.010	1.4E-21	0.352
37	rs6759321	RAB3GAP1	rs6759321		T/G	0.28	0.036	0.007	7.7E-07	0.073
38	rs2814982	SNRPC	rs2814982		C/T	0.88	0.027	0.009	3.8E-03	0.589
39	rs2618568	SNX5	rs2618568		C/A	0.37	0.044	0.006	1.8E-12	0.613

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
41	rs6882076	TIMD4-HAVCR1	rs6882076		C/T	0.65	0.051	0.006	6.0E-17	0.199
42	rs2954022	TRIB1	rs2954029	0.966	C/A	0.52	0.063	0.006	2.0E-27	0.592
43	rs581080	TTC39B	chr9:15295378		C/G	0.83	0.027	0.008	7.6E-04	0.156
44	rs7128198	UBASH3B	rs7941030	0.934	T/C	0.38	0.036	0.006	4.0E-09	0.349

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error. CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S10 Table. List of the selected SNPs from combined meta-analyses with their β-effect on TC and HWE p-value

Number	Article	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
1	I	rs1883025	ABCA1	rs1883025		C/T	0.76	0.068	0.007	6.0.E-21	0.463
2	D	rs2287623	ABCB11	rs2287623		G/A	0.41	0.027		4.0.E-12	0.319
3	I	rs4299376	ABCG8	rs4299376		G/T	0.27	0.069	0.007	1.5.E-25	0.598
4	I	rs507666	ABO	rs507666		A/G	0.18	0.067	0.008	2.0.E-18	0.934
5	I	rs3850634	ANGPTL3, DOCK7	rs3850634		T/G	0.68	0.076	0.006	3.8.E-34	0.937
6	I	rs964184	APO-cluster	rs964184		G/C	0.13	0.118	0.009	3.7.E-39	0.482
7	I	rs1041968	APOB	rs952275	1.000	A/G	0.48	0.095	0.006	4.6.E-54	0.123
8	I	rs7412	APOE	chr19:50103919		C/T	0.93	0.413	0.013	7.5.E-239	0.964
9	D	rs1077514	ASAP3	rs1077514		T/C	0.85	0.030		6.0.E-09	0.718
10	D	rs11065987	BRAP	rs11065987		A/G	0.59	0.031		2.0.E-16	0.509
11	D	rs2814982	C6orf106	rs2814982		C/T	0.88	0.044		4.0.E-15	0.589
12	I	rs646776	CELSR2-SORT1	rs646776		T/C	0.22	0.120	0.007	1.9.E-64	0.568
13	D	rs3764261	CETP	rs3764261		A/C	0.32	0.050		4.0.E-31	0.432
14	I	rs10401969	CILP2	rs10401969		T/C	0.92	0.123	0.011	1.7.E-27	0.595
15	D	rs7640978	CMTM6	rs7640978		C/T	0.91	0.038		2.0.E-08	0.297
16	D	rs4530754	CSNK1G3	rs4530754		A/G	0.54	0.023		2.0.E-09	0.121
17	I	rs4738684	CYP7A1	rs1030431	0.885	A/G	0.34	0.041	0.006	2.8.E-11	0.084
18	I	rs314253	DLG4	rs314253		T/C	0.63	0.037	0.007	2.5.E-08	0.412
19	D	rs12670798	DNAH11	rs12670798		C/T	0.25	0.036		1.0.E-16	0.168
20	I	rs2277862	ERGIC3	rs2277862		C/T	0.89	0.052	0.009	2.7.E-08	0.287
21	I	rs174554	FADS1-2-3	rs174546	1.000	A/G	0.63	0.062	0.006	5.1.E-24	0.450
22	I	rs115400054	FAM117B	rs6705330	1.000	C/T	0.88	0.054	0.009	5.4.E-09	0.055
23	D	rs492602	FLJ36070	rs492602		G/A	0.47	0.031		1.0.E-16	0.125
24	D	rs9488822	FRK	rs3798236	1.000	T/A	0.36	0.034		1.0.E-09	0.593
25	I	rs1260326	GCKR	rs1260326		T/C	0.36	0.045	0.006	2.5.E-13	0.633
26	I	rs2255141	GPAM	rs2255141		A/G	0.27	0.036	0.007	3.5.E-08	0.380
27	D	rs1997243	GPR146	rs1997243		G/A	0.16	0.033		3.0.E-10	0.596
28	I	rs7515577	GVI1-EVI5	rs6603981	1.000	A/C	0.80	0.042	0.007	4.2.E-09	0.704
29	D	rs1800562	HFE	rs1800562		G/A	0.93	0.056		2.0.E-12	0.778
30	I	rs3177928	HLA-area	rs3177928		A/G	0.16	0.055	0.008	6.7.E-11	0.786
31	I	rs12916	HMGCR	rs12916		C/T	0.40	0.082	0.006	2.9.E-40	0.900
32	I	rs1169288	HNF1A	rs1169288		C/A	0.33	0.037	0.007	2.1.E-08	0.639
33	D	rs1800961	HNF4A	rs1800961		C/T	0.95	0.106		1.0.E-24	0.647
34	I	rs11648003	HP-HPR-DHX38	chr16:70609849		G/A	0.22	0.070	0.007	2.8.E-23	0.976
35	D	rs17526895	INSIG2	rs17526895		G/A	0.92	0.042		6.0.E-09	0.212
36	I	rs514230	IRF2BP2	rs514230		T/A	0.54	0.048	0.006	1.1.E-15	0.167
37	D	rs2758886	KCNK17	rs2758886		A/G	0.30	0.023		3.0.E-08	0.707
38	I	rs112374545	LDLR	chr19:11049899		C/T	0.89	0.217	0.010	1.5.E-113	0.369
39	D	rs12027135	LDLRAP1	rs12027135		T/A	0.54	0.027		5.0.E-12	0.721
40	I	rs1532085	LIPC	rs1532085		A/G	0.40	0.049	0.006	4.6.E-16	0.688

Number	Article	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
41	I	rs7239867	LIPG	rs7239867		G/A	0.82	0.047	0.008	2.3.E-09	0.118
42	D	rs2030746	LOC84931	rs2030746		T/C	0.40	0.020		4.0.E-08	0.393
43	I	rs12208357	LPA	chr6:160463138		T/C	0.06	0.092	0.012	8.5.E-14	0.567
44	D	rs6818397	LRPAP1	rs6818397		G/A	0.42	0.025		1.0.E-10	0.783
45	D	rs970548	MARCH8-ALOX5	rs970548		C/A	0.26	0.025		8.0.E-09	0.787
46	D	rs4722551	MIR148A	rs4722551		C/T	0.20	0.029		7.0.E-09	0.633
47	D	rs2642442	MOSC1	rs2642442		T/C	0.67	0.035		3.0.E-11	0.555
48	D	rs3757354	MYLIP	rs3757354		C/T	0.76	0.035		2.0.E-15	0.142
49	D	rs1495741	NAT2	rs1495741		G/A	0.26	0.032		3.0.E-08	0.835
50	I	rs2072183	NPC1L1	rs2072183		C/G	0.27	0.041	0.007	3.2.E-08	0.100
51	I	rs7206971	OSBPL7	rs6504872	0.935	A/G	0.51	0.043	0.006	3.7.E-13	0.328
52	I	rs2479409	PCSK9	rs2479409		G/A	0.31	0.066	0.007	4.9.E-21	0.597
53	D	rs4883201	PHC1-A2ML1	rs4883201		A/G	0.88	0.035		2.0.E-09	0.581
54	D	rs11603023	PHLDB1	rs11603023		T/C	0.42	0.022		1.0.E-08	0.418
55	D	rs11136341	PLEC1	rs11785060	1.000	G/A	0.40	0.038		6.0.E-09	0.231
56	D	rs4253772	PPARA	rs4253772		T/C	0.11	0.032		1.0.E-08	0.833
57	I	rs1699337	PPARG	rs1151996	1.000	G/A	0.65	0.043	0.006	9.3.E-12	0.523
58	I	rs9987289	PPP1R3B	rs9987289		G/A	0.90	0.097	0.010	1.4.E-21	0.352
59	D	rs13315871	PXK	rs13315871		G/A	0.90	0.036		4.0.E-08	0.213
60	D	rs7570971	RAB3GAP1	rs7570971		A/C	0.35	0.030		1.0.E-13	0.334
61	I	rs2618568	SNX5	rs2618568		C/A	0.37	0.044	0.006	1.8E-12	0.613
62	D	rs10102164	SOX17	rs10102164		A/G	0.21	0.030		5.0.E-11	0.666
63	D	rs10128711	SPTY2D1	rs10128711		C/T	0.70	0.031		1.0.E-11	0.844
64	D	rs11220462	ST3GAL4	rs11220462		A/G	0.14	0.047		6.0.E-15	0.642
65	I	rs6882076	TIMD4-HAVCR1	rs6882076		C/T	0.65	0.051	0.006	6.0.E-17	0.199
66	D	rs138777	TOM1	rs138777		A/G	0.36	0.021		5.0.E-08	0.072
67	D	rs6029526	TOP1	rs6072249	1.000	A/T	0.47	0.040		1.0.E-16	0.999
68	I	rs2954022	TRIB1	rs2954029	0.966	C/A	0.52	0.063	0.006	2.0.E-27	0.592
69	D	rs581080	TTC39B	chr9:15295378		C/G	0.79	0.038		1.0.E-13	0.156
70	I	rs7128198	UBASH3B	rs7941030	0.934	T/C	0.38	0.036	0.006	4.0.E-09	0.349
71	D	rs10904908	VIM-CUBN	rs10904908		G/A	0.43	0.025		3.0.E-11	0.869
72	D	rs3780181	VLDLR	rs3780181		A/G	0.92	0.044		7.0.E-10	0.371

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error, I: meta-analysis from Engage Consortium (from Surakka and al.), D: meta-analysis from the Global Lipids Genetics Consortium (from Willer and al.). CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S11 Table. List of SNPs from the Global Lipids Genetics Consortium meta-analysis with their β-effect on TG and HWE p-value

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	GWAS p-value	HWE p-value
1	rs1832007	AKR1C4	rs1832007		A/G	0.82	0.033	2E-12	0.385
2	rs2131925	ANGPTL3	rs3850634	0.965	T/G	0.66	0.066	3E-74	0.937
3	rs964184	APOA1	rs964184		G/C	0.16	0.234	7E-224	0.482
4	rs2412710	CAPN3	rs2412710		A/G	0.04	0.099	2E-11	0.647
5	rs3764261	CETP	rs3764261		C/A	0.68	0.040	2E-25	0.432
6	rs10401969	CILP2	rs10401969		T/C	0.91	0.121	1E-69	0.595
7	rs11649653	CTF1	rs11649653		C/G	0.60	0.027	2E-07	0.874
8	rs2068888	CYP26A1	rs2068888		G/A	0.55	0.024	2E-11	0.340
9	rs174546	FADS1-2-3	rs174546		T/C	0.36	0.045	7E-38	0.450
10	rs2929282	FRMD5	rs2929282		T/A	0.07	0.072	2E-09	0.600
11	rs9930333	FTO	rs1121980	1.000	A/G	0.43	0.021	3E-08	0.812
12	rs4846914	GALNT2	rs4846914		G/A	0.41	0.040	7E-31	0.441
13	rs1260326	GCKR	rs1260326		T/C	0.39	0.115	2E-239	0.633
14	rs7248104	INSR	rs7248104		G/A	0.58	0.022	5E-10	0.386
15	rs2972146	IRS1	rs1515100	0.891	T/G	0.63	0.028	3E-15	0.082
16	rs10761731	JMJD1C	rs10761739	1.000	A/T	0.56	0.031	8E-12	0.218
17	rs442177	KLHL8	rs442177		T/G	0.58	0.031	1E-18	0.835
18	rs1532085	LIPC	rs1532085		A/G	0.40	0.031	2E-18	0.688
19	rs12678919	LPL	rs12678919		A/G	0.87	0.170	2E-199	0.411
20	rs11613352	LRP1	rs11613352		C/T	0.74	0.028	9E-14	0.165
21	rs6831256	LRPAP1	rs6831256		G/A	0.42	0.026	2E-12	0.082
22	rs9686661	MAP3K1	rs9686661		T/C	0.20	0.038	3E-16	0.432
23	rs38855	MET	rs38855		A/G	0.53	0.019	2E-08	0.749
24	rs4719841	MIR148A	rs4719841		C/T	0.20	0.023	9E-11	0.938
25	rs8077889	MPP3	rs8077889		C/A	0.22	0.025	1E-08	0.212
26	rs645040	MSL2L1	rs645040		T/G	0.77	0.029	2E-12	0.124
27	rs1495741	NAT2	rs1495741		G/A	0.26	0.040	3E-12	0.835
28	rs3198697	PDXDC1	rs3198697		C/T	0.57	0.020	2E-08	0.411
29	rs731839	PEPD	rs731839		G/A	0.35	0.022	3E-09	0.109
30	rs12748152	PIGV-NROB2	rs12748152		T/C	0.09	0.037	1E-09	0.672
31	rs11776767	PINX1	rs2271357	1.000	C/G	0.37	0.022	3E-11	0.291
32	rs5756931	PLA2G6	rs5756931		T/C	0.60	0.020	3E-08	0.872
33	rs6065906	PLTP	rs6065906		C/T	0.19	0.053	2E-34	0.093
34	rs719726	RSPO3	chr6:127456494		T/C	0.51	0.020	3E-08	0.138
35	rs6882076	TIMD4	rs6882076		C/T	0.64	0.029	2E-15	0.199
36	rs2954029	TRIB1	rs2954029		A/T	0.53	0.076	1E-107	0.592
37	rs998584	VEGFA	rs1358980	0.837	A/C	0.49	0.029	3E-15	0.786
38	rs4765127	ZNF664	rs11057408	1.000	G/T	0.65	0.029	2E-08	0.834

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error. CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S12 Table. List of the selected SNPs from the Engage Consortium meta-analysis with their β-effect on TG and HWE p-value

Number	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
1	rs2035403	AFF1-KLHL8	chr4:88238015		G/A	0.39	0.039	0.006	1.8E-10	0.654
2	rs2131925	ANGPTL3, DOCK7	rs3850634	0.965	T/G	0.68	0.074	0.006	5.1E-32	0.937
3	rs4665710	APOB	rs1042034	1.000	C/A	0.76	0.082	0.007	1.1E-31	0.192
4	rs964184	APO-cluster	rs964184		G/C	0.13	0.244	0.009	1.7E-157	0.482
5	rs439401	APOE	rs439401		C/T	0.65	0.073	0.007	1.5E-26	0.547
6	rs2540948	CEP68	rs2540950	0.929	T/C	0.65	0.036	0.006	6.6E-09	0.617
7	rs7205804	CETP	rs7205804		G/A	0.56	0.034	0.006	6.0E-08	0.288
8	rs10401969	CILP2	rs10401969		T/C	0.92	0.120	0.012	2.0E-25	0.595
9	rs17585887	CITED2	rs668459	1.000	T/C	0.44	0.039	0.006	7.1E-11	0.722
10	rs174546	FADS1-2-3	rs174546		T/C	0.38	0.053	0.006	3.2E-18	0.450
11	rs2929282	FRMD5	rs2929282		T/A	0.04	0.046	0.014	1.5E-03	0.600
12	rs10864728	GALNT2	rs4846914	0.965	A/G	0.39	0.052	0.006	4.5E-16	0.441
13	rs1260326	GCKR	rs1260326		T/C	0.36	0.123	0.006	4.8E-88	0.633
14	rs2255811	GPR85	rs2255811		G/A	0.25	0.041	0.007	2.3E-08	0.697
15	rs419132	HLA-area	rs419132		G/A	0.20	0.056	0.008	4.7E-12	0.267
16	rs2943645	IRS1	rs2943645		T/C	0.63	0.029	0.006	3.2E-06	0.162
17	rs10761731	JMJD1C	rs10761739	1.000	A/T	0.58	0.034	0.006	1.9E-08	0.218
18	rs1077835	LIPC	rs1077834	1.000	G/A	0.22	0.059	0.008	1.9E-14	0.243
19	rs7759633	LPA	rs5014650	0.800	G/A	0.87	0.051	0.009	8.6E-09	0.508
20	rs12678919	LPL	rs12678919		A/G	0.91	0.194	0.011	1.0E-71	0.411
21	rs61352607	LRP1	rs11613352	1.000	G/T	0.73	0.038	0.007	1.2E-08	0.165
22	rs6831256	LRPAP1	rs6831256		G/A	0.41	0.037	0.006	1.5E-09	0.082
23	rs9638182	MLXIPL	rs11974409	1.000	T/G	0.81	0.100	0.008	1.2E-40	0.058
24	rs645040	MSL2L1	rs645040		T/G	0.80	0.040	0.007	6.8E-08	0.124
25	rs12748152	PIGV-NROB2	rs12748152		T/C	0.09	0.038	0.010	2.8E-04	0.672
26	rs4810479	PLTP	rs4810479		C/T	0.27	0.052	0.007	1.9E-13	0.750
27	rs340839	PROX1	rs340839		A/G	0.47	0.039	0.006	4.4E-10	0.700
28	rs72959041	RSPO3	chr6:127496586		A/G	0.06	0.075	0.014	4.8E-08	0.602
29	rs8077889	SOST-DUSP3	rs8077889		C/A	0.19	0.011	0.008	1.3E-01	0.212
30	rs1553318	TIMD4-HAVCR1	rs6882076	0.883	C/G	0.65	0.042	0.006	2.2E-11	0.199
31	rs2954029	TRIB1	rs2954029		A/T	0.52	0.082	0.006	4.4E-44	0.592
32	rs2412710	UBR1, CAPN3	rs2412710		A/G	0.02	0.086	0.024	2.9E-04	0.647
33	rs1358980	VEGFA	rs1358980		T/C	0.47	0.039	0.007	3.3E-09	0.786

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error. CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S13 Table. List of the selected SNPs from combined meta-analyses with their β-effect on TG and HWE p-value

Number	Article	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
1	I	rs2035403	AFF1-KLHL8	chr4:88238015		G/A	0.39	0.039	0.006	1.8E-10	0.654
2	D	rs1832007	AKR1C4	rs1832007		A/G	0.82	0.033		2.0E-12	0.385
3	I	rs2131925	ANGPTL3, DOCK7	rs3850634	0.965	T/G	0.68	0.074	0.006	5.1E-32	0.937
4	I	rs964184	APO-cluster	rs964184		G/C	0.13	0.244	0.009	1.7E-157	0.482
5	I	rs4665710	APOB	rs1042034	1.000	C/A	0.76	0.082	0.007	1.1E-31	0.192
6	I	rs439401	APOE	rs439401		C/T	0.65	0.073	0.007	1.5E-26	0.547
7	I	rs2540948	CEP68	rs2540950	0.929	T/C	0.65	0.036	0.006	6.6E-09	0.617
8	D	rs3764261	CETP	rs3764261		C/A	0.68	0.040		2.0E-25	0.432
9	I	rs10401969	CILP2	rs10401969		T/C	0.92	0.120	0.012	2.0E-25	0.595
10	I	rs17585887	CITED2	rs668459	1.000	T/C	0.44	0.039	0.006	7.1E-11	0.722
11	D	rs11649653	CTF1	rs11649653		C/G	0.60	0.027		2.0E-07	0.874
12	D	rs2068888	CYP26A1	rs2068888		G/A	0.55	0.024		2.0E-11	0.340
13	I	rs174546	FADS1-2-3	rs174546		T/C	0.38	0.053	0.006	3.2E-18	0.450
14	D	rs2929282	FRMD5	rs2929282		T/A	0.07	0.072		2.0E-09	0.600
15	D	rs9930333	FTO	rs1121980	1.000	A/G	0.43	0.021		3.0E-08	0.812
16	I	rs10864728	GALNT2	rs4846914	0.965	A/G	0.39	0.052	0.006	4.5E-16	0.441
17	I	rs1260326	GCKR	rs1260326		T/C	0.36	0.123	0.006	4.8E-88	0.633
18	I	rs2255811	GPR85	rs2255811		G/A	0.25	0.041	0.007	2.3E-08	0.697
19	I	rs419132	HLA-area	rs419132		G/A	0.20	0.056	0.008	4.7E-12	0.267
20	D	rs7248104	INSR	rs7248104		G/A	0.58	0.022		5.0E-10	0.386
21	D	rs2972146	IRS1	rs1515100	0.891	T/G	0.63	0.028		3.0E-15	0.082
22	I	rs10761731	JMJD1C	rs10761739	1.000	A/T	0.58	0.034	0.006	1.9E-08	0.218
23	I	rs1077835	LIPC	rs1077834	1.000	G/A	0.22	0.059	0.008	1.9E-14	0.243
24	I	rs7759633	LPA	rs5014650	0.800	G/A	0.87	0.051	0.009	8.6E-09	0.508
25	I	rs12678919	LPL	rs12678919		A/G	0.91	0.194	0.011	1.0E-71	0.411
26	I	rs61352607	LRP1	rs11613352	1.000	G/T	0.73	0.038	0.007	1.2E-08	0.165
27	I	rs6831256	LRPAP1	rs6831256		G/A	0.41	0.037	0.006	1.5E-09	0.082
28	D	rs9686661	MAP3K1	rs9686661		T/C	0.20	0.038		3.0E-16	0.432
29	D	rs38855	MET	rs38855		A/G	0.53	0.019		2.0E-08	0.749
30	D	rs4719841	MIR148A	rs4719841		C/T	0.20	0.023		9.0E-11	0.938
31	I	rs9638182	MLXIPL	rs11974409	1.000	T/G	0.81	0.100	0.008	1.2E-40	0.058
32	D	rs645040	MSL2L1	rs645040		T/G	0.77	0.029		2.0E-12	0.124
33	D	rs1495741	NAT2	rs1495741		G/A	0.26	0.040		3.0E-12	0.835
34	D	rs3198697	PDXDC1	rs3198697		C/T	0.57	0.020		2.0E-08	0.411
35	D	rs731839	PEPD	rs731839		G/A	0.35	0.022		3.0E-09	0.109
36	D	rs12748152	PIGV-NROB2	rs12748152		T/C	0.09	0.037		1.0E-09	0.672
37	D	rs11776767	PINX1	rs2271357	1.000	C/G	0.37	0.022		3.0E-11	0.291
38	D	rs5756931	PLA2G6	rs5756931		T/C	0.60	0.020		3.0E-08	0.872
39	I	rs4810479	PLTP	rs4810479		C/T	0.27	0.052	0.007	1.9E-13	0.750
40	I	rs340839	PROX1	rs340839		A/G	0.47	0.039	0.006	4.4E-10	0.700

Number	Article	SNP	Nearest gene	Cardiometabochip position	LD (R^2)	Allele (effect/other)	EAF	ß-effect (effect/other)	SE	GWAS p-value	HWE p-value
41	I	rs72959041	RSPO3	chr6:127496586		A/G	0.06	0.075	0.014	4.8E-08	0.602
42	D	rs8077889	MPP3	rs8077889		C/A	0.22	0.025		1.0E-08	0.212
43	D	rs6882076	TIMD4	rs6882076		C/T	0.64	0.029		2.0E-15	0.199
44	I	rs2954029	TRIB1	rs2954029		A/T	0.52	0.082	0.006	4.4E-44	0.592
45	D	rs2412710	CAPN3	rs2412710		A/G	0.04	0.099		2.0E-11	0.647
46	I	rs1358980	VEGFA	rs1358980		T/C	0.47	0.039	0.007	3.3E-09	0.786
47	D	rs4765127	ZNF664	rs11057408	1.000	G/T	0.65	0.029		2.0E-08	0.834

EAF: effect allele frequency, LD: linkage disequilibrium, SE: standard error, I: meta-analysis from Engage Consortium (from Surakka and al.), D: meta-analysis from the Global Lipids Genetics Consortium (from Willer and al.). CardioMetabochip position = SNP identification used to extract genotyping data from psychiatric cohort. HWE p-value = p-value calculated with genotyping data from psychiatric cohort.

S14 Table. Association of rescaled PRS (SNPs selected from each meta-analysis) with lipid traits in GAMM adjusted for age, sex, BMI, medications and smoking status.

	number of SNPs	n	Estimates [95% CI]	Explained variability [%]	Explained variability by GRS [%]	p-value
wPRS_HDL_ds_dMA	65	242	0.01 [0.01 - 0.02]	19.24	4.11	<0.01
wPRS_LDL_ds_dMA	55	232	0.02 [0.00 - 0.03]	13.28	0.75	0.02
wPRS_TC_ds_dMA	69	239	0.03 [0.02 - 0.05]	15.82	1.85	<0.01
wPRS_TG_ds_dMA	38	216	0.06 [0.04 - 0.08]	26.16	6.32	<0.01
wPRS_HDL_ds_iMA	46	233	0.02 [0.01 - 0.03]	18.33	3.45	<0.01
wPRS_LDL_ds_iMA	39	214	0.03 [0.01 - 0.05]	15.29	1.48	<0.01
wPRS_TC_ds_iMA	44	234	0.04 [0.03 - 0.07]	15.99	2.35	<0.01
wPRS_TG_ds_iMA	33	213	0.06 [0.03 - 0.07]	24.06	4.23	<0.01
wPRS_HDL_rs_dMA	65	105	0.02 [0.01 - 0.03]	36.64	5.29	<0.01
wPRS_LDL_rs_dMA	55	102	0.03 [0.01 - 0.06]	8.24	3.24	<0.01
wPRS_TC_rs_dMA	69	106	0.05 [0.02 - 0.07]	14.13	3.44	0.01
wPRS_TG_rs_dMA_	38	90	0.03 [0.00 - 0.05]	26.47	2.62	0.03
wPRS_HDL_rs_iMA	46	98	0.03 [0.01 - 0.04]	41.37	6.65	<0.01
wPRS_LDL_rs_iMA_	39	93	0.05 [0.03 - 0.08]	14.14	8.13	<0.01
wPRS_TC_rs_iMA	44	102	0.07 [0.03 - 0.10]	17.04	6.14	<0.01
wPRS_TG_rs_iMA_	33	87	0.04 [0.01 - 0.06]	27.74	4.77	<0.01
wPRS_HDL_ts_dMA	65	347	0.02 [0.01 - 0.02]	22.25	4.32	<0.01
wPRS_LDL_ts_dMA	55	334	0.02 [0.01 - 0.04]	10.83	1.13	<0.01
wPRS_TC_ts_dMA	69	345	0.03 [0.02 - 0.05]	14.8	2.09	<0.01
wPRS_TG_ts_dMA	38	306	0.05 [0.03 - 0.06]	25.38	5.08	<0.01
wPRS_HDL_ts_iMA	46	331	0.02 [0.01 - 0.03]	22.87	4.41	<0.01
wPRS_LDL_ts_iMA	39	307	0.04 [0.02 - 0.06]	13.33	2.91	<0.01
wPRS_TC_ts_iMA	44	336	0.05 [0.04 - 0.07]	15.72	3.06	<0.01
wPRS_TG_ts_iMA	33	300	0.05 [0.04 - 0.06]	24.52	4.39	<0.01

ds: discovery sample, rs: replication sample, ts: total sample, dMA: Willer meta-analysis, iMA: Surakka meta-analysis, MA_: not corrected for psychotropic medication categories, n: number of patients, CI: confidence interval. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.

S15 Table. Association of rescaled PRS (SNPs selected from each meta-analysis) with lipid traits in GAMM adjusted for age, sex, BMI, medications and smoking status, with PRS treated as a categorical variable in age-stratified samples.

	number of SNPs	n	Estimates [95% CI]	p-value
wPRS_median_HDL_ts_cMA_	73	331	0.13 [0.07 - 0.19]	<0.0001
wPRS_p25_HDL_ts_cMA_	73	167	0.28 [0.19 - 0.36]	<0.0001
wPRS_p10_HDL_ts_cMA_	73	68	0.35 [0.22 - 0.49]	<0.0001
wPRS_median_LDL_ts_cMA_	60	303	0.20 [0.04 - 0.36]	0.004
wPRS_p25_LDL_ts_cMA_	60	158	0.31 [0.11 - 0.53]	0.003
wPRS_p10_LDL_ts_cMA_	60	68	0.63 [0.27 - 1.00]	0.0004
wPRS_median_TC_ts_cMA_	72	336	0.32 [0.15 - 0.49]	<0.0001
wPRS_p25_TC_ts_cMA_	72	171	0.50 [0.28 - 0.74]	<0.0001
wPRS_p10_TC_ts_cMA_	72	76	0.66 [0.30 - 1.07]	0.0002
wPRS_median_TG_ts_cMA_	47	299	0.26 [0.13 - 0.38]	<0.0001
wPRS_p25_TG_ts_cMA_	47	146	0.47 [0.30 - 0.64]	<0.0001
wPRS_p10_TG_ts_cMA_	47	56	0.60 [0.19 - 0.91]	0.002

ts: total sample, cMA: combined meta-analyses, MA_: not corrected for psychotropic medication categories, n: number of patients, CI: confidence interval. wPRS_median = GAMM performed with PRS as a categorical variable with two groups: one with PRS lower than the median value and the other with PRS higher than the median value. Young = patients whose age is younger than the median age of patients. Old = patients whose age is older than the median age of patients. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.

S16 Table. Predictive statistics in the combined sample

Dependent variable	Logistic model	Sensitivity % (95%CI)	Specificity % (95%CI)	Accuracy % (95%CI)	AUC (95%CI)	P-value[3]
TC hypercholesterolemia	Clin[1]	72.2 (60.4-84.4)	63.3 (52.2-73.3)	70.0 (61.9-78.1)	0.70 (0.63-0.77)	0.08
	Clin + Gen [2]	73.3 (67.4-80.7)	67.7 (57.7-76.6)	71.9 (66.9-77.5)	0.73 (0.67-0.80)	
LDL hypercholesterolemia	Clin[1]	70.5 (57.7-78.4)	60.9 (51.4-72.4)	67.2 (59.9-72.9)	0.66 (0.59-0.73)	0.41
	Clin + Gen [2]	65.6 (55.5-80.2)	62.9 (50.5-73.3)	65.1 (58.7-72.9)	0.68 (0.61-0.74)	
HDL hypocholesterolemia	Clin[1]	71.2 (62.6-79.1)	67.6 (60.7-75.3)	69.3 (64.3-73.7)	0.73 (0.74-0.78)	**0.03**
	Clin + Gen [2]	70.5 (62.6-79.1)	73.1 (64.4-80.8)	72.4 (67.3-76.8)	0.76 (0.71-0.81)	
Hypertriglyceridemia	Clin[1]	70.0 (60.0-79.1)	71.3 (61.6-80.5)	70.4 (64.9-75.9)	0.74 (0.68-0.80)	0.57
	Clin + Gen [2]	70.9 (56.4-80.9)	67.1 (57.9-82.3)	68.9 (63.5-74.8)	0.75 (0.69-0.80)	

AUC: area under the curve.

[1] Logistic model including only clinical variables.

[2] Logistic model including clinical and genetic variables.

[3] P-values of difference between the AUC of the model containing clinical data and the model containing clinical and genetic data. 2000 bootstraps were used for the analysis.

S17 Table. Interaction tests between rescaled PRS and age, sex and BMI in GAMM on lipid traits for SNPs selected from combined meta-analyses in the combined sample

	p-value
HDL_age*wPRS_ts_cMA	0.25
HDL_sexe*wPRS_ts_cMA	0.19
HDL_BMI*wPRS_ts_cMA	0.31
LDL_age*wPRS_ts_cMA	0.32
LDL_sexe*wPRS_ts_cMA	0.19
LDL_BMI*wPRS_ts_cMA	0.02
TC_age*wPRS_ts_cMA	0.3
TC_sexe*wPRS_ts_cMA	0.04
TC_BMI*wPRS_ts_cMA	0.47
TG_age*wPRS_ts_cMA	0.14
TG_sexe*wPRS_ts_cMA	0.25
TG_BMI*wPRS_ts_cMA	0.20

ds: discovery sample, rs: replication sample, ts: total sample, cMA: combined meta-analyses, MA_: not corrected for psychotropic medication categories. Age*wPRS = interaction between age and genetic risk score, sex*wPRS = interaction between sex and genetic risk score, BMI*wPRS = interaction between BMI and genetic risk score. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.

S18 Table. Association of rescaled PRS (SNPs selected from each meta-analysis) with lipid traits in GAMM adjusted with age, sex, BMI, medications and smoking status with PRS treated as a categorical variable in stratified samples.

	number of SNPs	n	Estimates [95% CI] (mmol/l)	p-value
wPRS_median LDL_BMI_low_ts_cMA_	60	179	0.03 [-0.19 - 0.17]	0.42
wPRS_median LDL_BMI_high_ts_cMA_	60	155	0.46 [0.23 - 0.72]	<0.0001
wPRS_median TC_female_ts_cMA_	72	199	0.40 [0.18 - 0.62]	<0.0001
wPRS_median TC_male_ts_cMA_	72	137	0.27 [0.04 - 0.58]	0.01

ts: total sample, cMA: combined meta-analyses, MA_: not corrected for psychotropic medication categories, n: number of patients, CI: confidence interval. wPRS_median = GAMM performed with PRS as a categorical variable with two groups: one with PRS lower than the median value and the other with PRS higher than the median value. BMI_low = patients whose BMI is smaller than the median value. BMI_high = patients whose BMI is higher than the median value. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.

S19 Table. Explained variability of each covariates using GAMM with SNP selected from combined meta-analyses in the combined sample

Total sample Combined meta-analyses	Explained variability [%]	Variability explained without variable [%]	Variability explained by variable [%]
wGRS_HDL	22.79	18.46	**4.33**
BMI_HDL	22.79	16.20	**6.59**
Age_HDL	22.79	21.39	1.40
Gender_HDL	22.79	16.64	**6.15**
Smoker_HDL	22.79	22.52	0.27
Medication_HDL	22.79	22.51	0.28
wGRS_LDL	13.61	10.21	**3.40**
BMI_LDL	13.61	10.44	**3.17**
Age_LDL	13.61	10.94	**2.67**
Gender_LDL	13.61	12.77	0.84
Smoker_LDL	13.61	12.01	1.60
Medication_LDL	13.61	13.54	0.07
wGRS_TC	15.91	12.66	**3.25**
BMI_TC	15.91	13.22	**2.69**
Age_TC	15.91	12.65	**3.26**
Gender_TC	15.91	13.80	**2.11**
Smoker_TC	15.91	15.19	0.72
Medication_TC	15.91	15.70	0.21
wGRS_TG	24.97	20.14	**4.83**
BMI_TG	24.97	10.42	**14.55**
Age_TG	24.97	24.63	0.34
Gender_TG	24.97	23.02	1.95
Smoker_TG	24.97	24.34	0.63
Medication_TG	24.97	23.63	1.34

Explained variability = variability explained by the clinical and genetic data. Variability explained without variable = variability explained by the whole model without the considered variable. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.

S20 Table. Explained variability of each SNP groups using GAMM with SNPs selected from combined meta-analyses in the combined sample

	Total sample Combined meta-analyses	n SNPs	n obs	Explained variability [%]	Variability explained without genetics [%]	Variability explained by genetics [%]
ALL SNPs	**wPRS_HDL**	**73**	**331**	**22.79**	**18.46**	**4.33**
ALL SNPs β=1	wPRS_HDL	73	331	20.04	18.46	1.58
≤β p50 SNPs	wPRS_HDL	36	361	18.04	17.77	0.27
>β p50 SNPs	wPRS_HDL	37	331	22.54	18.46	4.08
>β p95 SNPs	wPRS_HDL	4	358	21.71	18.16	3.55
ALL SNPs	**wPRS_LDL**	**60**	**303**	**13.61**	**10.21**	**3.40**
ALL SNPs β=1	wPRS_LDL	60	303	10.25	10.21	0.04
≤β p50 SNPs	wPRS_LDL	30	346	9.79	9.64	0.15
>β p50 SNPs	wPRS_LDL	30	307	15.03	10.42	4.61
>β p95 SNPs	wPRS_LDL	3	346	12.5	9.41	3.09
ALL SNPs	**wPRS_TC**	**72**	**336**	**15.91**	**12.66**	**3.25**
ALL SNPs β=1	wPRS_TC	72	336	13.81	12.66	1.15
≤β p50 SNPs	wPRS_TC	36	361	12.66	12.66	0.00
>β p50 SNPs	wPRS_TC	36	339	16.69	12.85	3.84
>β p95 SNPs	wPRS_TC	4	363	15.57	13.01	2.56
ALL SNPs	**wPRS_TG**	**47**	**299**	**24.97**	**20.11**	**4.86**
ALL SNPs β=1	wPRS_TG	47	299	22.72	20.11	2.61
≤β p50 SNPs	wPRS_TG	26	317	19.77	19.24	0.53
>β p50 SNPs	wPRS_TG	21	300	23.73	20.13	3.6
>β p95 SNPs	wPRS_TG	3	308	23.52	20.19	3.33

Explained variability = variability explained by the clinical and genetic data. Variability explained without genetics = variability explained by the whole model without considering genetics. ALL SNPs = wPRS constructed with the total number of SNPs. ALL SNPs β=1 = non-weighted PRS, i.e. PRS constructed with the total number of SNPs without considering specific β-effects (all β-effects=1). ≤β p50 SNPs = wPRS constructed with SNPs whose β-effects are lower or equal to the median of all β-effects. >β p50 SNPs = wPRS constructed with SNPs whose β-effects are higher than the median of all β-effects. >β p95 SNPs = wPRS constructed with SNPs whose β-effects are higher than the percentile 95 of all β-effects. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.

S21 Table. SNPs most involved in genetic explained variability of lipid phenotypes

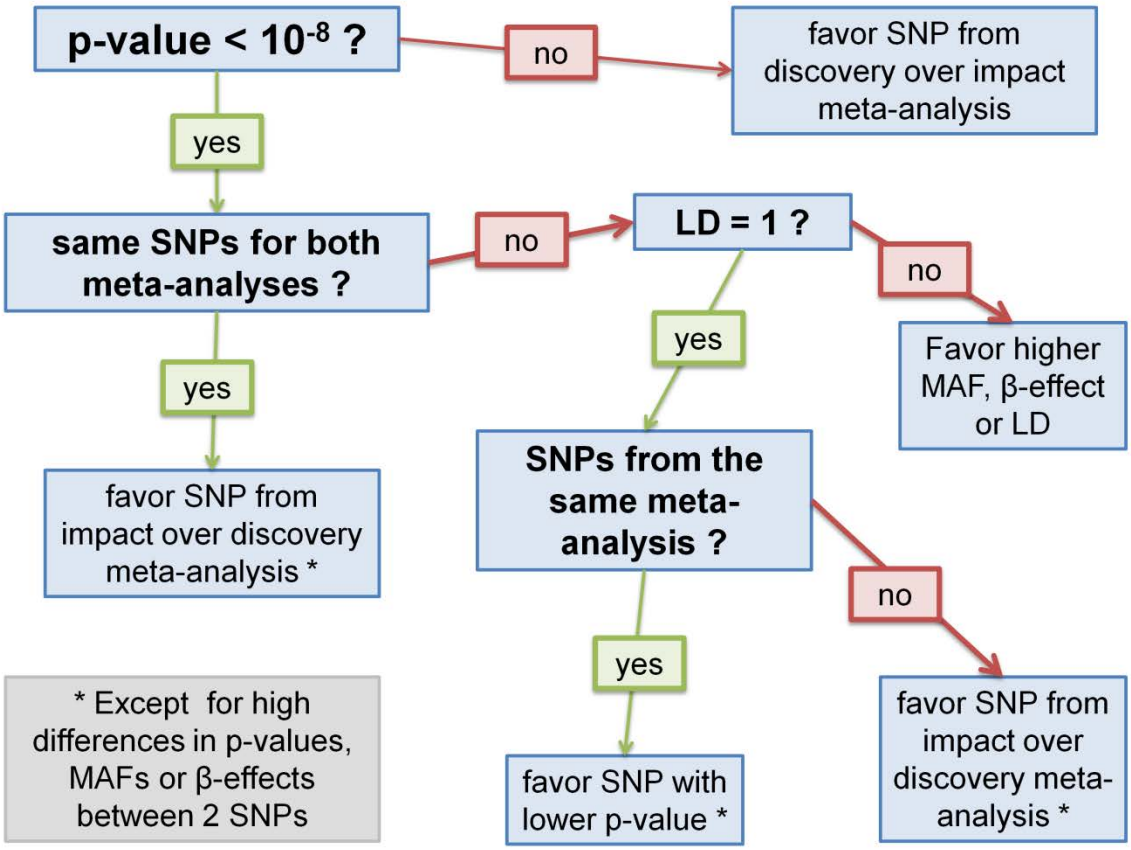
a.

HDL	rs3764261	**rs12678919**	rs1800961	rs78058190
LDL	rs1065853	**rs112374545**	**rs646776**	
TC	rs7412	**rs112374545**	rs10401969	**rs646776**
TG	rs964184	**rs12678919**	rs1260326	

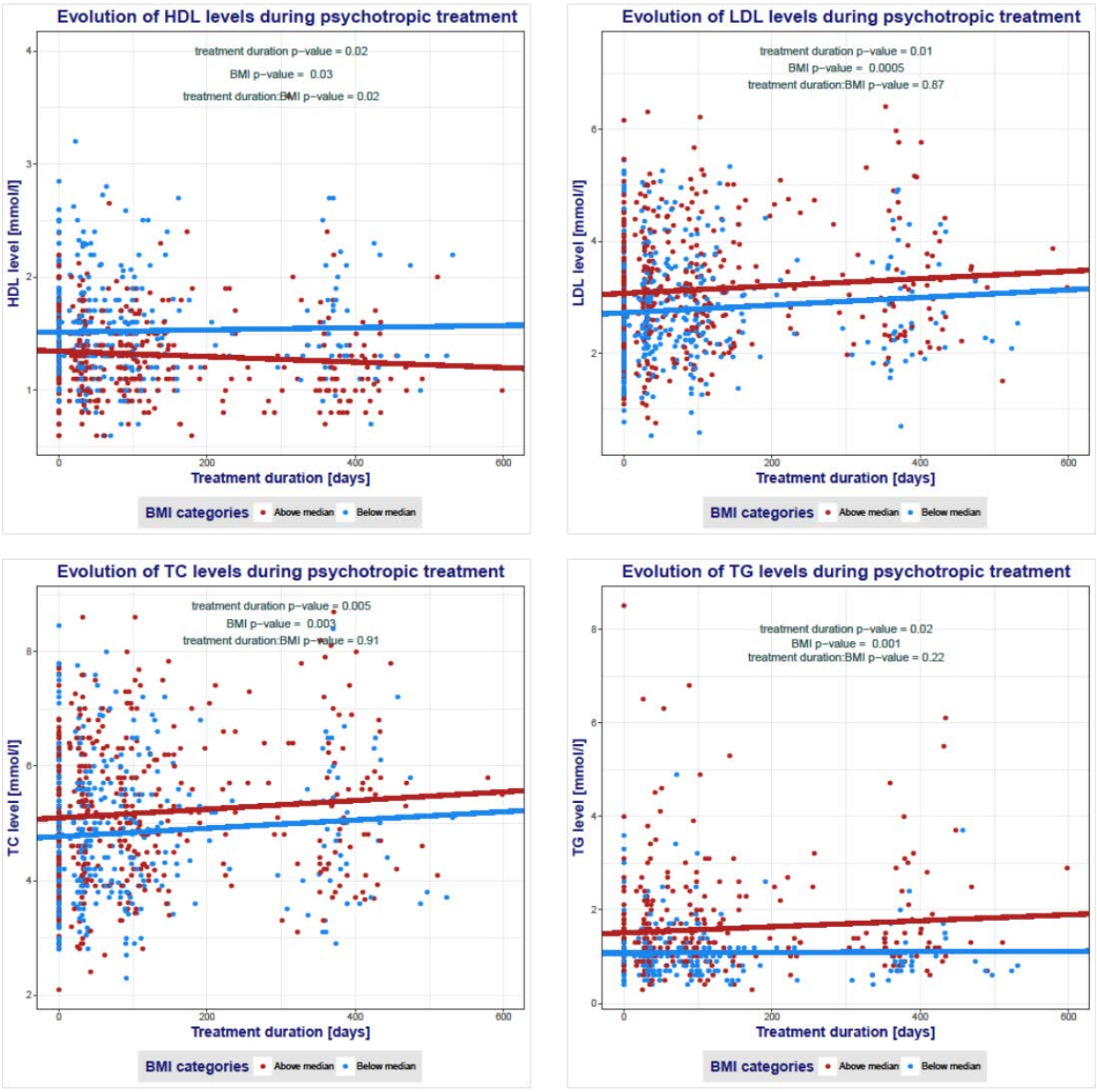
b.

SNP	Gene	Gene name	Remarks	Phenotypes[1]
rs3764261	CETP	Cholesteryl Ester Transfer Protein		HDL, LDL, TC, TG
rs12678919	**LPL**	**Lipoprotein lipase**		HDL, TG
rs1800961	HNF4A	Hetatocyte Nuclear Factor 4 Alpha	missense SNP	HDL, TC
rs78058190	PRKAG3	Protein Kinase AMP-Activated Non-Catalytic Subunit Gamma 3		HDL
rs1065853	APOE	Apolipoprotein E		LDL
rs112374545	**LDLR**	**Low density lipoprotein receptor**		LDL, TC
rs646776	**CELSR2**	**Cadherin EGF LAG Seven-Pass G-Type Receptor 2**		LDL, TC
rs7412	APOE	Apolipoprotein E	missense SNP	TC
rs10401969	CILP2	Cartilage Intermediate Layer Protein 2		LDL, TC, TG
rs964184	APOA1	Apolipoprotein A1		HDL, LDL, TC, TG
rs1260326	GCKR	Glucokinase (Hexokinase 4) Regulator	missense SNP	TC, TG

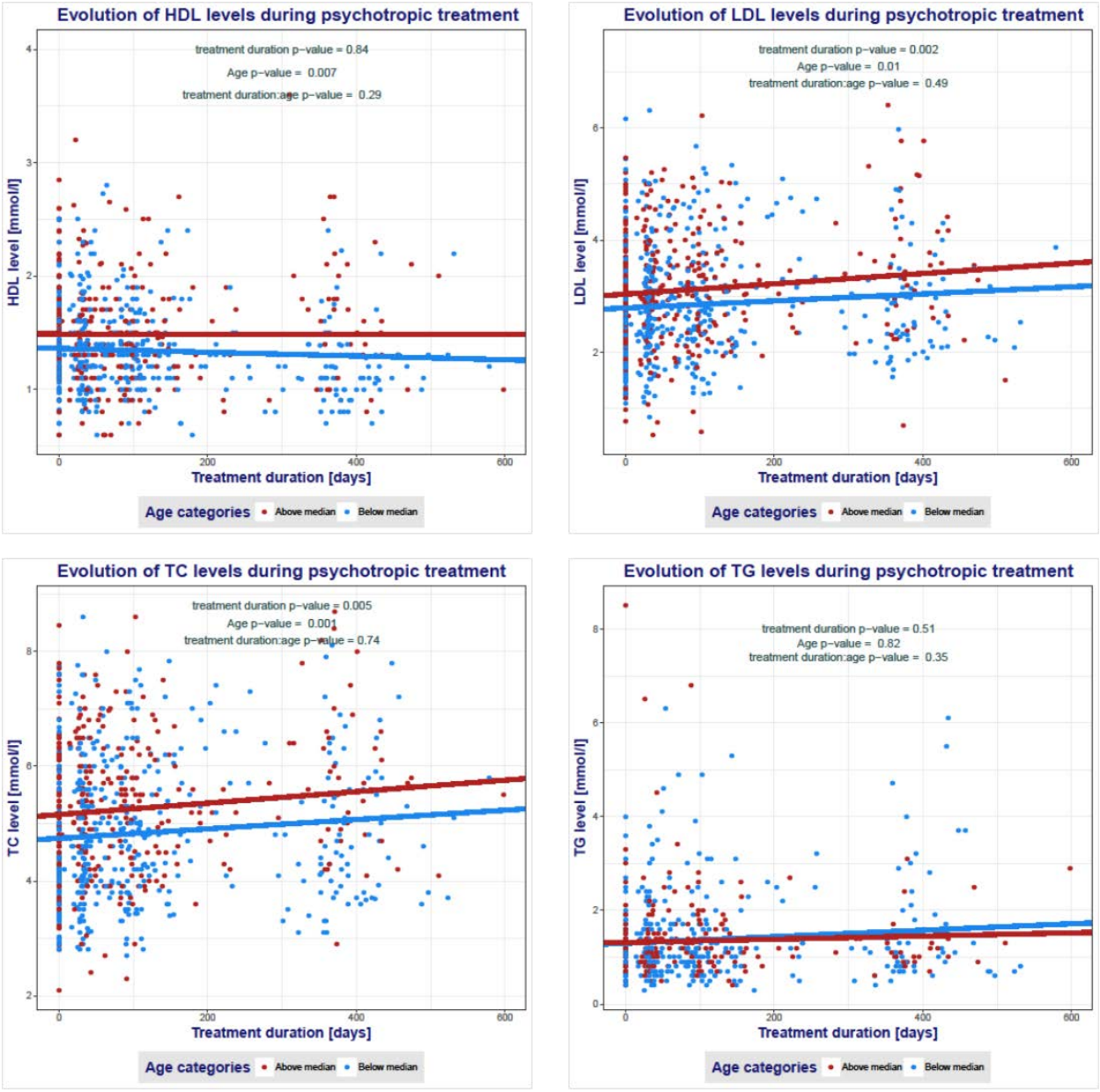
a. SNPs whose β-effects are higher than the percentile 95 of all β-effects (i.e. p95 SNPs) for HDL, LDL, TC and TG are shown, in decreasing order. P95 SNPs shared between two or more phenotypes are in bold. b. Characteristics of each p95 SNPs of a. [1]: other phenotypes significantly associated with corresponding SNP in the combined meta-analysis.



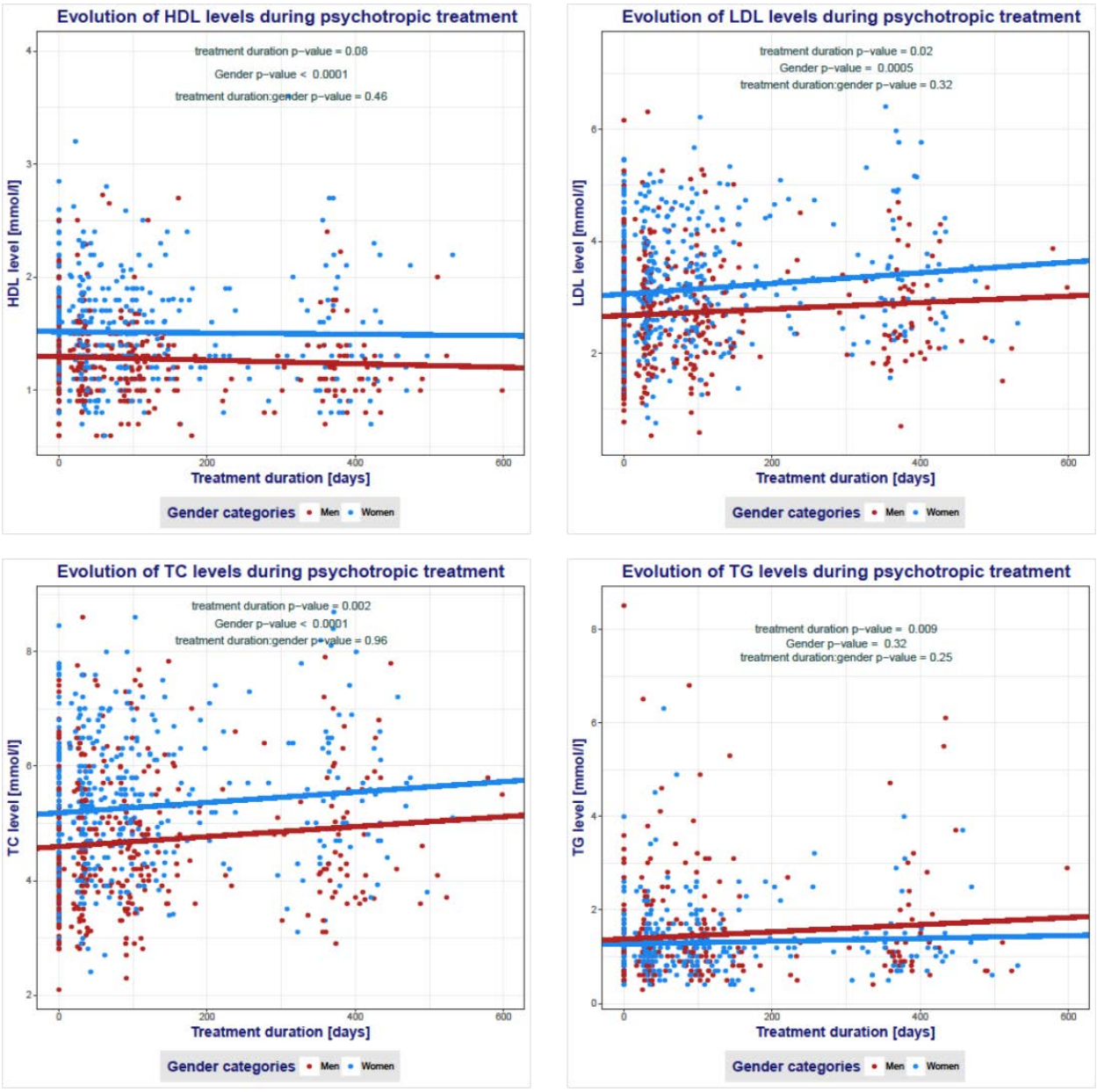
S1 Figure. Decision tree for the selection between two SNPs located in the same gene. LD: linkage disequilibrium, MAF: minor allele frequency. P-value of 10^{-8} = p-value considered as being GWAS significant. Impact: meta-analysis from Engage Consortium (from Surakka and al.). Discovery: meta-analysis from the Global Lipids Genetics Consortium (from Willer and al.).



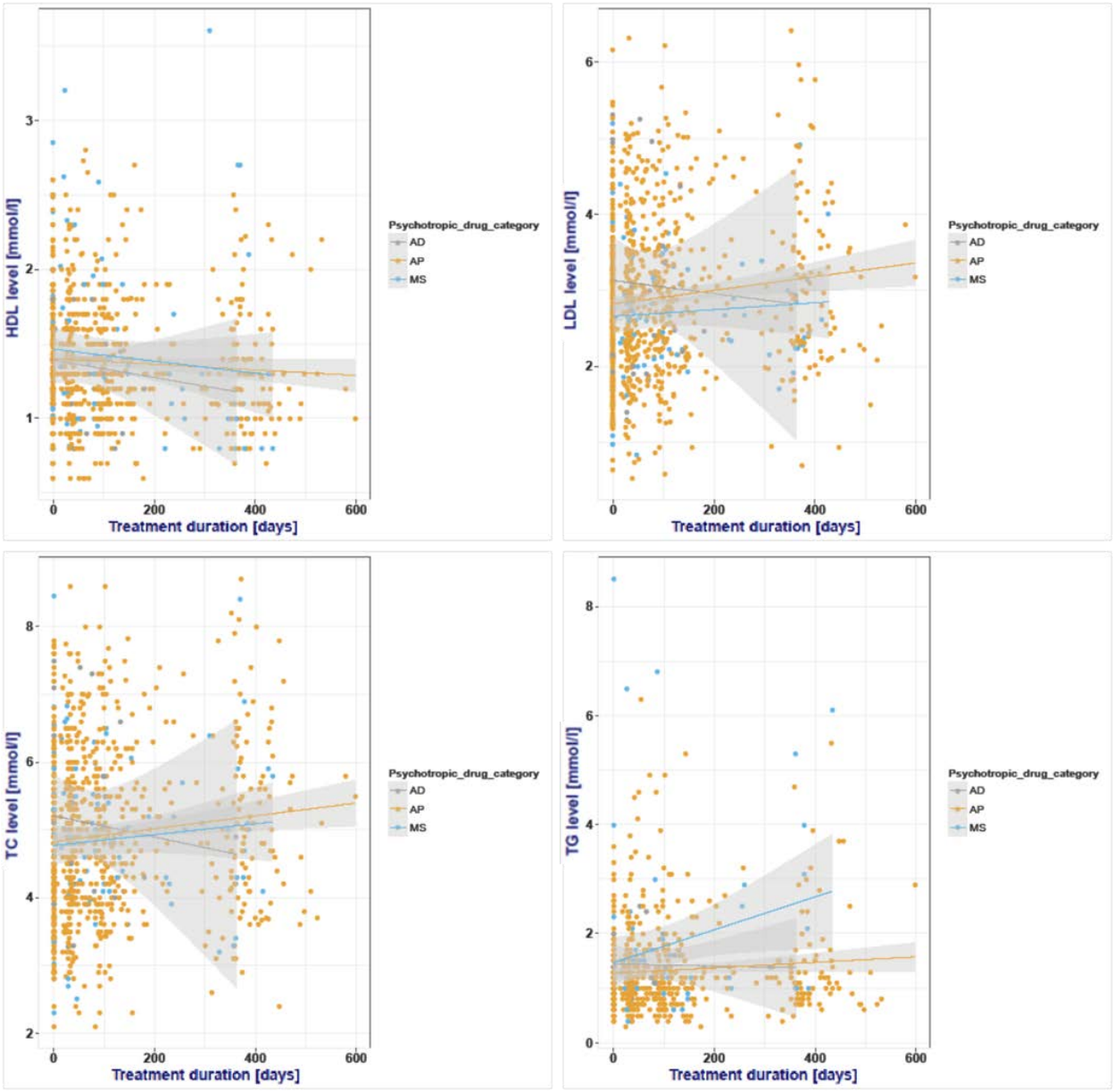
S2 Figure. Evolution of lipid levels during psychotropic treatment according to BMI: model including patients from the discovery sample. Blue dots represent patients whose BMI was lower or equal to the median (23.3 kg/m^2). Red dots represent patients whose BMI was higher than the median (23.3 kg/m^2). Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



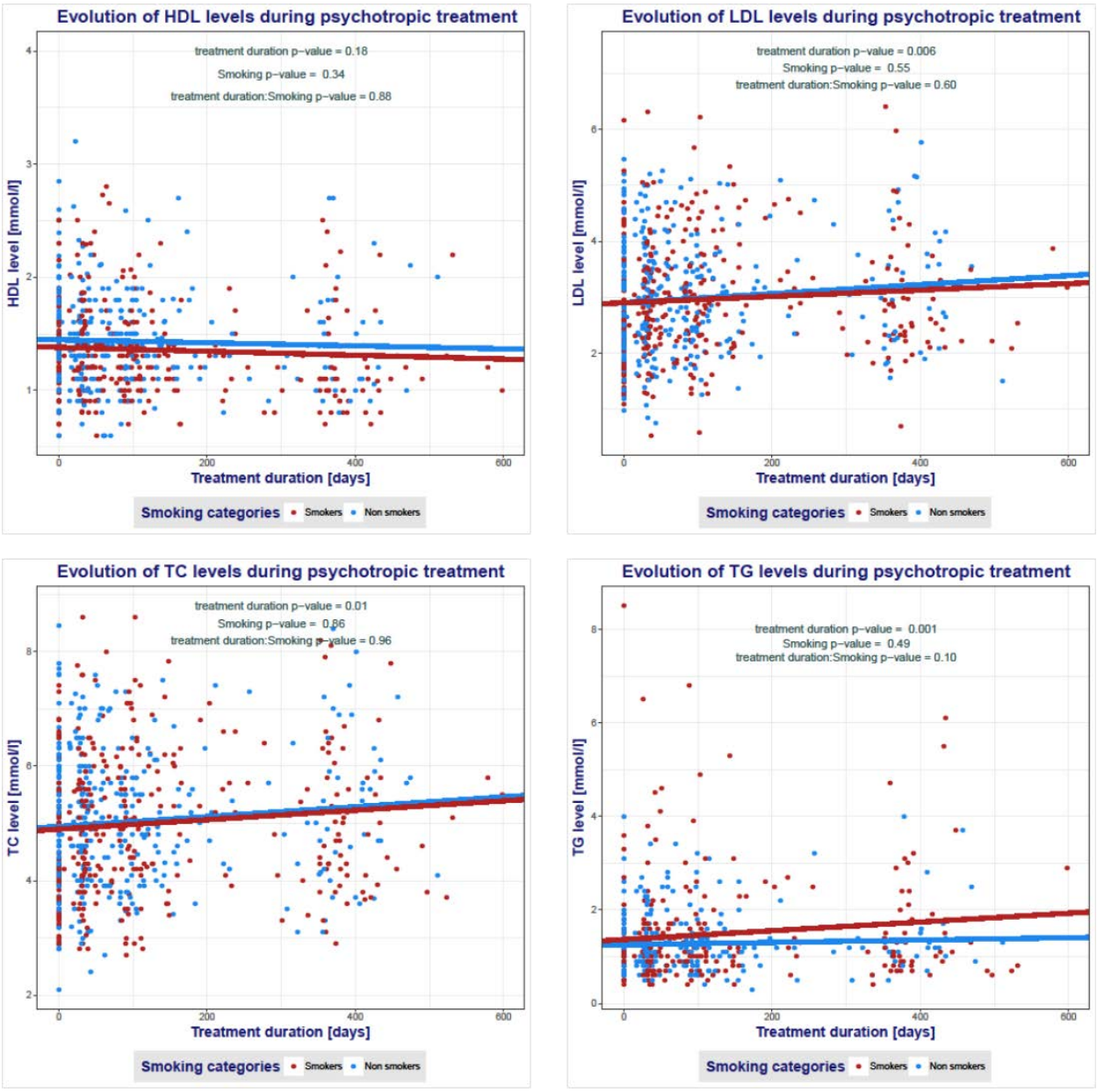
S3 Figure. Evolution of lipid levels during psychotropic treatment according to age: model including patients from the discovery sample. Blue dots represent patients younger or equal to the median value (48 years old). Red dots represent patients older than the median value (48 years old). Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



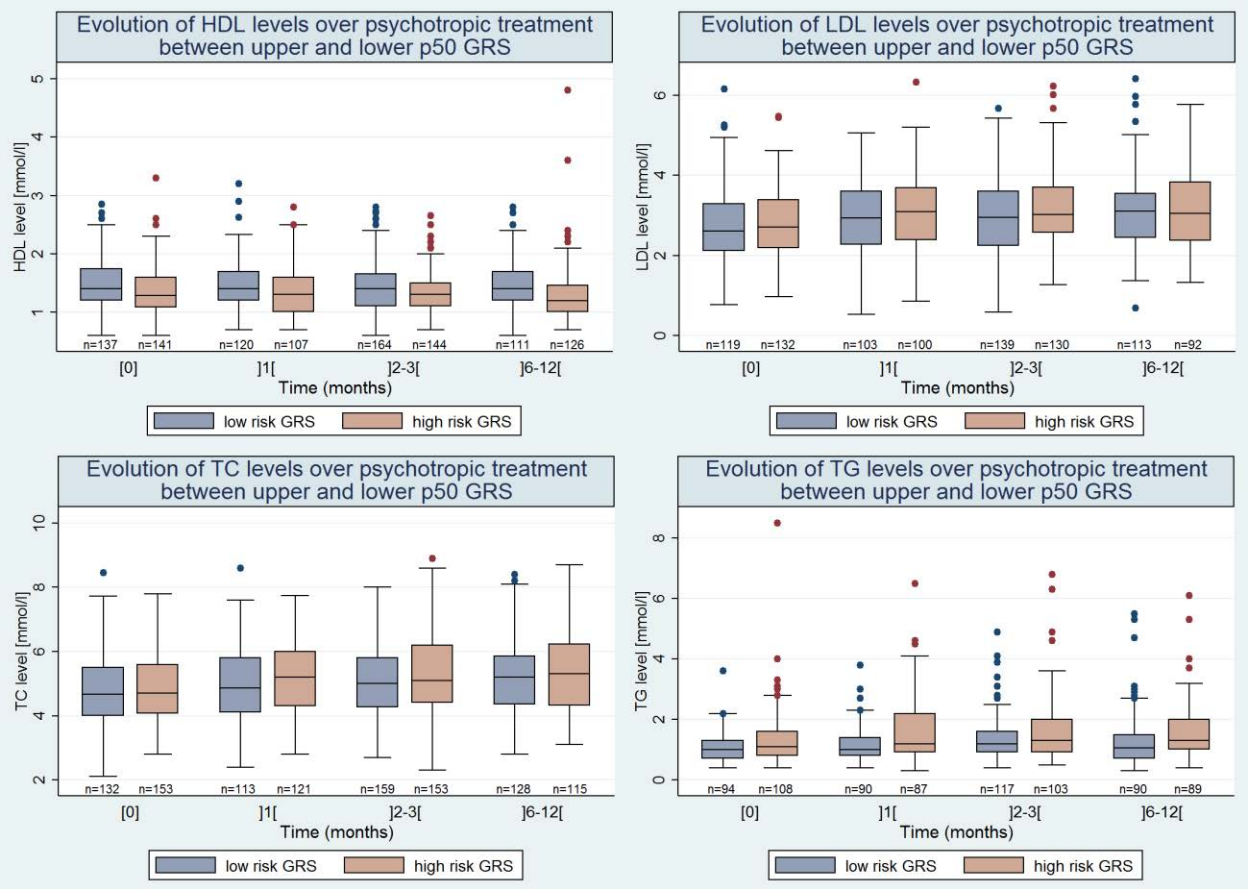
S4 Figure. Evolution of lipid levels during psychotropic treatment according to gender: model including patients from the discovery sample. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



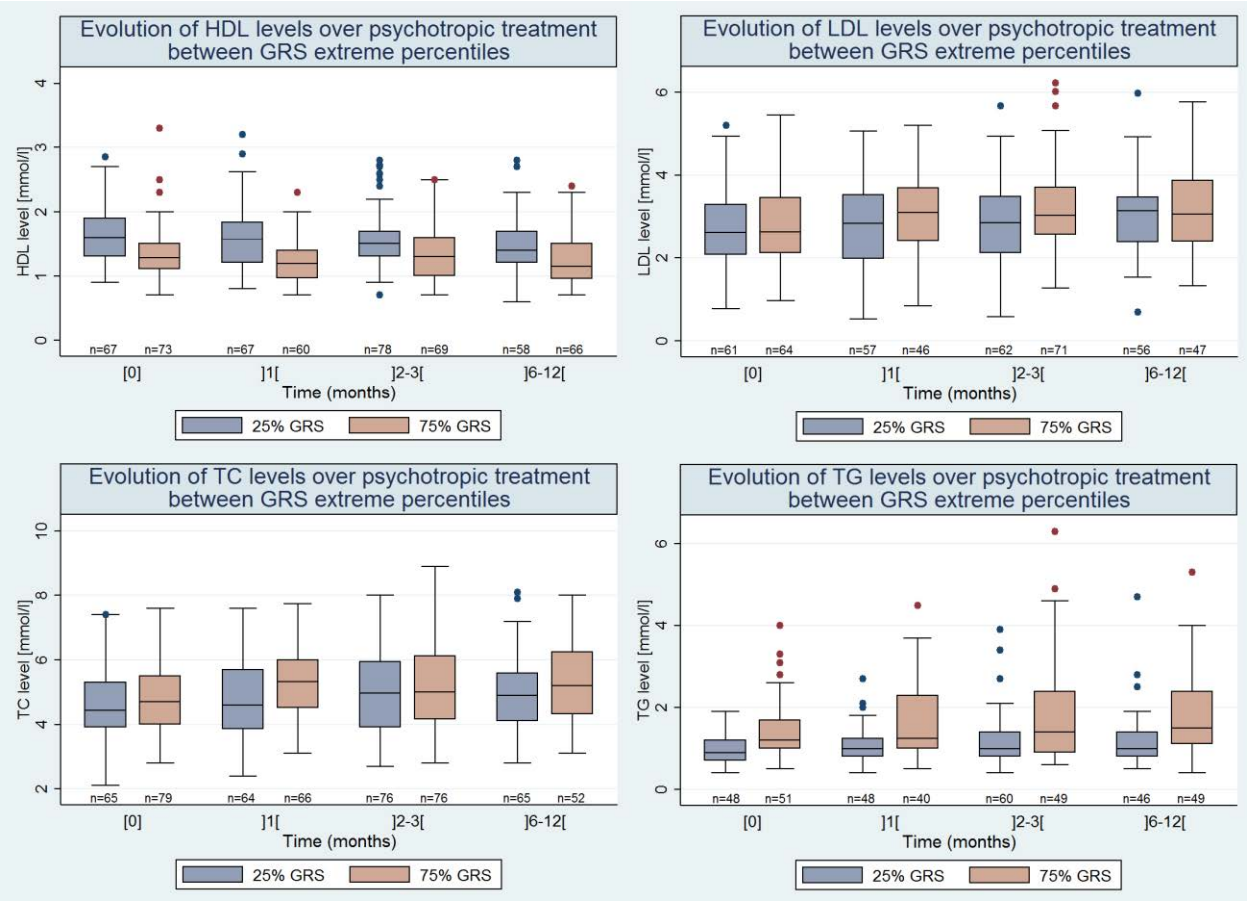
S5 Figure. Evolution of lipid levels during psychotropic treatment according to medication classes in the discovery sample. Patients receiving antipsychotics, mood stabilizers and antidepressants are represented in yellow, blue and grey dots, respectively. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



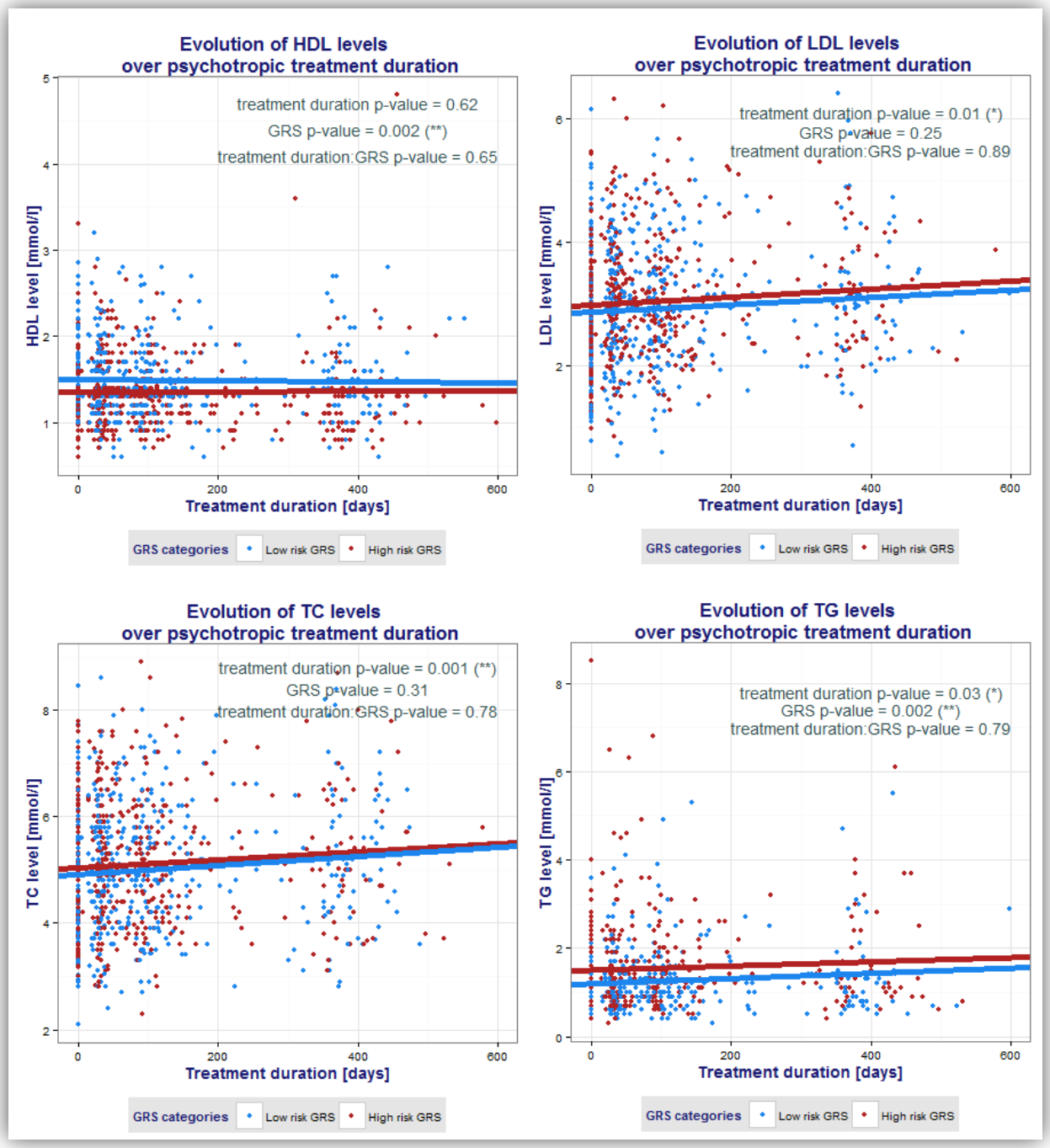
S6 Figure. Evolution of lipid levels during psychotropic treatment according to the smoking status: model including patients from the discovery sample. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



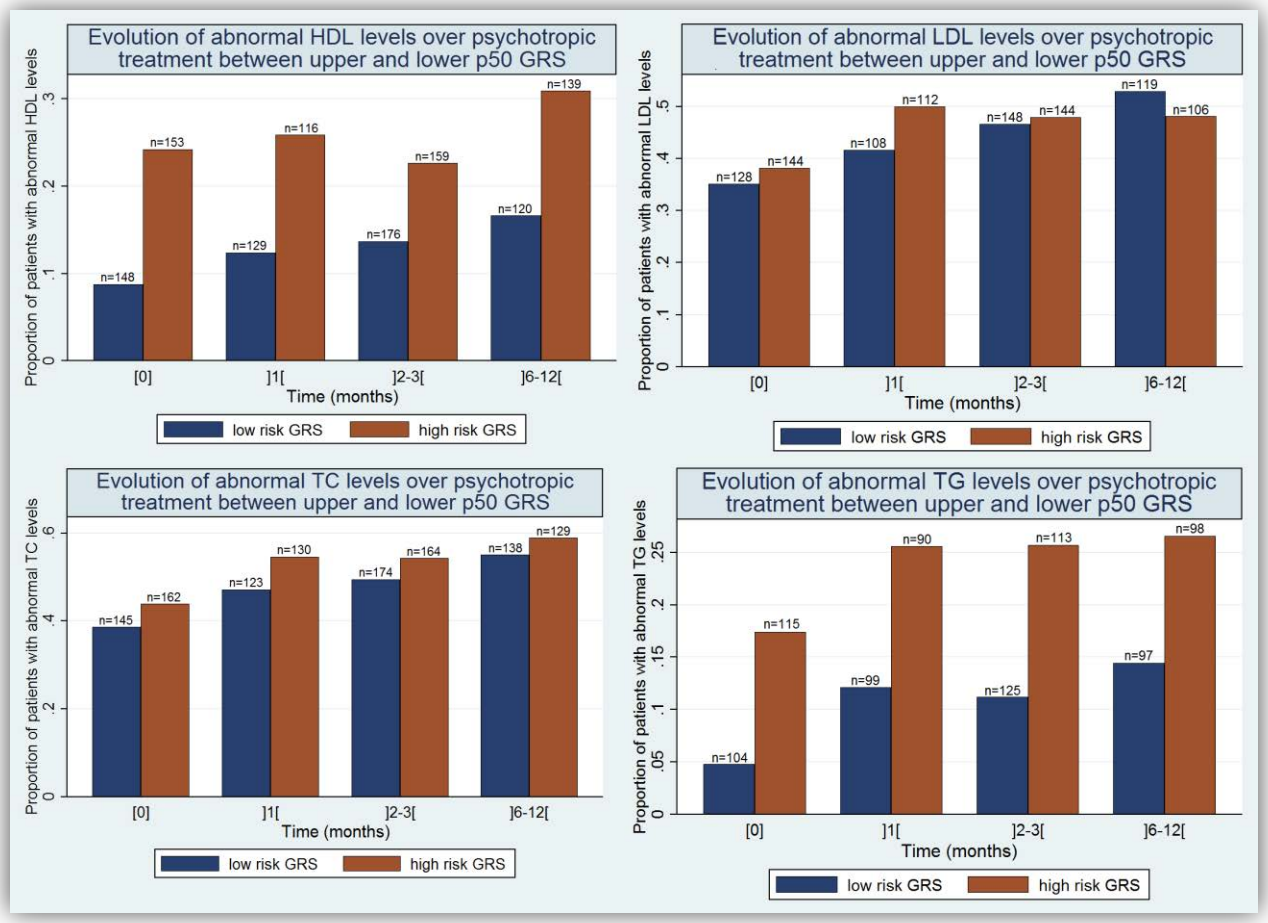
S7 Figure. Evolution of lipid variables during psychotropic treatment: boxplots including all patients. Low risk PRS = PRS lower than the median value. High risk PRS = PRS higher than the median value. Median, interquartiles and number of observations are indicated for each box. Months were defined as: month [0]: day 0, month]1[: ≥10 & <45 days, month]2-3[: ≥45 & <135 days, month]6-12[: ≥135 & <535 days. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



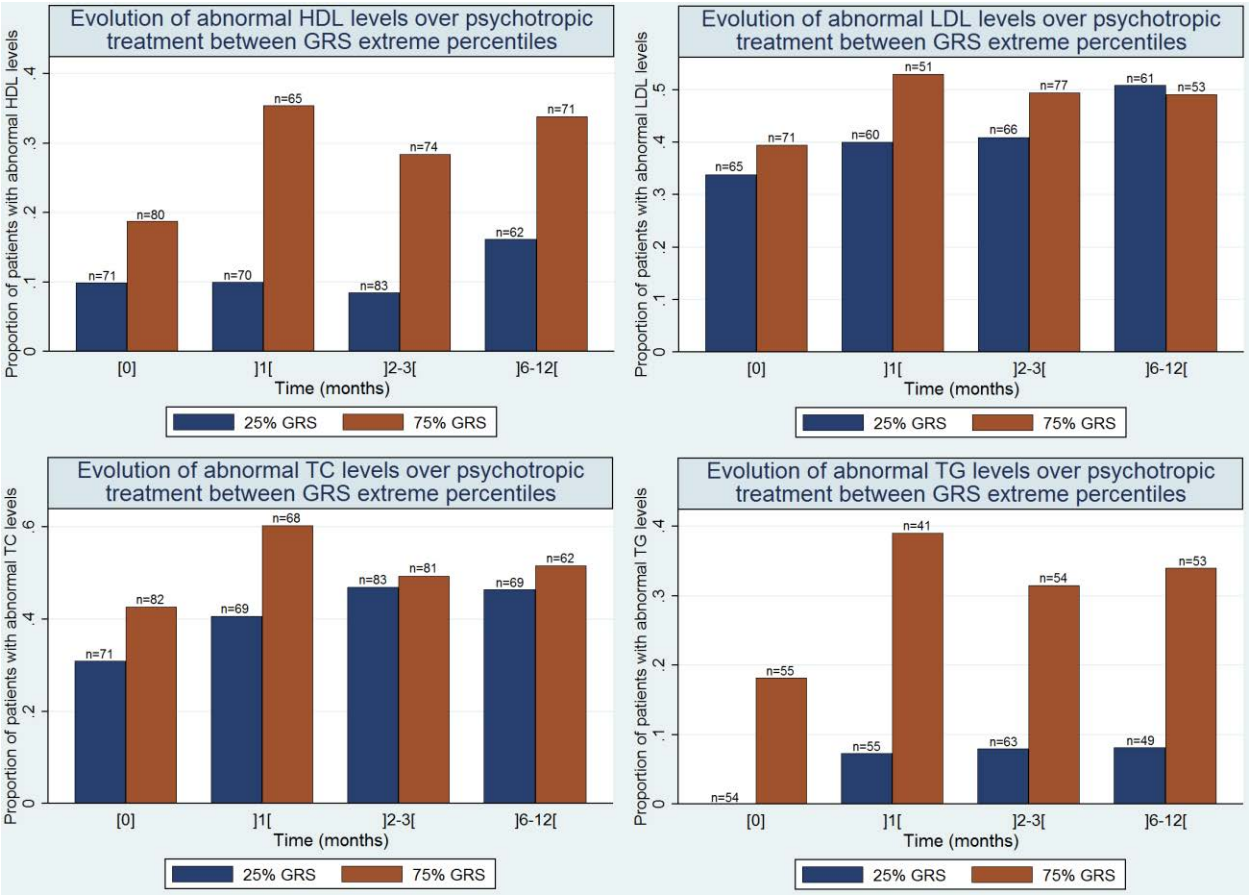
S8 Figure. Lipid variables evolution during psychotropic treatment: boxplots including only 50% of patients having extreme PRS values. 25% PRS = PRS lower than the 25th percentile. 75% PRS = PRS higher than the 75th percentile. Median, interquartiles and number of observations are indicated for each box. Months were defined as: month [0]: day 0, month]1[: ≥10 & <45 days, month]2-3[: ≥45 & <135 days, month]6-12[: ≥135 & <535 days. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



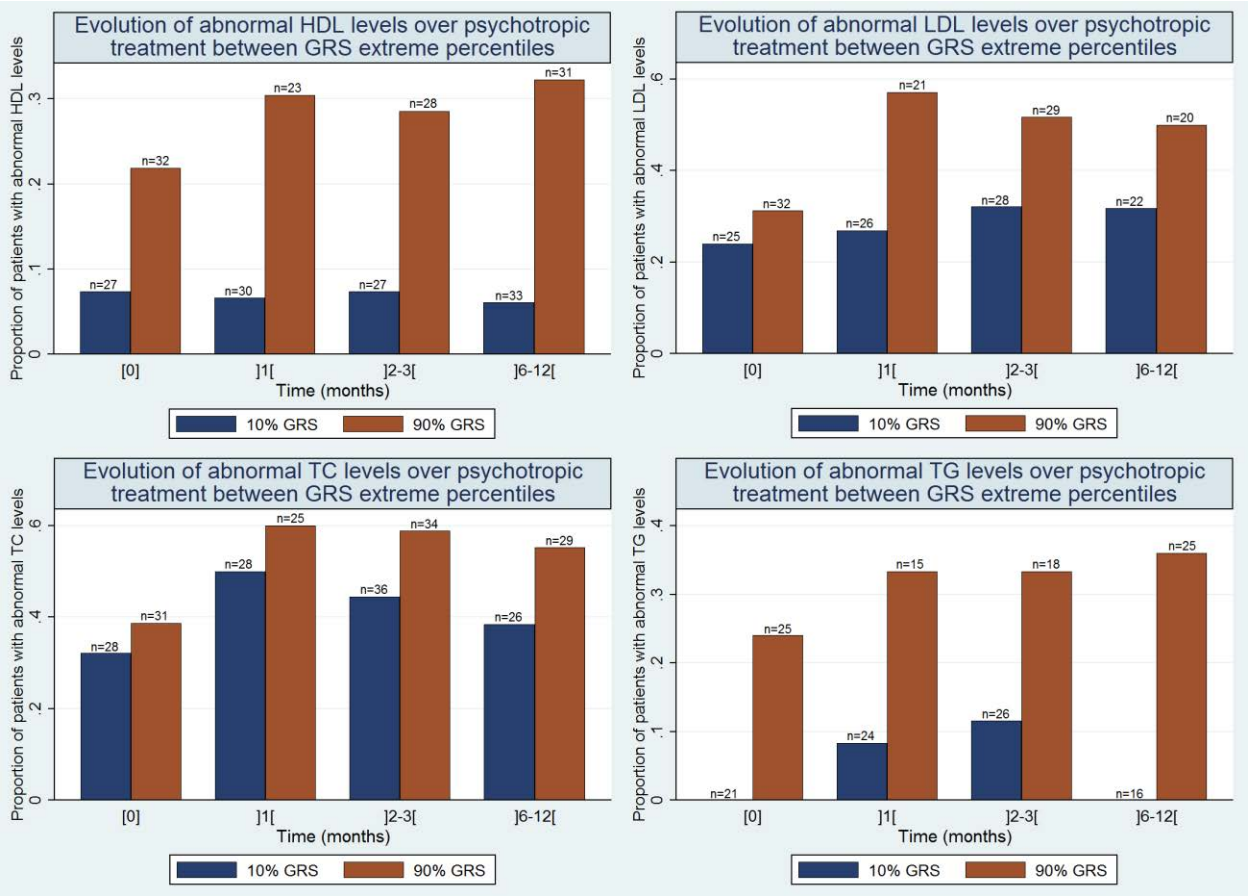
S9 Figure. Evolution of lipid levels during psychotropic treatment with linear mixed regression: model including all patients. Low risk PRS = PRS lower than the median value. High risk PRS = PRS higher than the median value. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



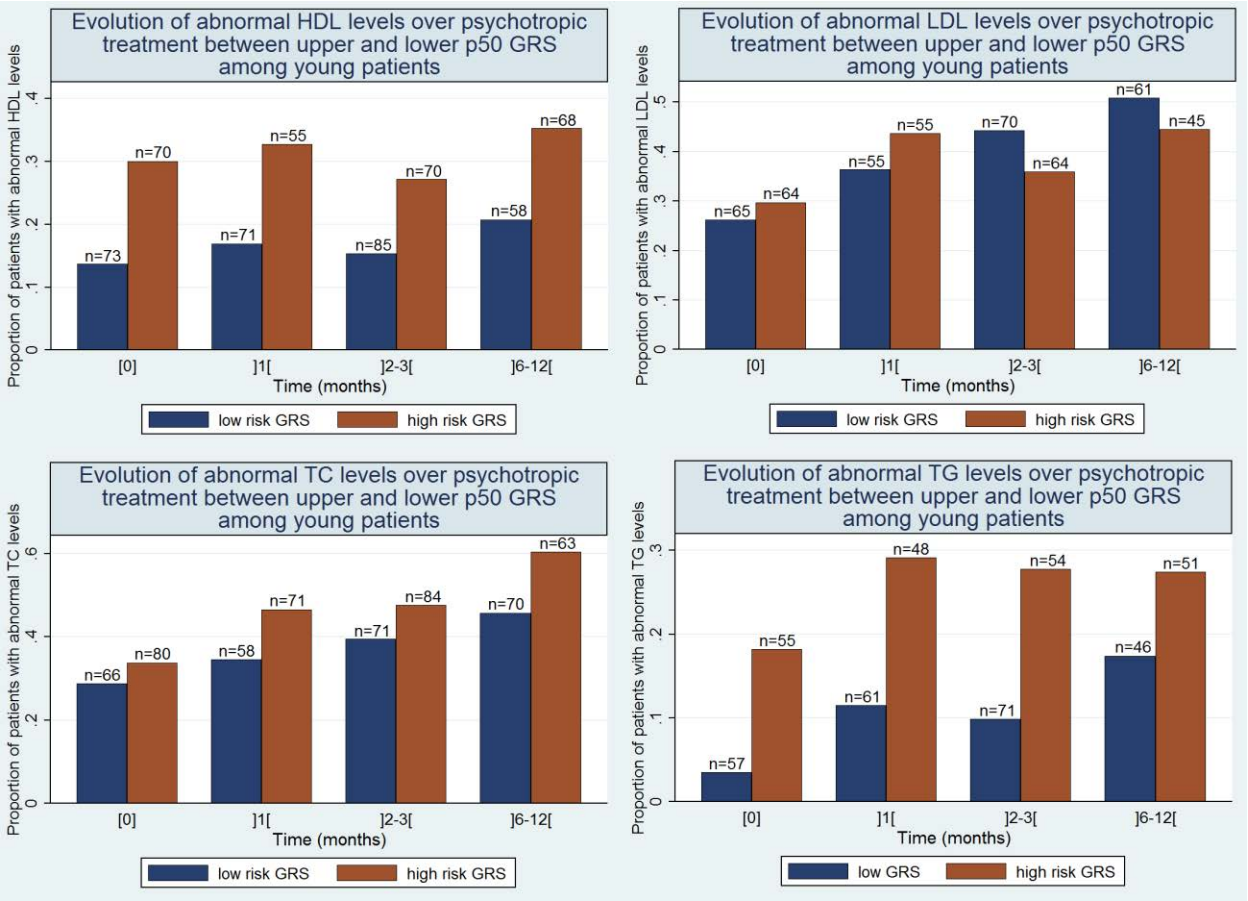
S10 Figure: Evolution of dyslipidemia prevalence for each lipid trait during psychotropic treatment: plots including all patients. Low risk PRS = PRS lower than the median value. High risk PRS = PRS higher than the median value. Numbers of observations are indicated for each barplot. Months were defined as: month [0]: day 0, month]1[: ≥10 & <45 days, month]2-3[: ≥45 & <135 days, month]6-12[: ≥135 & <535 days. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



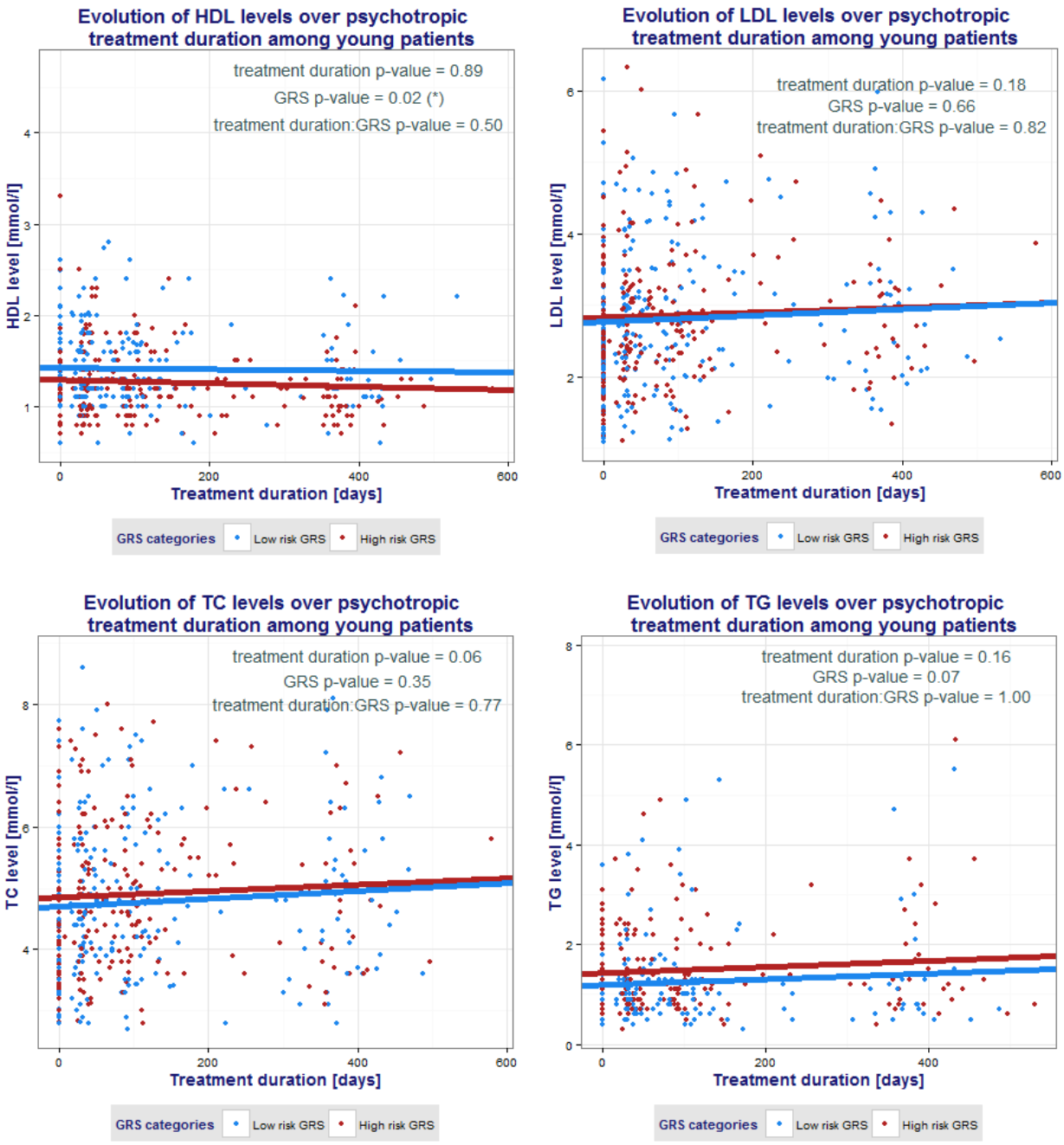
S11 Figure. Evolution of dyslipidemia prevalence for each lipid trait during psychotropic treatment: plots including only 50% of patients having extreme PRS values. 25% PRS = PRS lower than the 25th percentile. 75% PRS = PRS higher than the 75th percentile. Numbers of observations are indicated for each barplot. Months were defined as: month [0]: day 0, month]1[: ≥10 & <45 days, month]2-3[: ≥45 & <135 days, month]6-12[: ≥135 & <535 days. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



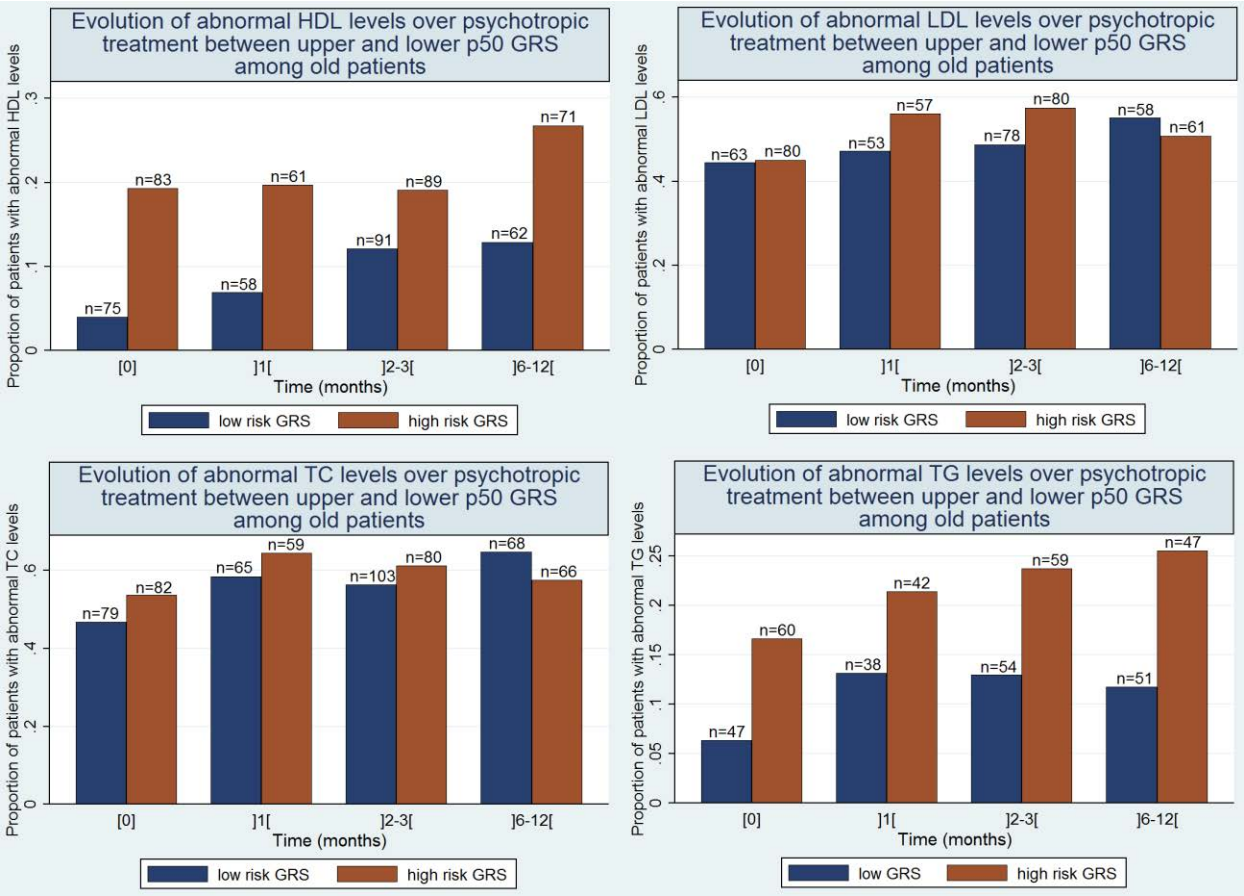
S12 Figure. Evolution of dyslipidemia prevalence for each lipid trait during psychotropic treatment: plots including only 20% of patients having extreme PRS values. 10% PRS = PRS lower than the 10th percentile. 90% PRS = PRS higher than the 90th percentile. Numbers of observations are indicated for each barplot. Months were defined as: month [0]: day 0, month]1[: ≥10 & <45 days, month]2-3[: ≥45 & <135 days, month]6-12[: ≥135 & <535 days. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



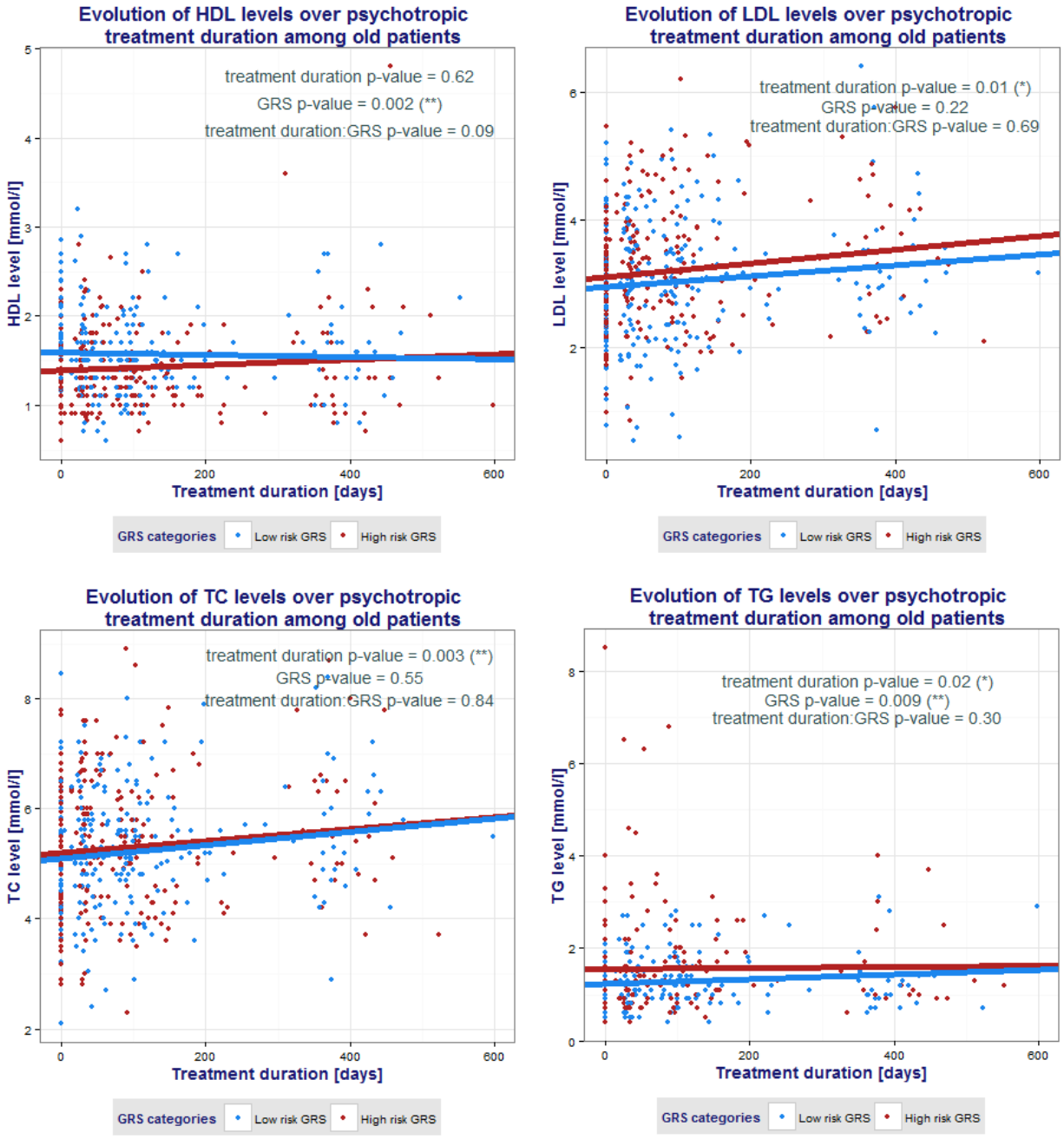
S13 Figure. Evolution of dyslipidemia prevalence for each lipid trait during psychotropic treatment: plots including only patients younger than the median age of patients. Low risk PRS = PRS lower than the median value. High risk PRS = PRS higher than the median value. Young = patients whose age is younger than the median age of patients. Numbers of observations are indicated for each barplot. Months were defined as: month [0]: day 0, month]1[: ≥10 & <45 days, month]2-3[: ≥45 & <135 days, month]6-12[: ≥135 & <535 days. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



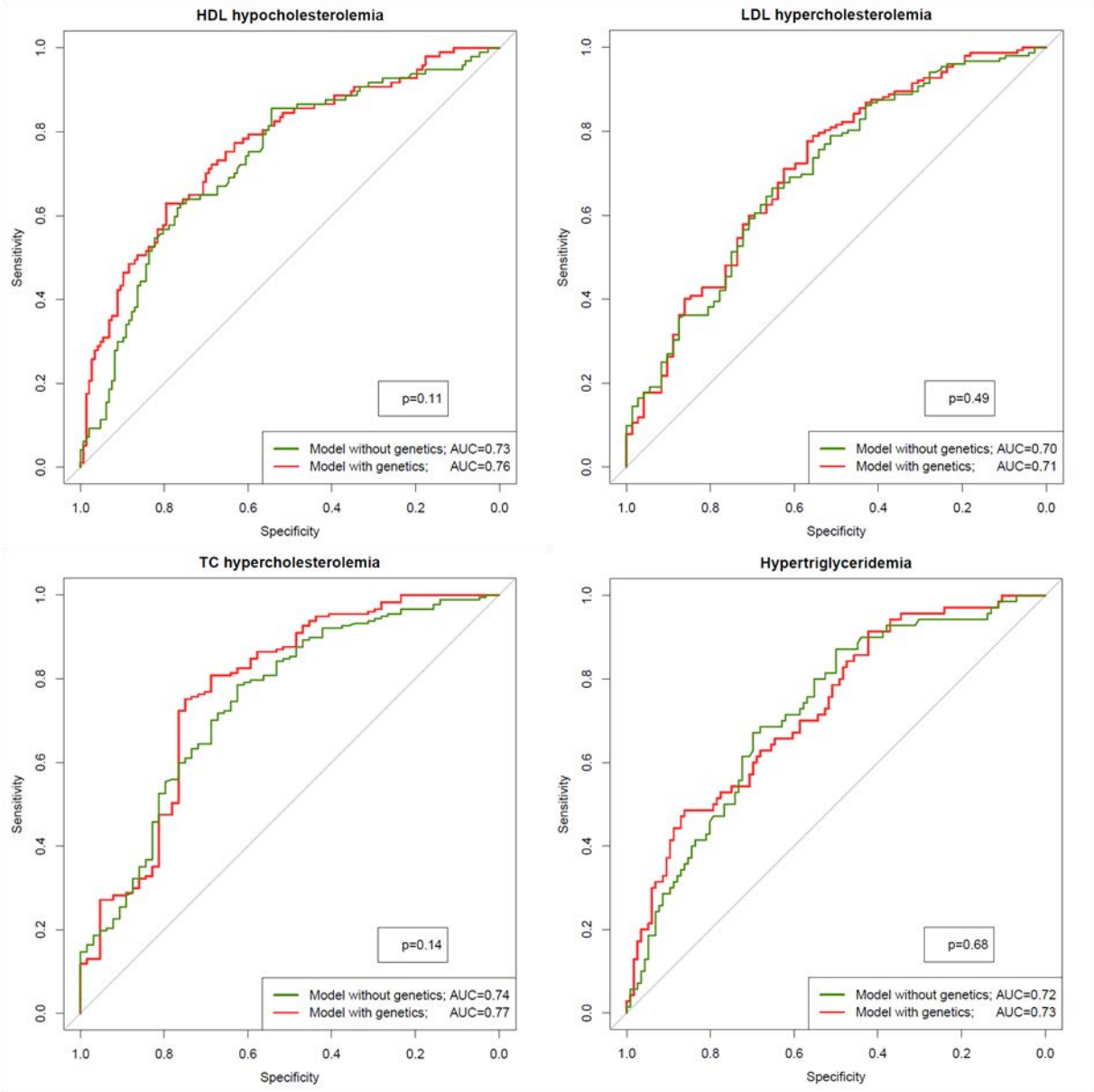
S14 Figure. Evolution of lipid levels during psychotropic treatment with linear mixed regression: model including only patients younger than the median age of patients. Low risk PRS = PRS lower than the median value. High risk PRS = PRS higher than the median value. Young = patients whose age is younger than the median age of patients. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



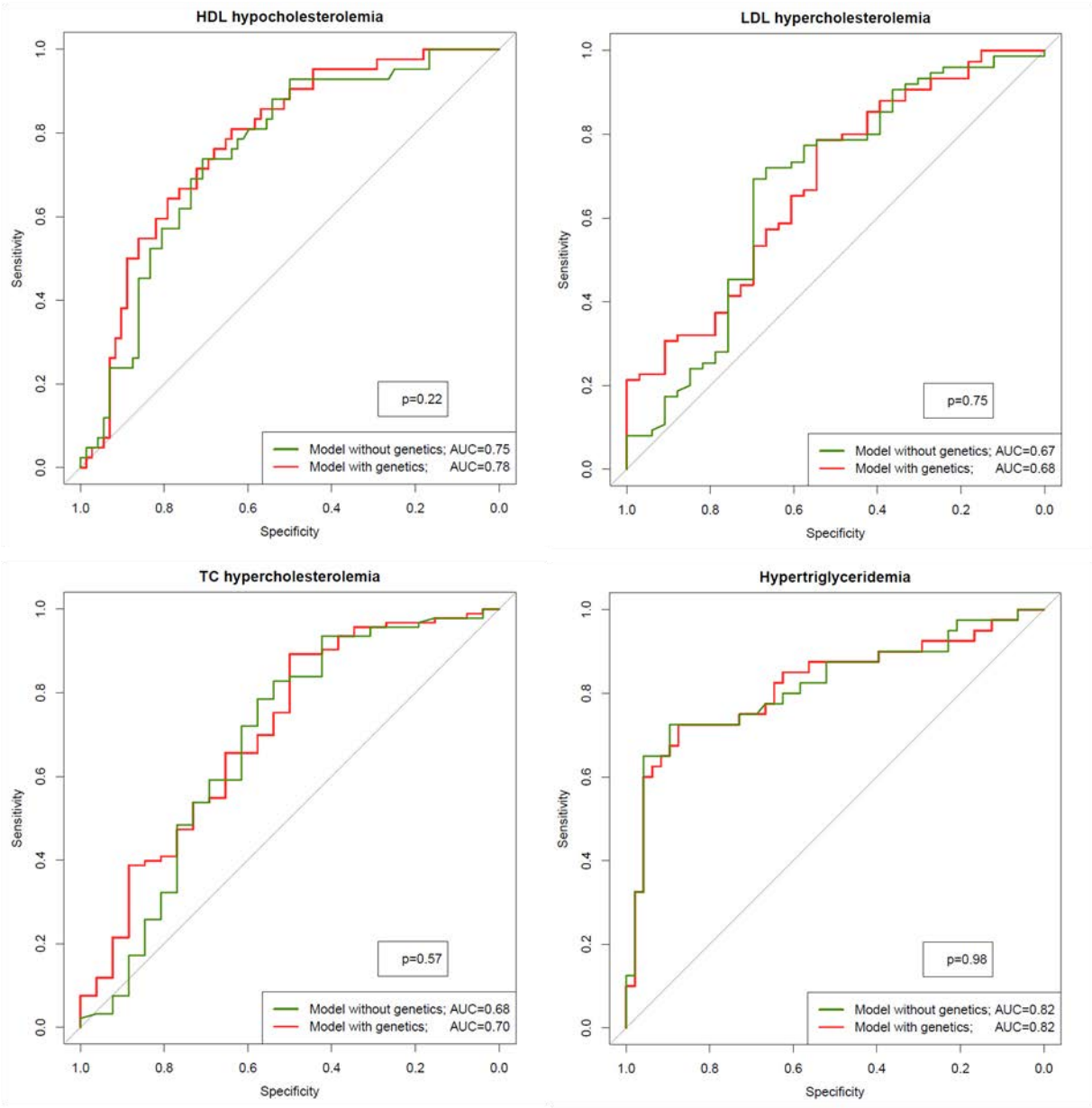
S15 Figure. Evolution of dyslipidemia prevalence for each lipid trait during psychotropic treatment: plots including only patients older than the median age of patients. Low risk PRS = PRS lower than the median value. High risk PRS = PRS higher than the median value. Old = patients whose age is older than the median age of patients. Numbers of observations are indicated for each barplot. Months were defined as: month [0]: day 0, month]1[: ≥10 & <45 days, month]2-3[: ≥45 & <135 days, month]6-12[: ≥135 & <535 days. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



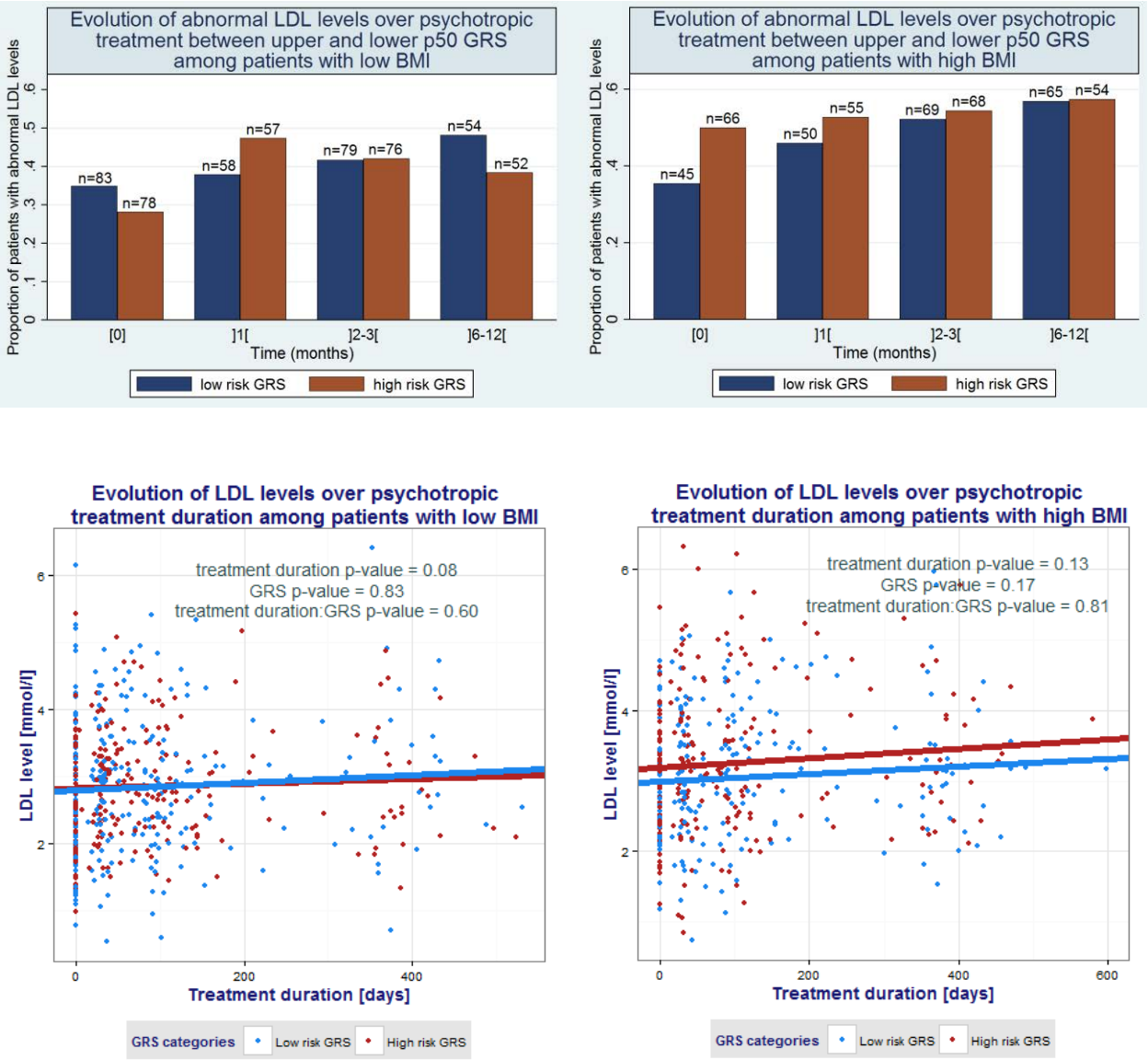
S16 Figure. Evolution of lipid levels during psychotropic treatment with linear mixed regression: model including only patients older than the median age of patients. Low risk PRS = PRS lower than the median value. High risk PRS = PRS higher than the median value. Old = patients whose age is older than the median age of patients. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



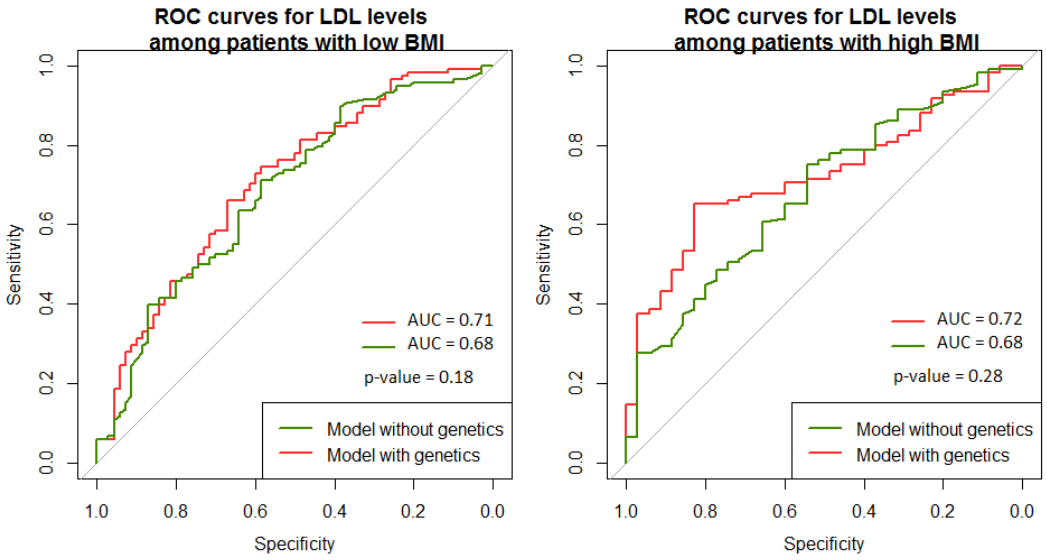
S17 Figure a. ROC curves for HDL hypocholesterolemia, LDL hypercholesterolemia, total hypercholesterolemia and hypertriglyceridemia in the discovery sample. The red curves correspond to the model including clinical and genetics components, whereas the green curves include only clinical values. Only fasting patients were included for TG analyses.



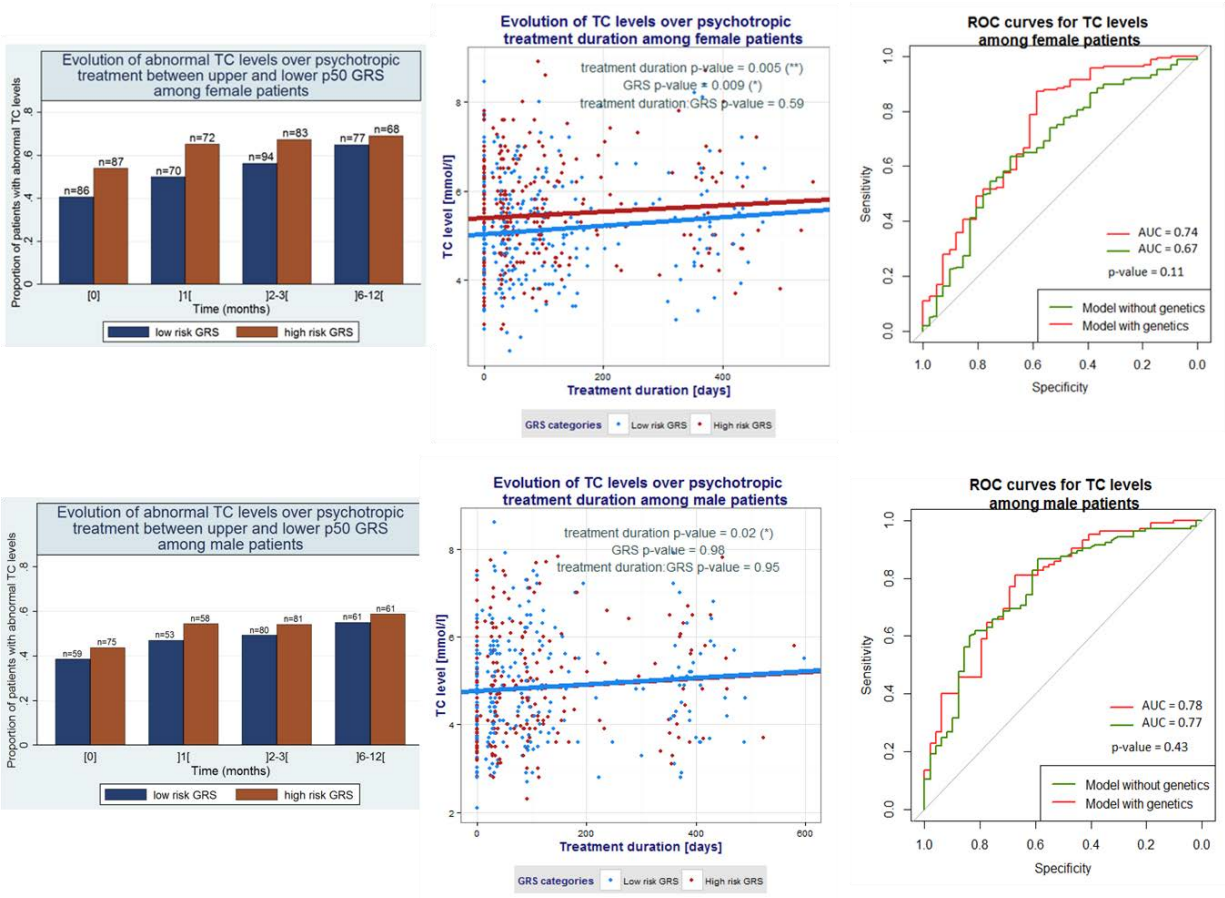
S17 Figure b. ROC curves for HDL hypocholesterolemia, LDL hypercholesterolemia, total hypercholesterolemia and hypertriglyceridemia in the replication sample. The red curves correspond to the model including clinical and genetics components, whereas the green curves include only clinical values. Only fasting patients were included for TG analyses.



S18 Figure. Evolution of dyslipidemia prevalence and lipid levels for LDL during psychotropic treatment: plots including all patients (low BMI patients one the left and high BMI patients on the right). Low risk PRS = PRS lower than the median value. High risk PRS = PRS higher than the median value. Numbers of observations are indicated for each barplot. Months were defined as: month [0]: day 0, month]1[: ≥10 & <45 days, month]2-3[: ≥45 & <135 days, month]6-12[: ≥135 & <535 days. Patients taking lipid-lowering medication were excluded.



S19 Figure. LDL ROC curves for combined samples (discovery + replication) among low BMI (left) and high BMI (right) patients. The red curves correspond to the model including clinical and genetics components, whereas the green curves include only clinical values.



S20 Figure. Evolution of dyslipidemia prevalence, evolution of TC levels during psychotropic treatment, and ROC curves for abnormal TC levels in female (top) and male (bottom) patients. Low risk PRS = PRS lower than the median value. High risk PRS = PRS higher than the median value. Numbers of observations are indicated for each barplot. Months were defined as: month [0]: day 0, month]1[: ≥10 & <45 days, month]2-3[: ≥45 & <135 days, month]6-12[: ≥135 & <535 days. Patients taking lipid-lowering medication were excluded.

References

1. Doran B, Guo Y, Xu J, Weintraub H, Mora S, Maron DJ*, 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.

2. 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.

3. Ansermot N, Brawand-Amey M, Kottelat A, Eap CB. Fast quantification of ten psychotropic drugs and metabolites in human plasma by ultra-high performance liquid chromatography tandem mass spectrometry for therapeutic drug monitoring. Journal of chromatography A. 2013; 1292:160-172.

4. Choong E, Rudaz S, Kottelat A, Guillarme D, Veuthey JL, Eap CB. Therapeutic drug monitoring of seven psychotropic drugs and four metabolites in human plasma by HPLC-MS. Journal of pharmaceutical and biomedical analysis. 2009; 50 (5):1000-1008.

5. Gradinaru J, Vullioud A, Eap CB, Ansermot N. Quantification of typical antipsychotics in human plasma by ultra-high performance liquid chromatography tandem mass spectrometry for therapeutic drug monitoring. Journal of pharmaceutical and biomedical analysis. 2014; 88:36-44.

6. Hiemke C, Baumann P, Bergemann N, Conca A, Dietmaier O, Egberts K*, et al*. AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011. Pharmacopsychiatry. 2011; 44 (6):195-235.

7. Voight BF, Kang HM, Ding J, Palmer CD, Sidore C, Chines PS*, et al*. The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. PLoS genetics. 2012; 8 (8):e1002793.

8. Yang J, Lee SH, Goddard ME, Visscher PM. Genome-wide complex trait analysis (GCTA): methods, data analyses, and interpretations. Methods in molecular biology (Clifton, NJ). 2013; 1019:215-236.

9. Che R, Motsinger-Reif AA. A new explained-variance based genetic risk score for predictive modeling of disease risk. Statistical applications in genetics and molecular biology. 2012; 11 (4):Article 15.

10. Belsky DW, Moffitt TE, Sugden K, Williams B, Houts R, McCarthy J*, et al*. Development and evaluation of a genetic risk score for obesity. Biodemography and social biology. 2013; 59 (1):85-100.

11. Hung CF, Breen G, Czamara D, Corre T, Wolf C, Kloiber S*, et al*. A genetic risk score combining 32 SNPs is associated with body mass index and improves obesity prediction in people with major depressive disorder. BMC medicine. 2015; 13:86.

12. Rukh G, Ahmad S, Ericson U, Hindy G, Stocks T, Renstrom F*, et al*. Inverse relationship between a genetic risk score of 31 BMI loci and weight change before and after reaching middle age. International journal of obesity (2005). 2016; 40 (2):252-259.

13. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology. 1983; 148 (3):839-843.

14. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. Caspian journal of internal medicine. 2013; 4 (2):627-635.

15. Janssens AC, Moonesinghe R, Yang Q, Steyerberg EW, van Duijn CM, Khoury MJ. The impact of genotype frequencies on the clinical validity of genomic profiling for predicting common chronic diseases. Genetics in medicine : official journal of the American College of Medical Genetics. 2007; 9 (8):528-535.

16. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nature reviews Endocrinology. 2012; 8 (2):114-126.

17. Kar D, Gillies C, Zaccardi F, Webb D, Seidu S, Tesfaye S*, et al*. Relationship of cardiometabolic parameters in non-smokers, current smokers, and quitters in diabetes: a systematic review and meta-analysis. Cardiovascular diabetology. 2016; 15 (1):158.

18. Tada H, Melander O, Louie JZ, Catanese JJ, Rowland CM, Devlin JJ*, et al*. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. European heart journal. 2016; 37 (6):561-567.

19. Delacretaz A, Preisig M, Vandenberghe F, Saigi Morgui N, Quteineh L, Choong E*, et al*. Influence of MCHR2 and MCHR2-AS1 Genetic Polymorphisms on Body Mass Index in Psychiatric Patients and In Population-Based Subjects with Present or Past Atypical Depression. PloS one. 2015; 10 (10):e0139155.

20. Choong E, Quteineh L, Cardinaux JR, Gholam-Rezaee M, Vandenberghe F, Dobrinas M*, et al*. 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.

21. Buscot MJ, Magnussen CG, Juonala M, Pitkanen N, Lehtimaki T, Viikari JS*, et al*. The Combined Effect of Common Genetic Risk Variants on Circulating Lipoproteins Is Evident in Childhood: A Longitudinal Analysis of the Cardiovascular Risk in Young Finns Study. PloS one. 2016; 11 (1):e0146081.

22. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M*, et al*. 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). Journal of hypertension. 2013; 31 (7):1281-1357.

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

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

Aurélie Delacrétaz, MSc [1] Frederik Vandenberghe, PhD [1] Mehdi Gholam-Rezaee, PhD [2] Nuria Saigi Morgui, PhD [1] Anaïs Glatard, PharmD [1] Jacques Thonney, MD [3] Alessandra Solida-Tozzi, MD [3] Stéphane Kolly, MD [3] Sylfa Fassassi Gallo, MD [3] Philipp Baumann, MD [3] Sylvie Berney, MD [3] Sandrine Valloton Zulauff, MD [3] Jean-Michel Aubry, MD [4] Roland Hasler, PhD [4] Karsten Ebbing, MD [5] Armin von Gunten, MPhil, MD [5] Philippe Conus, MD [3] Chin B Eap, PhD[1,6]

[1] Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland.

[2] Centre of Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland.

[3] Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly Switzerland.

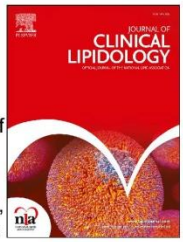
[4] Division of Psychiatric Specialties, University Hospital of Geneva, Geneva, Switzerland.

[5] Service of Old Age Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly Switzerland.

[6] School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland.

Manuscript accepted for publication in Journal of Clinical Lipidology

Accepted Manuscript



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

Aurélie Delacrétaz, MSc, Frederik Vandenberghe, PhD, Mehdi Gholam-Rezaee, PhD, Nuria Saigi Morgui, PhD, Anaïs Glatard, PharmD, Jacques Thonney, MD, Alessandra Solida-Tozzi, MD, Stéphane Kolly, MD, Sylfa Fassassi Gallo, MD, Philipp Baumann, MD, Sylvie Berney, MD, Sandrine Valloton Zulauff, MD, Jean-Michel Aubry, MD, Roland Hasler, PhD, Karsten Ebbing, MD, Armin von Gunten, MPhil, MD, Philippe Conus, MD, Chin B. Eap, PhD

PII: S1933-2874(17)30461-0

DOI: 10.1016/j.jacl.2017.10.002

Reference: JACL 1187

To appear in: *Journal of Clinical Lipidology*

Received Date: 18 July 2017

Revised Date: 3 October 2017

Accepted Date: 3 October 2017

Please cite this article as: Delacrétaz A, Vandenberghe F, Gholam-Rezaee M, Morgui NS, Glatard A, Thonney J, Solida-Tozzi A, Kolly S, Gallo SF, Baumann P, Berney S, Zulauff SV, Aubry J-M, Hasler R, Ebbing K, von Gunten A, Conus P, Eap CB, Early changes of blood lipid levels during psychotropic drug treatment as predictors of long-term lipid changes and of new onset dyslipidemia, *Journal of Clinical Lipidology* (2017), doi: 10.1016/j.jacl.2017.10.002.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

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

Aurélie Delacrétaz, MSc [1] Frederik Vandenberghe, PhD [1] Mehdi Gholam-Rezaee, PhD [2] Nuria Saigi Morgui, PhD [1] Anaïs Glatard, PharmD [1] Jacques Thonney, MD [3] Alessandra Solida-Tozzi, MD [3] Stéphane Kolly, MD [3] Sylfa Fassassi Gallo, MD [3] Philipp Baumann, MD [3] Sylvie Berney, MD [3] Sandrine Valloton Zulauff, MD [3] Jean-Michel Aubry, MD [4] Roland Hasler, PhD [4] Karsten Ebbing, MD [5] Armin von Gunten, MPhil, MD [5] Philippe Conus, MD [3] Chin B Eap, PhD[1,6]

[1] Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland.
[2] Centre of Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland.
[3] Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly Switzerland.
[4] Division of Psychiatric Specialties, University Hospital of Geneva, Geneva, Switzerland.
[5] Service of Old Age Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly Switzerland.
[6] School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland.

For correspondence:
Prof CB. Eap
Hôpital de Cery,
1008 Prilly – Lausanne, Switzerland
Tel: 00 41 21 314 26 04 Fax: 00 41 21 314 24 44
chin.eap@chuv.ch

ACCEPTED MANUSCRIPT

31

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

RUNNING TITLE

Early lipid changes during psychotropic treatment

KEYWORDS

Early lipid changes; predictors; metabolic follow-up; new onset dyslipidemia; psychotropic drugs

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

62

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

ABSTRACT

Background: Cardiovascular diseases and dyslipidemia represent a major health issue in psychiatry. Many psychotropic drugs can induce a rapid and substantial increase of blood lipid levels. *Objective*: This study aimed to determine the potential predictive power of an early change of blood lipid levels during psychotropic treatment on long-term change and on dyslipidemia development. *Methods*: Data were obtained from a prospective study including 181 psychiatric patients with metabolic parameters monitored during the first year of treatment and with adherence ascertained. Blood lipid levels (i.e. total- (TC), low-density lipoprotein- (LDL-C), high-density lipoprotein- (HDL-C), non-high-density lipoprotein- (non-HDL-C) cholesterol and fasting triglycerides (TG)) were measured at baseline and after 1, 3 and/or 12 months of treatment. *Results*: Receiver operating characteristic analyses indicated that early (i.e. after one month of psychotropic treatment) increases (≥5%) for TC, LDL-C, TG and non-HDL-C and decrease (≥5%) for HDL-C were the best predictors for clinically relevant modifications of blood lipid levels after 3 months of treatment (≥30% TC, ≥40% LDL-C, ≥45% TG, ≥55% non-HDL-C increase and ≥20% HDL-C decrease; sensitivity 70-100%, specificity 53-72%). Predictive powers of these models were confirmed by fitting longitudinal multivariate models in the same cohort ($p \leq 0.03$) as well as in a replication cohort ($n=79$; $p \leq 0.003$). Survival models showed significantly higher incidences of new onset dyslipidemia (TC, LDL-C and non-HDL-C hypercholesterolemia, HDL-C hypocholesterolemia and hypertriglyceridemia) for patients with early changes of blood lipid levels compared to others ($p \leq 0.01$). *Conclusion*: Early modifications of blood lipid levels following prescription of psychotropic drugs inducing dyslipidemia should therefore raise questions on clinical strategies to control long-term dyslipidemia.

ACCEPTED MANUSCRIPT

INTRODUCTION

Individuals with severe mental illness, in particular schizophrenia, bipolar and major depressive disorders have a 10 to 25-year reduced life expectancy compared to subjects from the general population [1-8]. Most of this premature mortality has been attributed to cardiovascular diseases resulting from the metabolic syndrome [9]. Several risk factors implying complex mechanisms may explain this excess cardiovascular risk, including psychiatric disease-related factors, unhealthy lifestyle, poverty and adverse effects of treatment [10, 11]. Thus, the use of psychotropic medications such as antipsychotics (most atypical but also some typical), mood stabilizers (e.g. lithium and valproate) and some antidepressants (e.g. mirtazapine) can increase the risk of metabolic disorders including obesity, type 2 diabetes, hypertension and dyslipidemia [12].

Components of the metabolic syndrome may develop early during psychotropic treatment [13-15] and may initiate a steady process leading to cardiometabolic diseases in the long-term, highlighting the importance to prospectively monitor metabolic parameters during treatment [16]. A threshold of 5% weight gain during the first month of psychotropic treatment was recently defined as a robust predictor for subsequent important weight gain [13]. To date, nothing is known about any other early metabolic threshold for predicting worsening of cardiometabolic parameters during treatment with psychotropic drugs. Dyslipidemia, defined as high LDL-cholesterol (LDL-C) and/or low HDL-cholesterol (HDL-C) and/or high triglyceride (TG) levels, constitutes an important risk factor for cardiovascular diseases as its prevalence has been shown to reach 55% in schizophrenia patients receiving psychotropic drugs [17]. This side effect induced by psychotropic drugs has long been considered as resulting from psychotropic-drug

induced weight gain. However, new data revealed that these lipogenic adverse effects may occur very early during treatment and may even precede weight gain, displaying weight-independent molecular effects in addition to weight-related ones [11, 15, 18 19, 20].

To our knowledge, only one study investigated the predictive value of early on mid-term lipid changes [21]. This study observed that a lack of early (i.e. from 6 to 12 weeks) elevation in triglyceride concentration of 0.23 mmol/l (20 mg/dL) was predictive of later (i.e. from 24 to 28 weeks) lack of substantial triglyceride increase in patients receiving olanzapine, ziprasidone or aripiprazole [21]. Notably, the latter study was a post-hoc analysis of clinical trials examining the effects of specific drugs, with restrictions on the number of prescribed drugs, conditions that are not comparable to the usual clinical practice. Moreover, the longest treatment duration was of 28 weeks, with no data on longer term.

Although no threshold of serum lipid concentration was defined as being a sign to reconsider psychotropic treatment [22], the National Cholesterol Education Program (ATPIII) states that increases of 50 mg/dL (0.57 mmol/l) for TG, of 40 mg/dL (1.04 mmol/l) for total cholesterol (TC) and of 30 mg/dL (0.77 mmol/l) for low-density lipoprotein cholesterol are considered as sufficient for a categorical-risk change from “borderline-high” to “high” and are therefore clinically significant [23]. When referring to the upper values of the clinical ranges, these increases correspond to approximately 29% of TG (0.57/2), 21% of TC (1.04/5) and 26% of LDL-C (0.77/3).

Because of the high mortality and morbidity associated with dyslipidemia, an early detection of patients who are at higher risk of developing an important change in plasma lipid levels during psychotropic treatment is of major clinical relevance. In the present

study, we sought to determine, in a cohort of patients taking psychotropic medication with adherence ascertained by therapeutic drug monitoring, how plasma lipid changes during the first month of treatment could predict mid- and long-term plasma lipid changes and new onset dyslipidemia (NOD).

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

METHODS

Study design

Since 2007, a longitudinal observational study is ongoing in the Department of Psychiatry of the Lausanne University Hospital. Patients starting a psychotropic treatment with amisulpride, aripiprazole, clozapine, haloperidol, lithium, mirtazapine, olanzapine, quetiapine, risperidone and/or valproate were included, as described in the flowchart (**S1 Figure**). The present study included patients with informed consent from an ongoing pharmacogenetic study (PsyMetab) as described elsewhere [24]. In addition, data of patients in the clinical follow-up (PsyClin) were obtained in the hospital or in outpatients centers during a medical examination based on the department guideline for metabolic follow-up performed on a routine basis [16]. Monitoring for physical health risk factors include prospective assessments of body mass index (BMI), waist circumference, fasting glucose, lipid profile, blood pressure and tobacco smoking during treatment [25]. When a treatment was stopped for more than 2 weeks, or if a drug was replaced by another drug on the list, the follow-up was restarted from baseline. In case of the introduction of a second studied drug, the follow-up was restarted and the last introduced drug considered as the main treatment. Because of the noninterventional post hoc analysis study design, no informed consent was requested from the clinical follow-up patients. Both studies were approved by the ethics committee of the Lausanne University Hospital.

Only patients with available lipid levels at least at baseline, first month (15 to 45 days of treatment; median of 32 days (interquartile range (IQR): 28-36)) and another month, i.e. either month 3 (45 to 135 days of treatment; median of 94 days (IQR: 88-106)) or month

12 (136 to 535 days of treatment; median of 365 days (IQR: 277-392)) without any lipid-lowering drug (**S1 Table**) were included for the determination of early thresholds. For analyses of NOD incidence, only patients without dyslipidemia at baseline were included (**S1 Figure**; see Supplementary Material (paragraph 1.2)).

Statistical analyses

Marginal analyses were conducted using Wilcoxon-Mann-Whitney rank-sum tests to compare continuous variables across groups and Chi-squared and Fisher's exact tests to assess associations among categorical variables.

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

To assess the predictive value of an early change of blood lipid levels (i.e. during the first month of treatment) on long-term lipid change (3 and 12 months), sensitivity, specificity, positive predictive value and negative predictive value were calculated using the pROC R package [26]. Sensitivity was defined as the percentage of patients predicted as high-risk patients among all truly high-risk patients. Specificity was defined as the percentage of patients predicted as low-risk patients among all truly low-risk patients.

Thresholds for early lipid changes were examined in 5% increments (from 5 up to 35, whenever the number of observations was sufficient) to find the best predictors for long-term increases of TC, LDL-C, TG and non-HDL-C increase and HDL-C decrease (increments of 5% from 5 up to 55, whenever the number of observations was sufficient). These analyses allowed assessing the best relation between sensitivity and specificity to find acceptable thresholds for short and long term blood lipid changes. More details in Supplementary Material (paragraph 1.4.1).

ACCEPTED MANUSCRIPT

192

ACCEPTED MANUSCRIPT

Confirmatory analyses in discovery and replication samples

The nlme package of R was used to fit a linear mixed effect model on long-term lipid changes adjusted for age, gender, baseline BMI, treatment duration, smoking status, current psychotropic drug and early weight gain (≥5%) groups. More details in Supplementary Material (paragraph 1.4.2).

Short-term lipid changes and new onset dyslipidemia

Kaplan-Meier estimates with log-rank tests, logistic mixed regression and Cox regression tests adjusting for variables mentioned below were used to compare the incidence of dyslipidemia development between early and non-early lipid change groups, i.e. TC ≥5% vs TC <5%, LDL-C ≥5% vs LDL-C <5%, TG ≥5% vs TG <5%, HDL-C ≤-5% vs HDL-C >-5% and non-HDL-C ≥5% vs non-HDL-C <5%, using the survival package of R. More details in Supplementary Material (paragraph 1.4.3). Statistical significance was determined by a p-value ≤0.05. Statistical analyses were performed using Stata 12 (StataCorp, College Station TX, USA) and R environment for statistical computing version 3.3.1.

ACCEPTED MANUSCRIPT

RESULTS

Demographics and evolution of metabolic parameters

One hundred and eighty one patients who did not receive any lipid lowering agent during psychotropic treatment were included (**Table 1**, **S2 Table**). More details in Supplementary data (paragraph 2.1).

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

For the selection of predictors, thresholds with the highest sensitivity combined with high area under the curve (AUC) values were chosen to maximize the detection of patients at high risk for important lipid profile worsening in the long-term.

Early (i.e. after one month of psychotropic treatment) increase (≥5%) for TC, LDL-C TG and non-HDL-C and decrease (≥5%) for HDL-C were the best predictors for clinically relevant modifications of blood lipid levels after 3 months of treatment (≥30% TC, ≥40% LDL-C, ≥45% TG, ≥55% non-HDL-C increase and ≥20% HDL-C decrease; sensitivity 70-100%, specificity 53-72%) (**S3 Table**) and one of best predictors after 12 months of treatment (**S4 Table**). More details in Supplementary data (paragraph 2.2).

Demographic and clinical characteristics of the psychiatric discovery sample according to defined thresholds are shown in **Table 1** (more details in Supplementary data (paragraph 2.3)).

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

The above-mentioned thresholds of 5% for TC, LDL-C, TG, non-HDL-C increase and 5% for HDL-C decrease were confirmed as being significant predictors for subsequent increase of TC, LDL-C, TG and non-HDL-C, and of HDL-C decrease after 3 months of

psychotropic treatment in linear mixed models (**S5 Table**). Patients exceeding early thresholds had 25% ($p<0.0001$) higher TC increase (TCi), 34% ($p=0.0001$) higher LDL-C increase (LDLi), 40% ($p=0.03$) higher TG increase (TGi), 36% ($p<0.0001$) higher non-HDL-C increase (non-HDLi) and 14% ($p<0.0001$) higher HDL-C decrease (HDLd) after 3 months compared to patients who did not reach such thresholds. Of note, some clinical variables were associated with these lipid changes as well (more details in Supplementary data (paragraph 2.4)).

These early thresholds of lipid change were replicated in an independent psychiatric sample (**S6 Table**). In the replication sample, patients reaching early thresholds had 22%, 29%, 57%, 31% and 21% higher TCi, LDLi, TGi, non-HDLi and HDLd after 3 and/or 12 months of psychotropic treatment compared to patients who did not ($p\leq0.003$).

Of note, patients exceeding early thresholds for TC, LDL-C, non-HDL-C and TG had a 3% higher weight increase compared to patients who did not reach such thresholds ($p\leq0.004$; data not shown).

Influence of early lipid thresholds on new onset dyslipidemia

Demographic and clinical data of patients with no dyslipidemia at baseline, namely in patients who did not receive any lipid-lowering drugs at baseline and for whom baseline lipid levels were within normal range, are reported in **S7 Table**. An important proportion of patients developed NOD during the first year of psychotropic treatment (more information in Supplementary data).

Incidence of NOD during treatment is displayed in **Figure 1**. It is noteworthy that survival rate curves sharply divided over time according to early threshold groups (**Figure 2**). Thus, the incidence of NOD was significantly higher in patients with TCi≥5%, LDLi≥5%, HDLd≥5%, TGi≥5% and non-HDLi≥5% compared to patients without early lipid changes ($p=1*10^{-6}$; $p=3*10^{-7}$; $p=2*10^{-7}$; $p=0.01$ and $p=1*10^{-3}$, respectively). These results were confirmed by Cox and logistic regressions and were replicated in an independent psychiatric sample for TCi≥5%, LDLi≥5% and non-HDLi ≥5% threshold groups (data not shown). **S8 Table** shows clinical risk factors associated with NODs. Apart from early lipid increase thresholds, some factors such as sex, early weight gain group and medication group were also associated with dyslipidemia incidence (**S2 Figure)**.

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

S9 Table and **Figure 3** display dyslipidemia incidence according to the number of early exceeded thresholds (EET) after the first month of treatment, namely according to the number of reached lipid phenotype (either TCi≥5%, LDLi≥5%, TGi≥5% and/or HDLd≥5%). When developing one or more EET during the first month of treatment, the risk of developing dyslipidemia at a later stage in any of the four lipid variables was increased 14.4 fold, independently of the nature of EET.

ACCEPTED MANUSCRIPT

284

285

ACCEPTED MANUSCRIPT

DISCUSSION

The present study aimed to explore whether early lipid increase during the first month of psychotropic treatment may predict further important lipid increase and/or dyslipidemia development in patients receiving psychotropic drugs. In the present psychiatric sample, dyslipidemia prevalence of 37% for TC, 32% for LDL-C, 17% for HDL-C and 11% for TG were observed at baseline. These values are higher than those reported in the RAISE study (Recovery After an Initial Schizophrenia Episode) [17], possibly because of the shorter lifetime exposition to psychotropic treatment in the later (less than 6 months) than in the present psychiatric sample (around 8 years) and/or to the less stringent criterion used to define dyslipidemia in RAISE study. Nonetheless, in the present study a worsening of lipid parameters was observed during treatment despite of the high prevalence already observed at baseline, in parallel with a deterioration of other metabolic parameters. It is unlikely that the increase of dyslipidemia observed over time was due to a loss of follow-up of patients with no metabolic disturbances. Indeed, follow-up was required whatever the metabolic status of patients. In addition, an increase of dyslipidemia was observed after one month despite the same numbers of patients at both periods. This emphasizes the importance to prospectively monitor metabolic (including lipid) parameters during psychotropic treatment in all patients starting a psychotropic medication [16]. Thus, the potential for psychotropic drugs to cause or to exacerbate metabolic syndrome in patients is not restricted to at-risk patients (e.g. drug naive, first episode disease, non-obese or young patients) [11]. Because clinicians have been found to have a poor adherence to guidelines for metabolic monitoring worldwide [27-29], there is a need for programs to help educate

providers and to facilitate monitoring of these cardiometabolic risk factors. Beside, a poor quality of management of potential physical health problems in psychiatric patients has also been recognized [28]. For instance, a study investigating cardiometabolic risks in first-episode schizophrenic patients showed that only a small proportion of patients with dyslipidemia were treated with lipid-lowering agent, underlining an under-recognition of lipid abnormalities [17], which is consistent with other studies from Mitchell and collaborators [27, 30, 31] and with the low proportion (i.e. less than 10%) of patients with hyperlipidemia who receive lipid-lowering drugs in the present psychiatric sample. To date, no consensus has been established among clinicians with regard to thresholds of lipid increase that would need a reconsideration of the psychotropic treatment. Nevertheless, recent guidelines from the European Society of Cardiology and European Atherosclerosis Society were proposed for the management of dyslipidemia in patients receiving antipsychotics [32]. These recommendations emphasize the importance of starting primary prevention earlier rather than later in psychiatric patients receiving psychotropic medication associated with metabolic disturbances [33]. According to the National Institute for Health and Care Excellence (NICE) [34] and to the Joint British Societies [35] guidelines on the management of cardiovascular risk, all people with dyslipidemia should receive advice about diet, exercise, weight management and smoking cessation. If lifestyle advice is ineffective in normalizing the lipid profile, a statin should be considered after screening for the risk of cardiovascular disease [25].

The present study showed that an early lipid increase of 5% or more for TC, LDL-C, TG and non-HDL-C and an early decrease of 5% or more for HDL-C were the best predictors for subsequent important lipid changes after 3 and 12 months of psychotropic

treatment. These predictors displayed high sensitivities, meaning that among all truly at-risk patients at 3 and 12 months, high percentages of patients were classified as being at risk during the first month of treatment. Additionally, these predictive models had high negative predictive values for the five lipid traits after 3 and 12 months, implying that most patients who did not reach early lipid threshold did not have substantial increase of lipid levels after 3 and 12 months of psychotropic treatment. Since a 1% reduction in LDL-C on average was shown to reduce risks for hard coronary heart disease events by approximately 1% in short-term controlled trials [23], our clinical predictive thresholds to prevent important lipid level increases appear clinically relevant. As from a clinical point of view, it is better to misclassify a patient in the high-risk group rather than to miss a truly high-risk patient, the present study aimed at maximizing sensitivity, with a lesser focus on specificity. Such as misclassification may result in possible unnecessary preemptive advices about diet, exercise, weight management and smoking cessation for low-risk patients identified as high risk, which can be considered beneficial whatever the metabolic status of the patient.

The present findings are in agreement and expand those from a previous study in our Department, underlining the importance of a 5% weight increase during the first month of treatment to predict further important weight gain during longer-term treatment [13]. Additionally, the present TG negative predictive value is in accordance with the results of a previous post-hoc randomized clinical trial reporting that a lack of early (i.e. from 6 to 12 weeks) elevation in triglyceride concentration was predictive of later (i.e. from 24 to 28 weeks) lack of substantial triglyceride increase in patients receiving olanzapine, ziprasidone or aripiprazole [21]. Notably, predictors of a 5% increase in lipid levels were

355 also significant in age-stratified, gender-stratified and medication-stratified subgroups of
356 patients. These findings emphasize the robustness of these clinical predictors and
357 should motivate clinicians to systematically monitor early lipid changes for each patient
358 subgroups and not only in patients with known risk factors (e.g. young patients,
359 women). Additional multivariate analyses showed that an early increase of weight (5%
360 or more) [13] was not associated with longer-term lipid increases for TC, LDL-C, non-
361 HDL-C and TG, meaning that both lipids and weight should be monitored during
362 treatment. These results are in accordance with a study that observed a lack of early
363 predictive value of BMI to explain dyslipidemia on the long-term in patients receiving
364 olanzapine and risperidone [36].

365 In line with the expected metabolic effects, i.e. olanzapine, clozapine and valproate
366 being associated with the highest risk of dyslipidemia, risperidone and quetiapine
367 conferring an intermediate risk, and aripiprazole and amisulpride being at lower risk [37],
368 the incidence of LDL-C dyslipidemia was significantly associated with risk-categorized
369 drugs. Psychotropic drug categories were not associated with significant difference of
370 dyslipidemia incidence for the remaining lipid phenotypes. This does not mean that the
371 prescribed drugs did not have risk differences but rather underlines the relevance of the
372 5% predictor independently of the drug prescribed. Of note, some studies have
373 documented significant reductions in TC and LDL-C in patients treated with valproate [38,
374 39]. Additional analyses considering valproate as conferring a low risk for TC and LDL-C
375 hyperlipidemia did not modify the present results (data not shown). Finally, the present
376 study showed that patients who reached one or more early lipid thresholds of 5% during
377 the first month of treatment had a 14 fold risk of developing subsequent dyslipidemia,

regardless of the nature of lipid phenotype, highlighting the need to implement clinical strategies to control long-term dyslipidemia.

Of note, according to NICE guidelines [34], the consideration of non-HDL-C instead of LDL-C is regarded as more appropriate, because this gives a measure of all of the lipids that may promote arterial plaque production. In addition, LDL-C is not directly measured but requires a calculation using a fasting sample and for triglyceride levels to be less than 4.5 mmol/l, whereas the measurement of non-HDL-C does not. In the present study, non-HDL-C and LDL-C analyses provided consistent results, which strengthen the clinical predictive value of LDL-C.

Several limitations of the present study need to be mentioned. Firstly, the majority of patients were not drug naive, and the observed lipid level increase may have resulted from past treatments. However, such patients constitute the majority of psychiatric populations, which therefore may even strengthen the clinical validity of the present findings. Secondly, the follow-up period lasted a median period of time of 378 days and even if most lipid trait worsening occurred within the period covered by the present study, it would be interesting to investigate the validity of these findings in longer-term treatment durations. Thirdly, 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 their effects were not taken into account. Finally, although 10 psychotropic drugs known as potentially leading to weight gain and/or worsening of other metabolic parameters were analyzed in the present study, the results cannot be extrapolated to other drugs. The major strength of this study is its longitudinal design with prospective monitoring of plasma lipid levels. In addition, the use of therapeutic

401 drug monitoring allowed assessing patient adherence at each time of treatment, which
402 is a critical issue to exclude false negatives (i.e. patients not taking the drug with no lipid
403 increase).

404 In conclusion, this study underlines the importance of metabolic monitoring following the
405 introduction of antipsychotic drugs, mood stabilizers or some antidepressants for all
406 patients, regardless of gender, age, baseline BMI and previous treatment history. Lipid
407 level increases and a decrease of HDL-C by 5% or more during the first month of
408 treatment should be used by clinicians as an early warning sign to consider such
409 patients as being at higher risk for further important lipid level increases and/or
410 dyslipidemia development during longer term treatment. Of note, we also previously
411 demonstrated that a threshold of >5% weight gain could be used as the best predictor of
412 important long-term weight gain. Clinical strategies such as preemptive lifestyle
413 interventions should be implemented to prevent these adverse effects. The causative
414 psychotropic drug should be replaced if clinically possible, after a careful evaluation of
415 the risk-benefit ratio of a drug switch, considering the major impact of obesity and/or
416 metabolic symptoms including dyslipidemia and their major consequences on morbidity
417 and mortality.

418

419

ACCEPTED MANUSCRIPT

Acknowledgement

The authors are grateful to all participating psychiatrists, medical and nursing (Jacques Herrgott, Daniel Ducraux, Didier Wrobel, Marco Di Camillo, Yoann Levet, Charlotte Leon, Sabrina Kormann, Hugo Correia Da Rocha Capela, Justine Brea, Olivier Lafoy, Valentin Monnier, Boris Pourre, Mélanie Lenzi) staff who were involved in the metabolic monitoring program.

Author contributions

CBE had full access to all of 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 CBE. AD, FV, NSM, AG, JT, AST, SK, SF, PB, SB, SVZ, JA, RH, KE, AvG and PC were involved in data acquisition. Statistical analysis and interpretation was provided by AD and MGR. Drafting of the manuscript was provided by AD. Critical revision of the manuscript for important intellectual content was provided by all authors. CBE and PC obtained funding for the study. Administrative, technical or material support was provided by AvG, PC and CBE. All authors gave their approval for the present article.

Funding

This work has been funded in part by the Swiss National Research Foundation (CBE and PC: 320030-120686, 324730-144064 and 320030-173211). The funding sources had no role in the writing of the manuscript or in the decision to submit it for publication.

ACCEPTED MANUSCRIPT

443 **Author disclosure information**

444 CBE received honoraria for conferences or teaching CME courses from Astra Zeneca,
445 Forum für Medizinische Fortbildung, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme,
446 Mepha, Otsuka, Servier and Vifor-Pharma in the past 3 years, and for writing a review
447 article for the journal “Dialogues in clinical neurosciences” (Servier) He received an
448 unrestricted educational research grant from Takeda in the past 3 years. AvG received
449 honoraria for a conference or workshop participation from Vifor and Schwabe in the
450 previous 3 years. All authors declare no conflict of interest in relation to the content of
451 the paper.

452

453

454

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

REFERENCES

1. Roshanaei-Moghaddam B, Katon W. Premature mortality from general medical illnesses among persons with bipolar disorder: a review. *Psychiatric services (Washington, D.C.).* 2009;60:147-156.
2. Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophrenia research.* 2011;131:101-104.
3. Tiihonen J, Lonnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet.* 2009;374:620-627.
4. Miller C, Bauer MS. Excess mortality in bipolar disorders. *Current psychiatry reports.* 2014;16:499.
5. Ringen PA, Engh JA, Birkenaes AB, Dieset I, Andreassen OA. Increased mortality in schizophrenia due to cardiovascular disease - a non-systematic review of epidemiology, possible causes, and interventions. *Frontiers in psychiatry.* 2014;5:137.
6. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. *JAMA psychiatry.* 2013;70:931-939.
7. Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Current opinion in psychiatry.* 2012;25:83-88.
8. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World psychiatry : official journal of the World Psychiatric Association.* 2014;13:153-160.
9. Khan A, Faucett J, Morrison S, Brown WA. 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;70:1091-1099.
10. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends in molecular medicine.* 2011;17:97-107.
11. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nature reviews. Endocrinology.* 2012;8:114-126.
12. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World psychiatry : official journal of the World Psychiatric Association.* 2015;14:119-136.
13. Vandenberghe F, Gholam-Rezaee M, Saigi-Morgui N, et al. Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment. *The Journal of clinical psychiatry.* 2015;76:e1417-1423.
14. Srihari VH, Phutane VH, Ozkan B, et al. Cardiovascular mortality in schizophrenia: defining a critical period for prevention. *Schizophrenia research.* 2013;146:64-68.
15. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *Jama.* 2009;302:1765-1773.
16. 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.

ACCEPTED MANUSCRIPT

17. 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;71:1350-1363.

18. Cai HL, Tan QY, Jiang P, et al. A potential mechanism underlying atypical antipsychotics-induced lipid disturbances. *Translational psychiatry.* 2015;5:e661.

19. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *The American journal of psychiatry.* 2003;160:290-296.

20. 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 Arch Psychiatry.* 2014;26:339-346.

21. Hoffmann VP, Case M, Stauffer VL, Jacobson JG, Conley RR. Predictive value of early changes in triglycerides and weight for longer-term changes in metabolic measures during olanzapine, ziprasidone or aripiprazole treatment for schizophrenia and schizoaffective disorder post hoc analyses of 3 randomized, controlled clinical trials. *Journal of clinical psychopharmacology.* 2010;30:656-660.

22. American Diabetes A, American Psychiatric A, American Association of Clinical E, North American Association for the Study of O. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Obesity research.* 2004;12:362-368.

23. 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;106:3143-3421.

24. Choong E, Quteineh L, Cardinaux JR, et al. Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and the general adult population. *JAMA psychiatry.* 2013;70:1011-1019.

25. Cooper SJ, Reynolds GP, Barnes T, et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *Journal of psychopharmacology (Oxford, England).* 2016;30:717-748.

26. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC bioinformatics.* 2011;12:77.

27. Mitchell AJ, Delaffon V, Vancampfort D, Correll CU, De Hert M. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. *Psychological medicine.* 2012;42:125-147.

28. Mitchell AJ, Lord O. Do deficits in cardiac care influence high mortality rates in schizophrenia? A systematic review and pooled analysis. *Journal of psychopharmacology (Oxford, England).* 2010;24:69-80.

29. Barnes TR, Bhatti SF, Adroer R, Paton C. Screening for the metabolic side effects of antipsychotic medication: findings of a 6-year quality improvement programme in the UK. *BMJ Open.* 2015;5:e007633.

30. De Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World psychiatry : official journal of the World Psychiatric Association.* 2011;10:52-77.

31. Mitchell AJ, Lord O, Malone D. Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis. *The British journal of psychiatry : the journal of mental science.* 2012;201:435-443.

32. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *European heart journal.* 2016;37:2999-3058.

ACCEPTED MANUSCRIPT

33. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *European psychiatry : the journal of the Association of European Psychiatrists.* 2009;24:412-424.

34. Duerden M, O'Flynn N, Qureshi N. Cardiovascular risk assessment and lipid modification: NICE guideline. *Br J Gen Pract.* 2015;65:378-380.

35. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart (British Cardiac Society).* 2005;91 Suppl 5:v1-52.

36. Bobo WV, Bonaccorso S, Jayathilake K, Meltzer HY. Prediction of long-term metabolic effects of olanzapine and risperidone treatment from baseline body mass index in schizophrenia and bipolar disorder. *Psychiatry research.* 2011;189:200-207.

37. 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;382:951-962.

38. Elmslie JL, Porter RJ, Joyce PR, Hunt PJ, Shand BI, Scott RS. Comparison of insulin resistance, metabolic syndrome and adiponectin in overweight bipolar patients taking sodium valproate and controls. *The Australian and New Zealand journal of psychiatry.* 2009;43:53-60.

39. Eiris JM, Lojo S, Del Rio MC, et al. Effects of long-term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy. *Neurology.* 1995;45:1155-1157.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

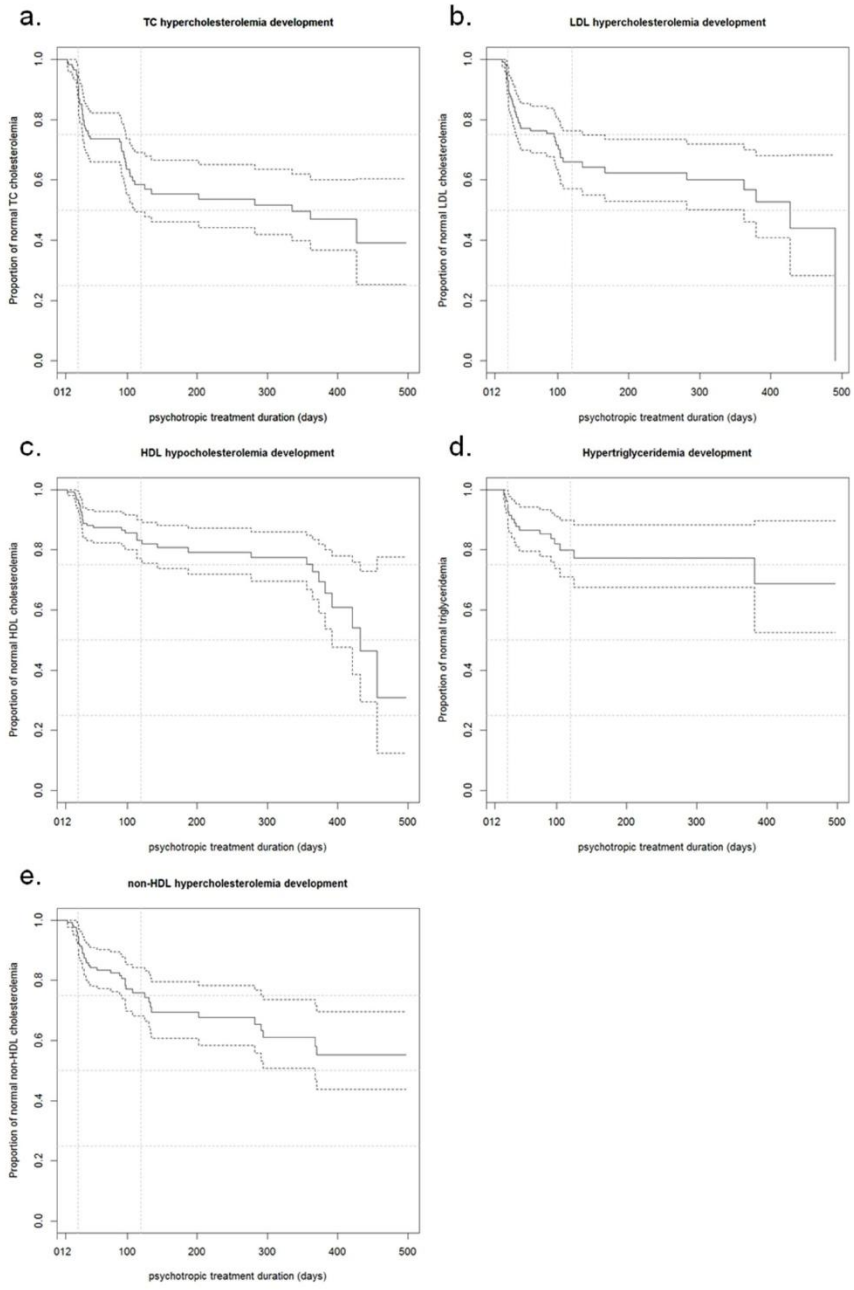
Table 1. Comparison of demographic parameters between patients with and without early changes of blood lipid levels

Demographic	All	TC < 5%	TC ≥ 5%	p-value	LDL-C <5%	LDL-C ≥5 %	p-value	TG < 5%	TG ≥ 5%	p-value	HDL-C > -5%	HDL-C ≤ -5%	p-value	non-HDL-C < 5%	non-HDL-C ≥ 5 %	p-value
Number of patients	181 (95 for TG)	102	79		92	70		41	54		100	73		91	82	
Age, median (IQR), y	33 (23-50)	35 (23-54)	30 (23-48)	0.32	35 (23-55)	31 (23-50)	0.55	30 (23-47)	31 (21-43)	0.56	32 (23-52)	33 (22-48)	0.66	34 (23-56)	31 (23-47)	0.54
Men, n(%)	96 (53)	52 (51.0)	44 (55.7)	0.53	45 (48.9)	40 (57.1)	0.3	20 (48.8)	32 (59.3)	0.31	51 (51.0)	43 (58.9)	0.3	46 (50.6)	48 (58.5)	0.29
Smoking, n(%)	82 (45.3)	45 (44.1)	37 (46.8)	0.93	43 (46.7)	31 (44.3)	0.67	18 (43.9)	29 (53.7)	0.56	46 (46.0)	34 (46.6)	0.6	40 (44)	40 (48.8)	0.78
Diagnosis, n(%)																
Psychotic disorders	69 (38.1)	32 (31.4)	37 (46.8)	**0.03**	27 (29.4)	32 (45.7)	**0.03**	14 (34.2)	20 (37)	0.77	39 (39.0)	26 (35.6)	0.65	29 (31.9)	36 (43.9)	0.1
Schizoaffective disorders	13 (7.2)	10 (9.8)	3 (3.8)	0.12	10 (10.9)	3 (4.3)	0.13	1 (2.4)	5 (9.3)	0.17	7 (7.0)	6 (8.2)	0.76	8 (8.8)	5 (6.1)	0.5
Bipolar disorders	28 (15.5)	18 (17.7)	10 (12.7)	0.36	16 (17.4)	9 (12.9)	0.43	8 (19.5)	10 (18.5)	0.9	12 (12.0)	14 (19.2)	0.19	15 (16.5)	11 (13.4)	0.57
Depressive disorders	26 (14.4)	15 (14.7)	11 (13.9)	0.42	16 (17.4)	10 (14.3)	0.41	6 (14.6)	10 (18.5)	0.62	18 (18.0)	8 (11.0)	0.75	16 (17.6)	10 (12.2)	0.5
Organic disorders	3 (1.7)	1 (1)	2 (2.5)	0.88	1 (1.1)	2 (2.9)	0.59				2 (2.0)	1 (1.4)	0.2	1 (1.1)	2 (2.4)	0.32
Other	14 (7.7)	7 (6.9)	7 (8.9)	0.62	5 (5.4)	7 (10.0)	0.27	3 (7.3)	4 (7.4)	0.99	7 (7.0)	5 (6.9)	0.97	4 (4.4)	8 (9.8)	0.17
Not available	28 (15.5)	19 (18.6)	9 (11.4)	0.18	17 (18.5)	7 (10.0)	0.13	9 (22)	5 (9.3)	0.08	15 (15.0)	13 (17.8)	0.62	18 (19.8)	10 (12.2)	0.18
Medication, n(%)																
Amisulpride	19 (10.5)	12 (11.8)	7 (8.9)	0.53	11 (12.0)	5 (7.1)	0.31	6 (14.6)	4 (7.4)	0.26	14 (14.0)	4 (4.6)	0.07	12 (13.2)	6 (7.3)	0.21
Aripiprazole	23 (12.7)	17 (16.7)	6 (7.5)	0.07	17 (18.5)	4 (5.7)	**0.02**	9 (22.0)	5 (9.3)	0.08	14 (14.0)	9 (12.3)	0.75	15 (16.5)	8 (9.8)	0.19
Clozapine	13 (7.2)	6 (5.9)	7 (8.9)	0.44	4 (4.4)	8 (11.4)	0.09	4 (9.8)	3 (5.6)	0.44	7 (7.0)	5 (6.9)	0.97	3 (3.3)	9 (11.0)	**0.05**
Haloperidol	1 (0.6)	1 (1)			1 (1.1)			0 (0)	0 (0)		1 (1.0)			1 (1.1)	0 (0)	0.34
Lithium	13 (7.2)	7 (6.9)	6 (7.6)	0.85	8 (8.7)	5 (7.1)	0.72	3 (7.3)	3 (5.6)	0.73	9 (9.0)	4 (5.5)	0.39	7 (7.7)	6 (7.3)	0.93
Mirtazapine	5 (2.8)	5 (4.9)			4 (4.4)			1 (2.4)	0 (0)	0.25	2 (2.0)	2 (2.7)	0.75	4 (4.4)	0 (0)	0.06
Olanzapine	33 (18.2)	14 (13.7)	19 (24.1)	0.07	13 (14.1)	17 (24.3)	0.1	4 (9.8)	11 (20.4)	0.16	19 (19.0)	12 (16.4)	0.66	11 (12.1)	20 (24.4)	**0.04**
Quetiapine	53 (29.3)	27 (26.5)	26 (32.9)	0.34	22 (23.9)	24 (34.3)	0.15	9 (22.0)	22 (40.7)	0.053	28 (28.0)	22 (30.1)	0.76	24 (26.4)	26 (31.7)	0.44
Risperidone	13 (7.2)	8 (7.8)	5 (6.3)	0.7	7 (7.6)	4 (5.7)	0.64	2 (4.9)	5 (9.3)	0.42	5 (5.0)	8 (11.0)	0.14	9 (9.9)	4 (4.9)	0.21
Valproate	8 (4.4)	5 (4.9)	3 (3.8)	0.72	5 (5.4)	3 (4.3)	0.74	3 (7.3)	1 (1.9)	0.19	1 (1.0)	7 (9.6)	**0.008**	5 (5.5)	3 (3.7)	0.57
Obesity prevalence (BMI ≥ 30kg/m^2), n(%)																
Baseline	19 (11.5)	12 (13.0)	7 (9.6)	0.49	10 (11.9)	8 (12.5)	0.91	3 (8.6)	5 (9.8)	0.85	8 (8.7)	10 (15.4)	0.19	11 (13.6)	7 (9.2)	0.39
1 year	12 (20.7)	6 (18.8)	6 (23.1)	0.69	6 (21.4)	5 (22.7)	0.91	1 (12.5)	3 (16.7)	0.78	5 (14.7)	7 (31.8)	0.13	5 (18.5)	7 (24.1)	0.61
Prevalence of metabolic syndrome IDF, n/total (%)[1]																
Baseline	16/87 (18.4)	7/52 (13.4)	9/35 (25.7)	0.15	9/52 (17.3)	6/32 (18.8)	0.87	7/39 (19.4)	9/51 (17.7)	0.83	10/49 (20.4)	6/38 (15.8)	0.58	8/47 (17.0)	8/40 (20.0)	0.73
1 year	10/33 (30.3)	4/19 (21.1)	6/14 (42.9)	0.18	4/19 (21.1)	5/13 (38.4)	0.28	3/13 (23.1)	7/20 (35.0)	0.47	5/19 (26.3)	5/14 (35.7)	0.56	3/16 (18.8)	7/17 (41.2)	0.16
Prevalence of raised fasting plasma glucose, n/total (%)[2]																
Baseline	20/96 (20.8)	13/57 (22.8)	7/39 (17.9)	0.57	12/54 (22.2)	5/35 (14.3)	0.35	9/41 (22)	10/53 (18.9)	0.71	10/52 (19.2)	9/41 (21.9)	0.75	12/50 (24.0)	7/43 (16.3)	0.36
Early weight gain (≥5%), n(%)																
1st month	31 (17.8)	9 (9.3)	22 (28.6)	**0.001**	11 (12.5)	16 (23.5)	0.07	3 (7.7)	10 (18.9)	0.13	15 (15.2)	14 (20.9)	0.34	10/87 (11.5)	19/79 (24.1)	**0.03**
Prevalence of hypercholesterolemia (≥ 5 mmol/l), n/total (%)																
Baseline	68/181 (37.6)	54/102 (52.9)	14/79 (17.7)	**<0.001**	44/92 (47.8)	11/70 (15.7)	**<0.001**	20/41 (48.8)	14/54 (25.9)	**0.02**	33/100 (33.0)	30/73 (41.1)	0.27	49/91 (53.9)	14/82 (17.1)	**<0.001**
1 month	78/181 (43.1)	37/102 (36.3)	41/79 (51.9)	**0.04**	30/92 (32.6)	35/70 (0.5)	**0.03**	16/41 (39.0)	18/54 (33.3)	0.57	44/100 (44.0)	28/73 (38.4)	0.46	33/91 (36.3)	39/82 (47.6)	0.13
3 months	79/163 (48.5)	44/94 (46.8)	35/69 (50.7)	0.62	36/84 (42.8)	28/60 (46.7)	0.65	16/37 (43.2)	25/51 (49.0)	0.59	41/93 (44.1)	32/62 (51.6)	0.36	39/85 (45.9)	34/70 (48.6)	0.74
12 months	45/84 (53.6)	25/48 (52.1)	20/36 (55.6)	0.75	18/42 (42.9)	18/33 (54.6)	0.32	8/16 (50.0)	6/22 (27.3)	0.15	20/46 (43.5)	22/35 (62.9)	0.08	21/41 (51.2)	21/40 (52.5)	0.91
Prevalence of LDL hypercholesterolemia (≥ 3 mmol/l), n/total (%)																
Baseline	52/162 (32.1)	39/91 (42.9)	13/71 (18.3)	**0.001**	40/92 (43.5)	12/70 (17.1)	**<0.001**	13/37 (35.1)	15/53 (28.3)	0.49	24/94 (25.5)	28/68 (41.2)	0.04	39/86 (45.4)	13/76 (17.1)	**<0.001**
1 month	61/162 (37.7)	27/91 (29.7)	34/71 (47.9)	**0.02**	25/92 (27.2)	36/70 (51.4)	**0.002**	11/37 (29.7)	20/53 (37.7)	0.43	31/94 (33.0)	30/68 (44.1)	0.15	26/86 (30.2)	35/76 (46.1)	**0.04**
3 months	56/136 (41.2)	30/81 (37.0)	26/55 (47.3)	0.23	29/80 (36.3)	27/56 (48.2)	0.16	14/33 (42.4)	16/45 (35.6)	0.54	31/82 (37.8)	25/54 (46.3)	0.33	30/78 (38.5)	26/58 (44.8)	0.46
12 months	33/69 (47.8)	17/41 (41.5)	16/28 (57.1)	0.2	17/42 (40.5)	16/27 (59.3)	0.13	6/14 (42.9)	6/19 (31.6)	0.51	17/39 (43.6)	16/30 (53.3)	0.42	17/38 (44.7)	16/31 (51.6)	0.57
Prevalence of hypertriglyceridemia (≥ 2 mmol/l), n/total (%)																
Baseline	11/95 (11.6)	9/55 (16.4)	2/40 (5.0)	0.09	4/54 (7.4)	2/36 (5.6)	0.73	9/41 (22.0)	2/54 (3.7)	**0.006**	5/52 (9.6)	4/41 (9.8)	0.98	7/49 (14.3)	2/44 (4.6)	0.11
1 month	15/95 (15.8)	6/55 (10.9)	9/40 (22.5)	0.13	6/54 (11.1)	7/36 (19.4)	0.27	3/41 (7.3)	12/54 (22.2)	**0.048**	3/52 (5.8)	11/41 (26.8)	**0.005**	4/49 (8.2)	10/44 (22.7)	**0.05**
3 months	14/85 (16.5)	7/51 (13.7)	7/34 (20.6)	0.4	5/49 (10.2)	5/31 (16.1)	0.44	6/37 (16.2)	8/48 (16.7)	0.96	7/46 (15.2)	6/37 (16.2)	0.9	6/47 (12.8)	7/36 (19.4)	0.41
12 months	9/37 (24.3)	4/22 (18.2)	5/15 (33.3)	0.29	3/21 (14.3)	4/14 (28.6)	0.3	3/16 (18.8)	6/21 (28.6)	0.49	4/21 (19.1)	4/15 (26.7)	0.59	1/17 (5.9)	7/19 (36.8)	**0.03**
Prevalence of HDL hypocholesterolemia (≤ 1 mmol/l), n/total (%)																
Baseline	30/173 (17.3)	15/96 (15.6)	15/77 (19.5)	0.51	10/92 (10.9)	14/70 (20.0)	0.11	8/39 (20.5)	4/54 (7.4)	0.06	24/100 (24.0)	6/73 (8.2)	**0.007**	17/91 (18.7)	13/82 (15.9)	0.62
1 month	36/173 (20.8)	21/96 (21.9)	15/77 (19.5)	0.7	16/92 (17.4)	14/70 (20.0)	0.67	10/39 (25.6)	12/54 (22.2)	0.7	13/100 (13.0)	23/73 (31.5)	**0.003**	21/91 (23.1)	15/82 (18.3)	0.44
3 months	28/153 (18.3)	17/86 (19.8)	11/67 (16.4)	0.6	11/82 (13.4)	10/60 (16.7)	0.59	7/35 (20.0)	7/50 (14.0)	0.46	15/93 (16.1)	13/60 (21.7)	0.39	17/84 (20.2)	11/69 (15.9)	0.49
12 months	25/80 (31.3)	11/45 (24.4)	14/35 (40.0)	0.14	10/42 (23.8)	11/32 (34.4)	0.32	4/15 (26.7)	9/22 (40.9)	0.37	13/45 (28.9)	12/35 (34.3)	0.61	10/41 (24.4)	15/39 (38.5)	0.18

Only patients without any lipid-lowering medication are included. P values were calculated using Wilcoxon ranksum tests for continuous variables and Chi2 tests for categorical variables. Values in bold are significant. Abbreviations: TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; non-HDL-C: non- high-density lipoprotein cholesterol.

[1] Metabolic syndrome was defined according to the IDF definition. Metabolic syndrome was present if patients had central obesity (men ≥94 cm; women ≥80 cm) and at least two other following factors: triglycerides ≥1.7 mmol/l (150 mg/dL) or lipid-lowering treatment; glucose ≥5.6 mmol/l (100 mg/dL) or type 2 diabetes treatment; blood pressure ≥130/85 mm Hg or treatment for hypertension; high-density lipoprotein cholesterol (men ≤1.03 mmol/l (40 mg/dL); women ≤1.29 mmol/l (50 mg/dL)).

[2] Raised fasting plasma glucose was defined according to the IDF definition, i.e. glucose ≥5.6 mmol/l or type 2 diabetes treatment, in fasting conditions. Of note, no patient suffered from type 2 diabetes at baseline (defined by receiving a type 2 diabetes treatment or if at least two fasting glucose levels ≥7 mmol/l, according to the American Diabetes Association)


a.
TC hypercholesterolemia development
Proportion of normal TC cholesterolemia
psychotropic treatment duration (days)
b.
LDL hypercholesterolemia development
Proportion of normal LDL cholesterolemia
psychotropic treatment duration (days)
c.
HDL hypocholesterolemia development
Proportion of normal HDL cholesterolemia
psychotropic treatment duration (days)
d.
Hypertriglyceridemia development
Proportion of normal triglyceridemia
psychotropic treatment duration (days)
e.
non-HDL hypercholesterolemia development
Proportion of normal non-HDL cholesterolemia
psychotropic treatment duration (days)

ACCEPTED MANUSCRIPT

Figure 1. **Survival curves for new onset dyslipidemia (NOD) by unadjusted Kaplan-Meier curves**.

a. Patient survival curve for NODTC (new onset TC hypercholesterolemia) b. Patient survival curve for NODLDL (new onset LDL-C hypercholesterolemia) c. Patient survival curve for NODTG (new onset hypertriglyceridemia) d. Patient survival curve for NODHDL (new onset HDL-C hypocholesterolemia). e. Patient survival curve for NODnon-HDL (new onset non-HDL-C hypercholesterolemia).

ACCEPTED MANUSCRIPT

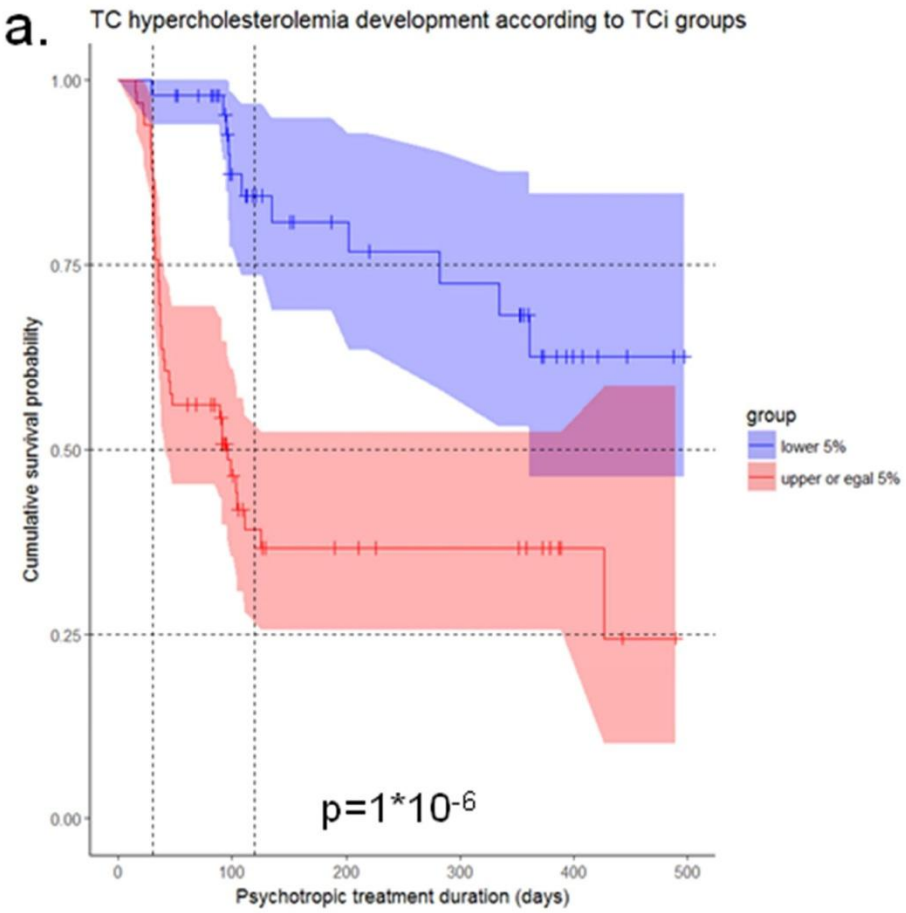


Figure 2. Survival curves for new onset dyslipidemia (NOD) by unadjusted Kaplan-Meier curves according to early lipid change groups.

a. Patient survival curves for NODTC (new onset TC hypercholesterolemia) according to early 5% TC increase threshold (n=114).

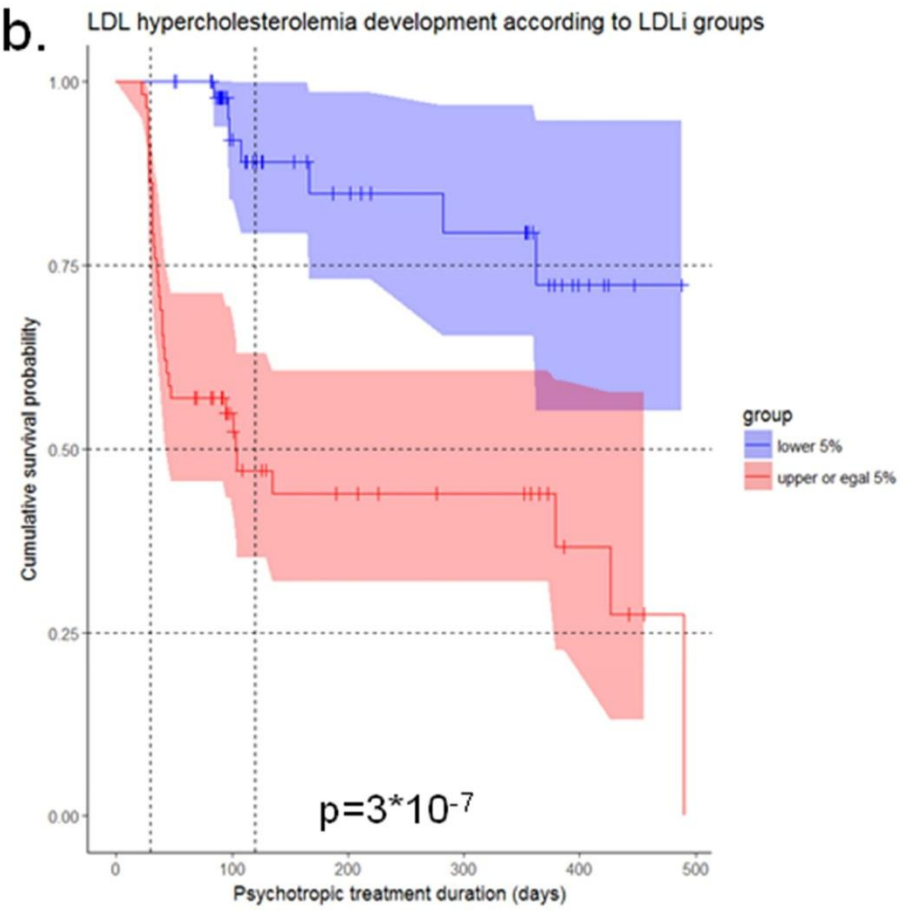


Figure 2. Survival curves for new onset dyslipidemia (NOD) by unadjusted Kaplan-Meier curves according to early lipid change groups.

b. Patient survival curves for NODLDL (new onset LDL-C hypercholesterolemia) according to early 5% LDL-C increase threshold (n=115).

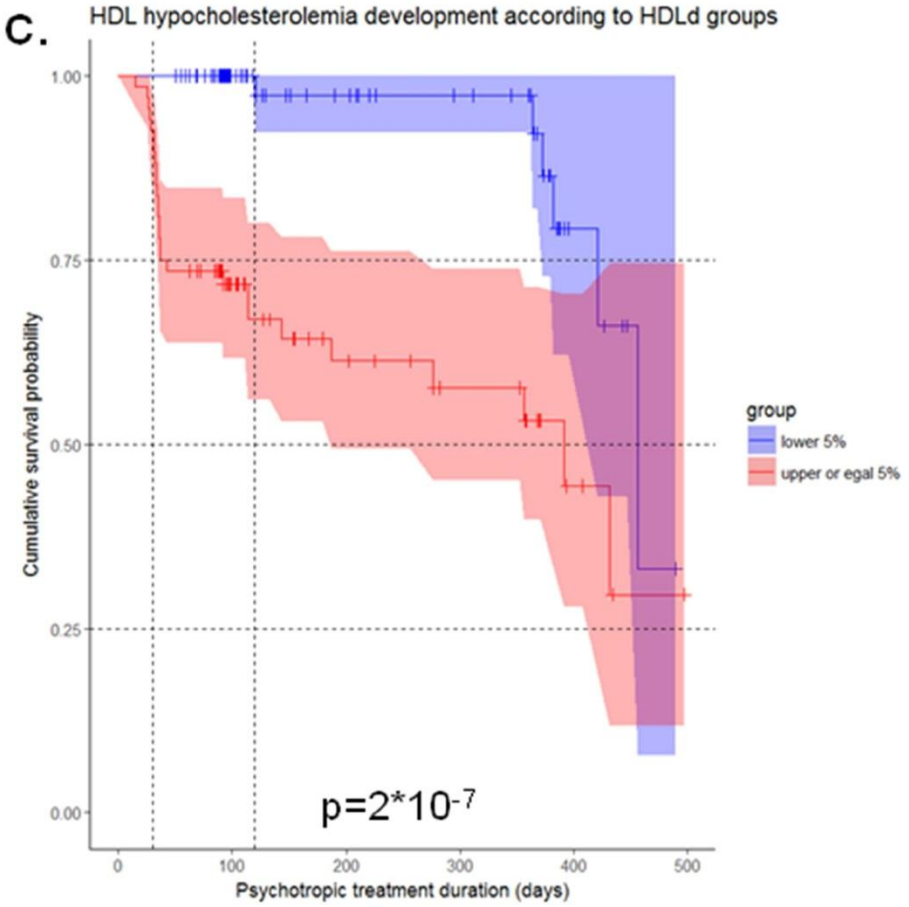


Figure 2. Survival curves for new onset dyslipidemia (NOD) by unadjusted Kaplan-Meier curves according to early lipid change groups.

c. Patient survival curves for NODTG (new onset hypertriglyceridemia) according to early 5% TG increase threshold (n=84).

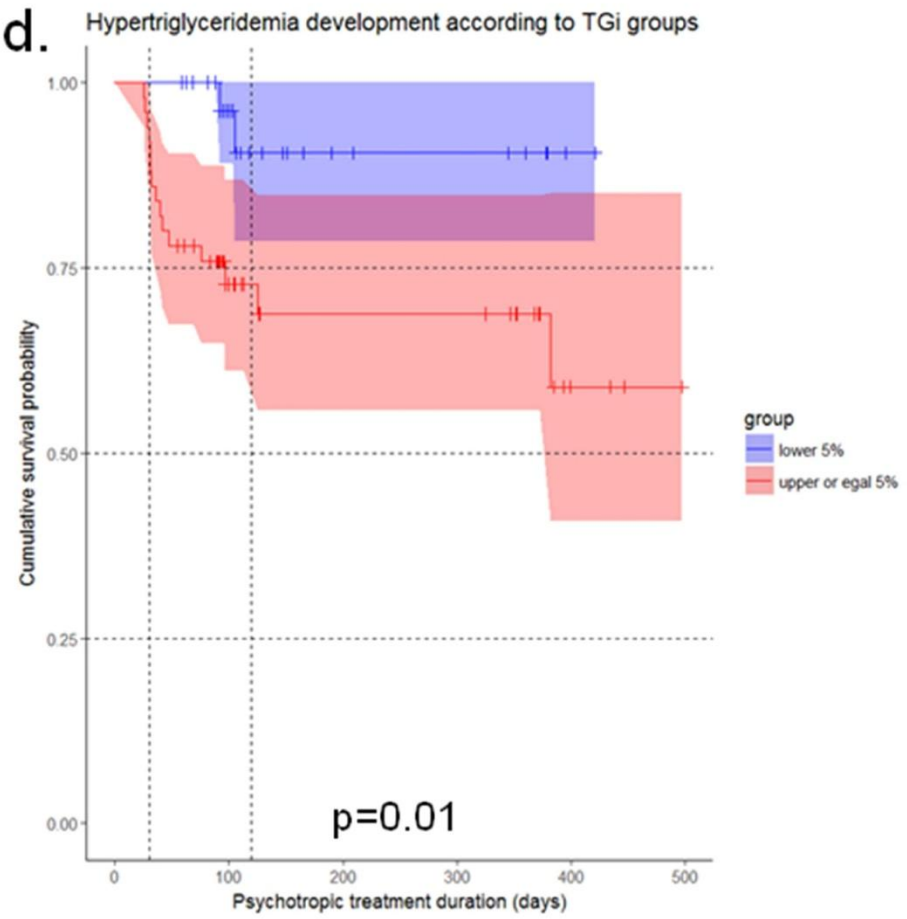


Figure 2. Survival curves for new onset dyslipidemia (NOD) by unadjusted Kaplan-Meier curves according to early lipid change groups.

d. Patient survival curves for NODHDL (new onset HDL-C hypocholesterolemia) according to early 5% HDL-C decrease threshold (n=152).

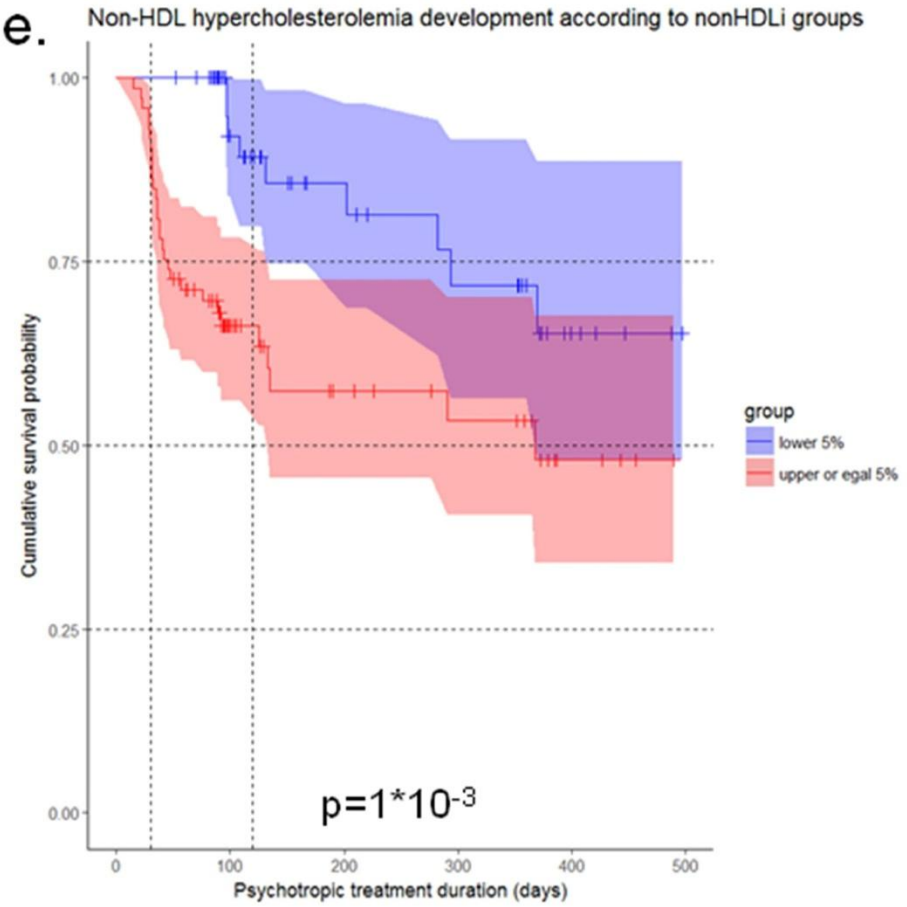


Figure 2. Survival curves for new onset dyslipidemia (NOD) by unadjusted Kaplan-Meier curves according to early lipid change groups.

e. Patient survival curves for NODnonHDL (new onset non-HDL-C hypercholesterolemia) according to early 5% non-HDL-C increase threshold (n=127).

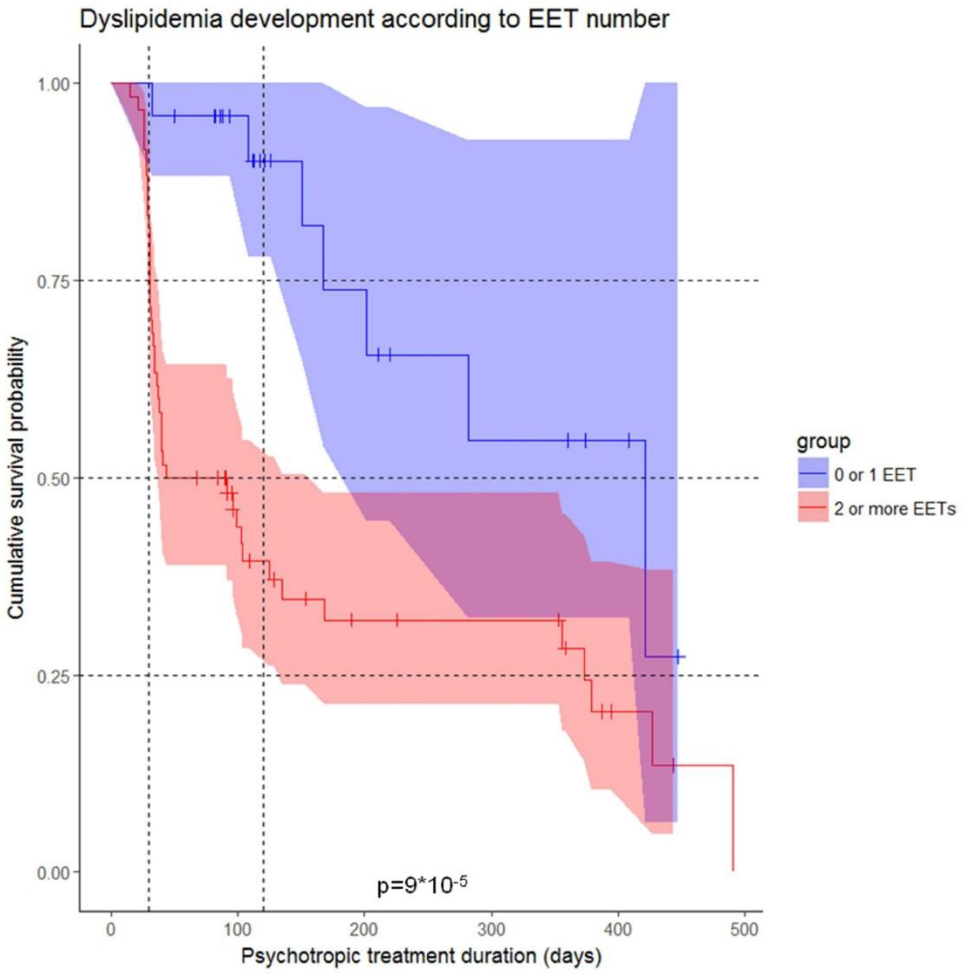


Figure 3. Survival curves for new onset dyslipidemia (NOD) by unadjusted Kaplan-Meier curves according to the number of early exceeded thresholds (EETs)

NOD was defined as positive if one (or more) of the four lipid traits outreached clinical thresholds and/or if patients received a lipid-lowering comedication during psychotropic treatment (n=86).

- Lipid parameters significantly worsened during psychotropic treatment
- Early changes of lipid levels could predict a longer-term lipid deterioration
- Early changes of lipid levels were good predictors of new onset dyslipidemia

ACCEPTED MANUSCRIPT

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 10^{th} (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	Antidiabetic drugs	Antihypertensive drugs
Atorvastatin	Desmopressin	Aliskiren
Ezetimibe	Glibenclamid	Amiloride hydrochlorothiazide
Fenofibrate	Gliclazide	Amlodipin
Fluvastatin	Glimepiride	Atenolol
Pravastatin	Insulin	Bisoprolol
Rosuvastatin	Metformin	Bosentan
Simvastatin	Pioglitazone	Candesartan
	Rosiglitazone	Captopril
	Sitagliptin	Carvedilol
	Vildagliptin	Celiprolol

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

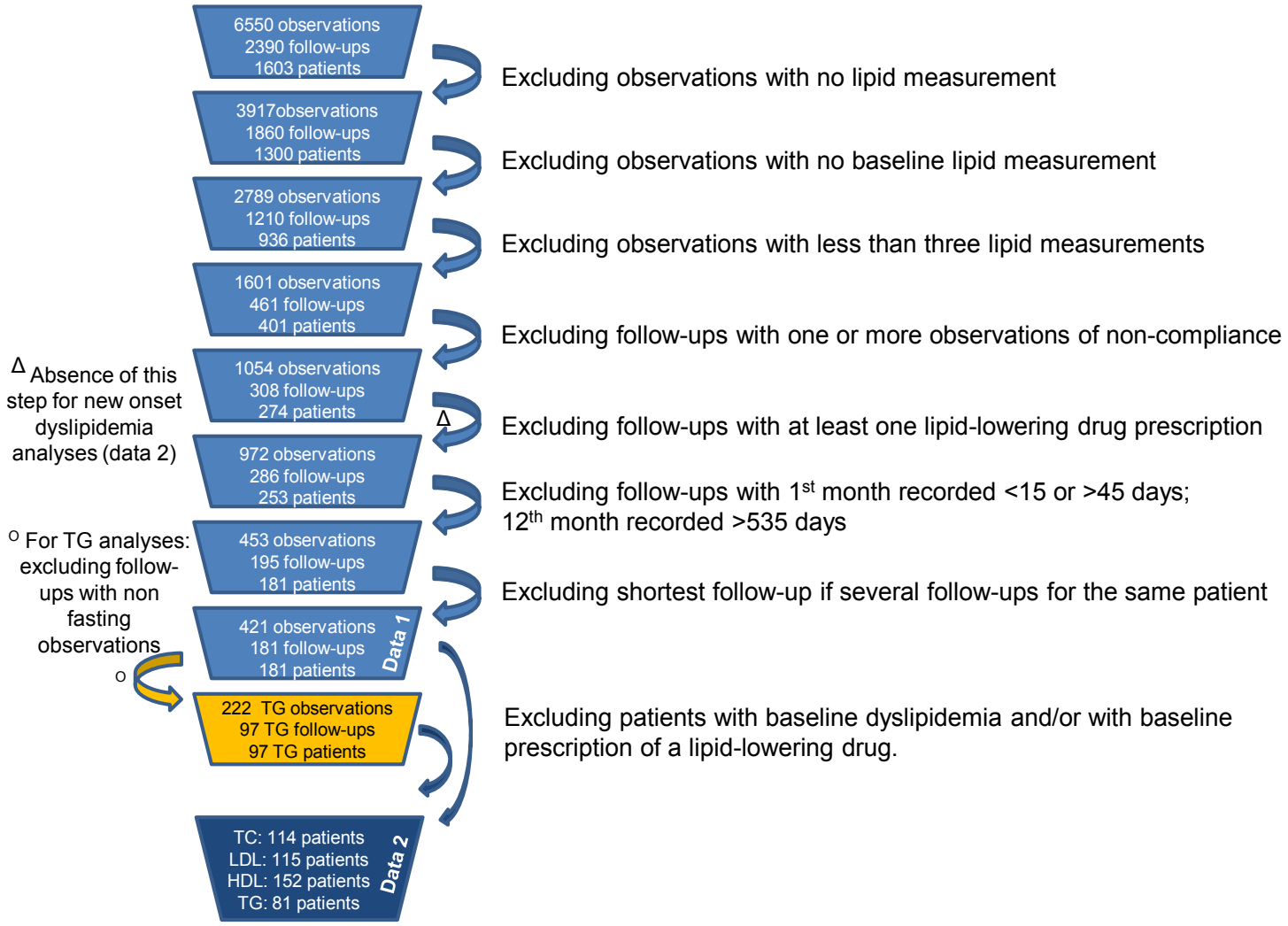
Number of early exceeded thresholds [1]		Patients developing **at least one** dyslipidemia during psychotropic treatment, n/total (%)	Non adjusted analyses Fisher		Adjusted analyses Logistic mixed model	
			Odd-ratio (CI 95%)	p-value	Adjusted odd-ratio (CI 95%)[2]	p-value
Control	0	3/12 (25%)	5.5 (1.2 - 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 Fisher		Adjusted analyses 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%)				

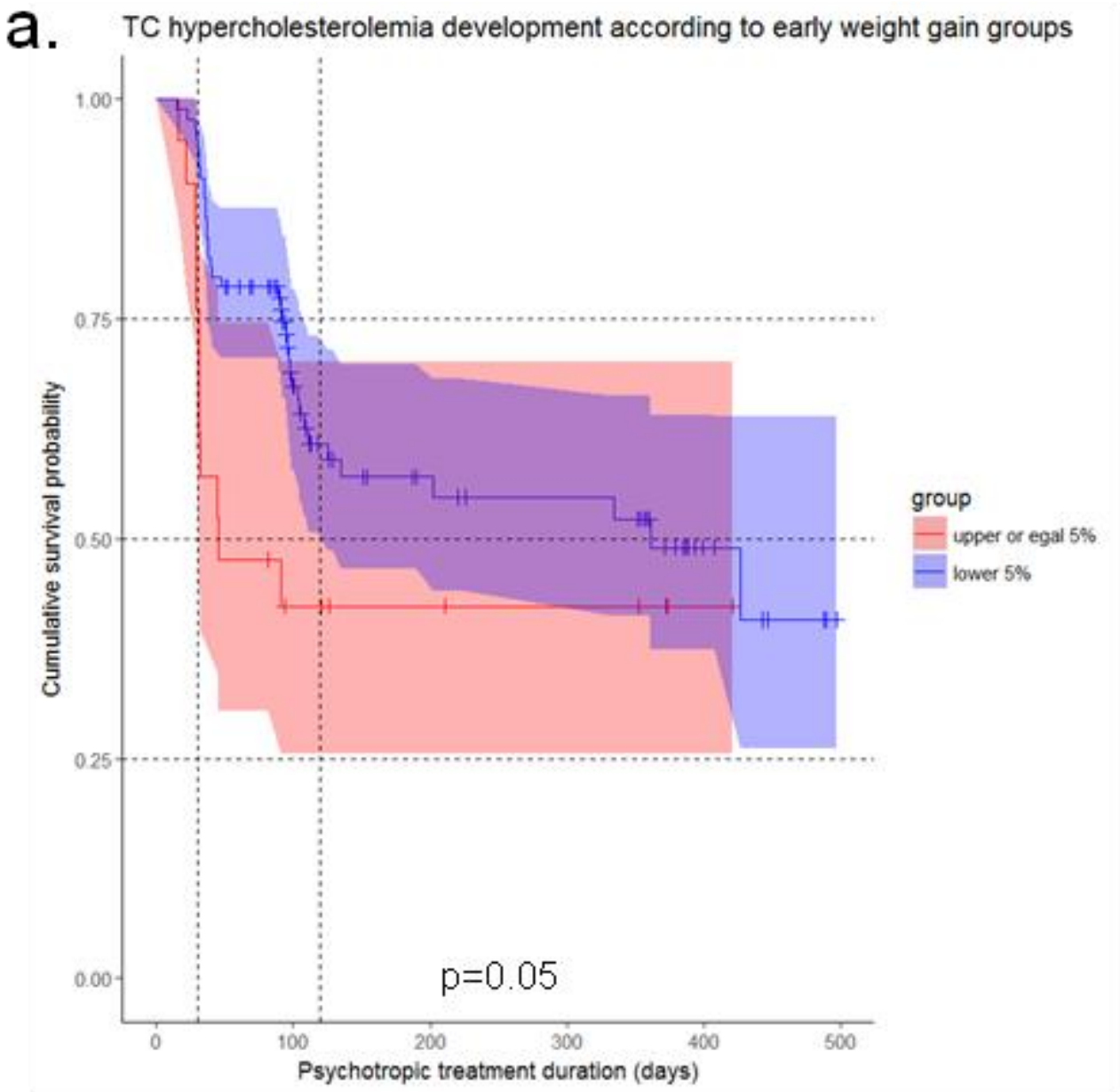
[1] Number of early exceeded thresholds refers to TCi≥5%, LDLi≥5%, TGi≥5% and/or HDLd≥5%

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



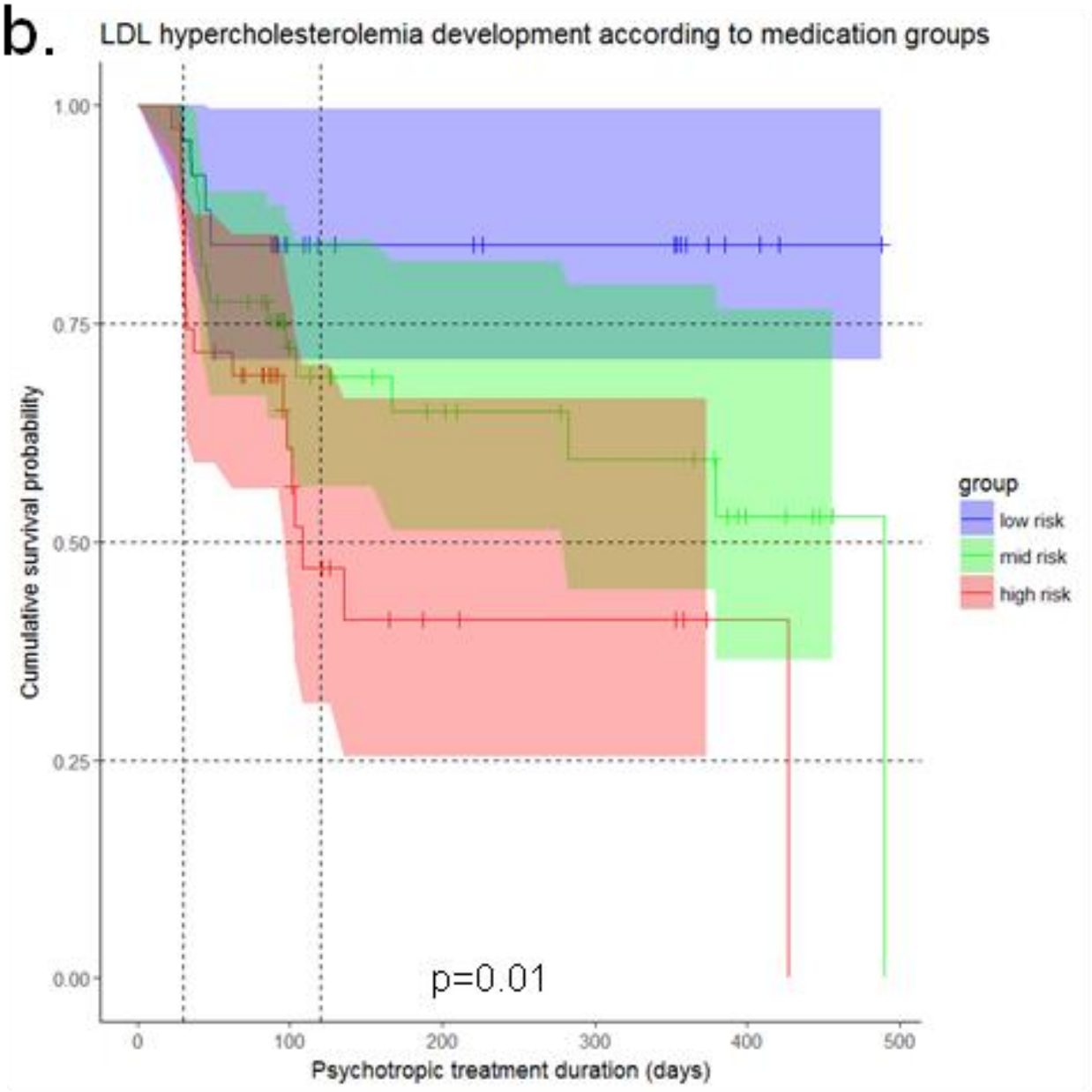
S1 Figure. Flow chart of patient selection

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.



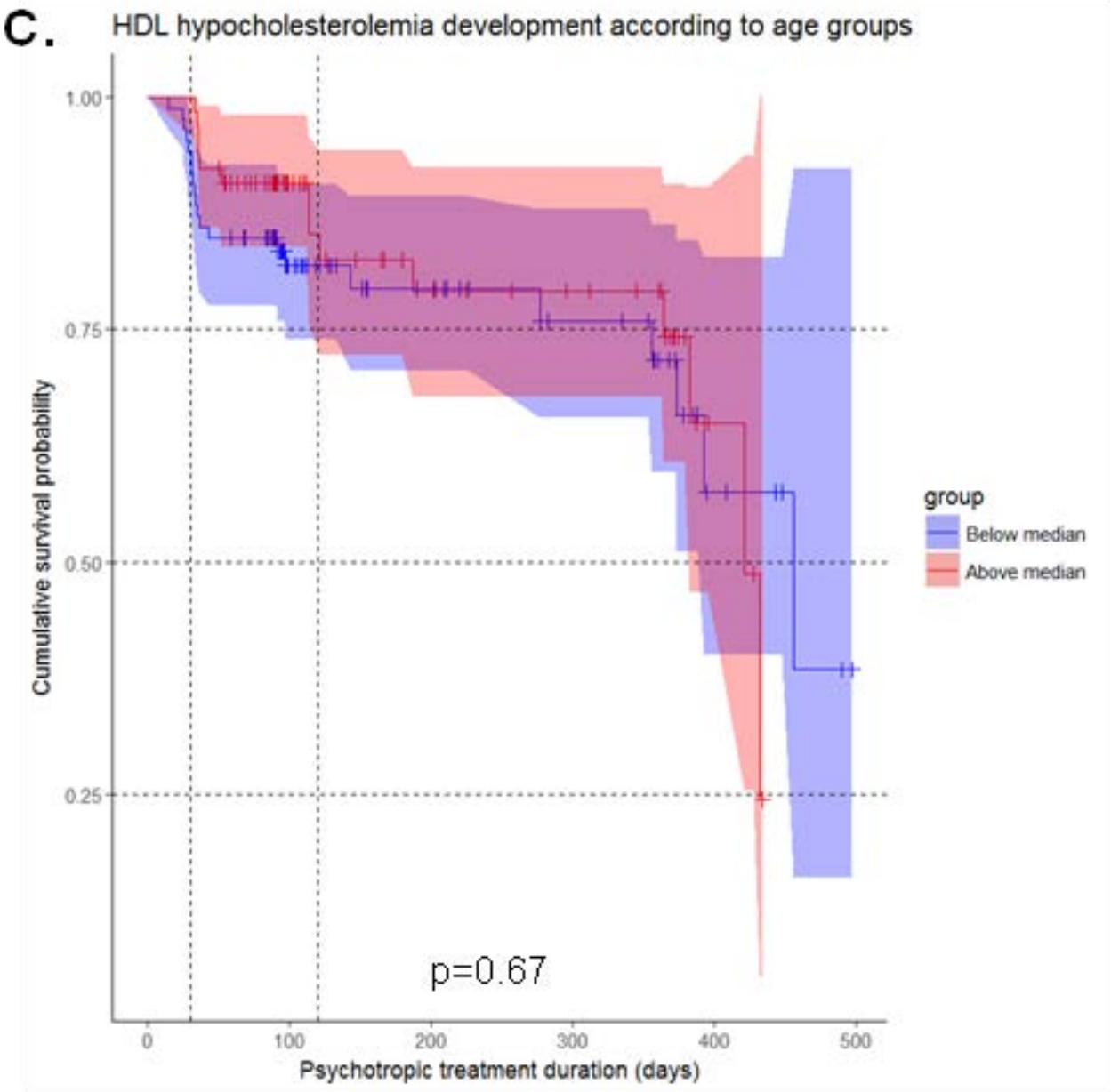
S2 Figure. **Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters**

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



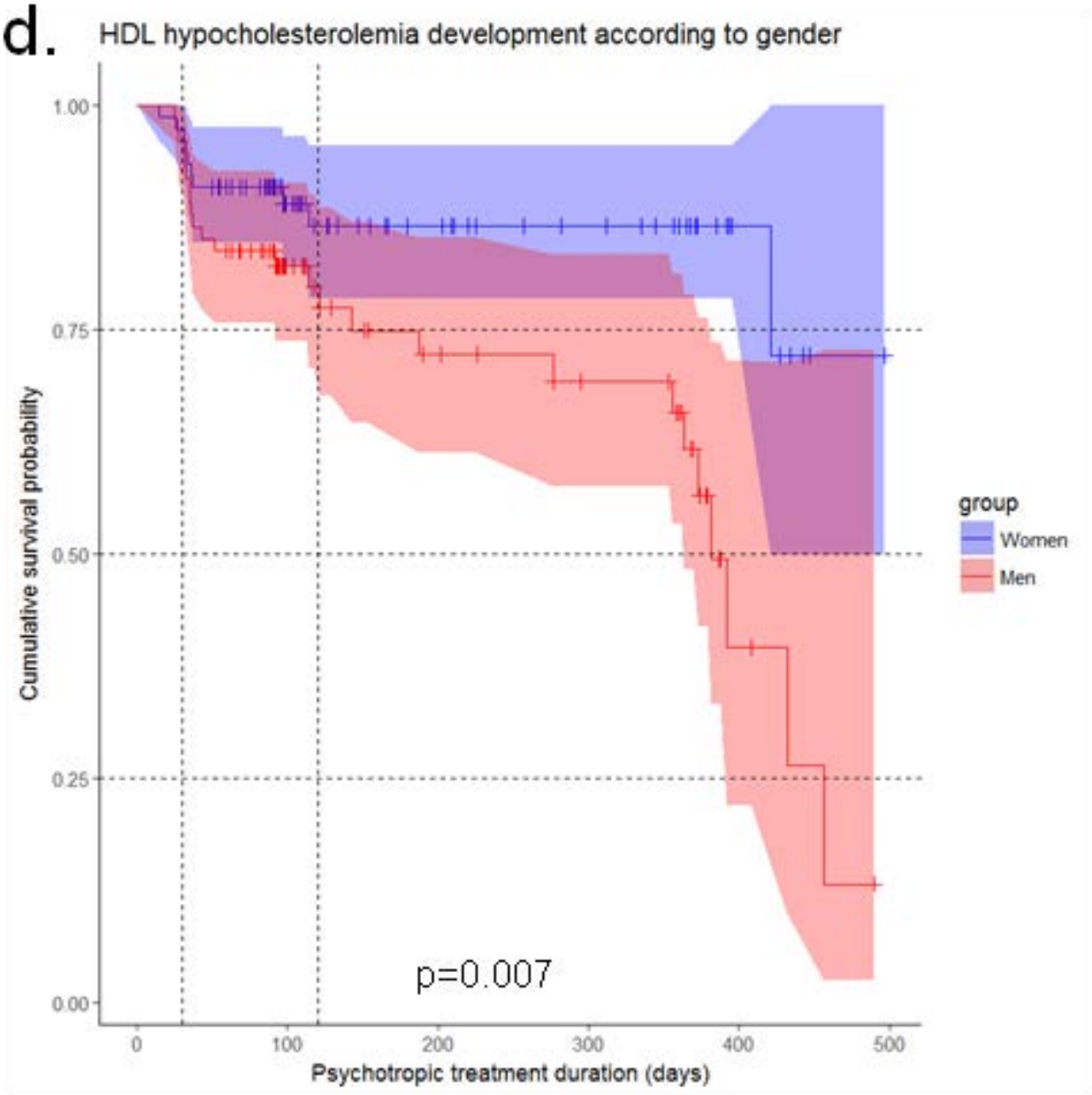
S2 Figure. **Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters**

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.



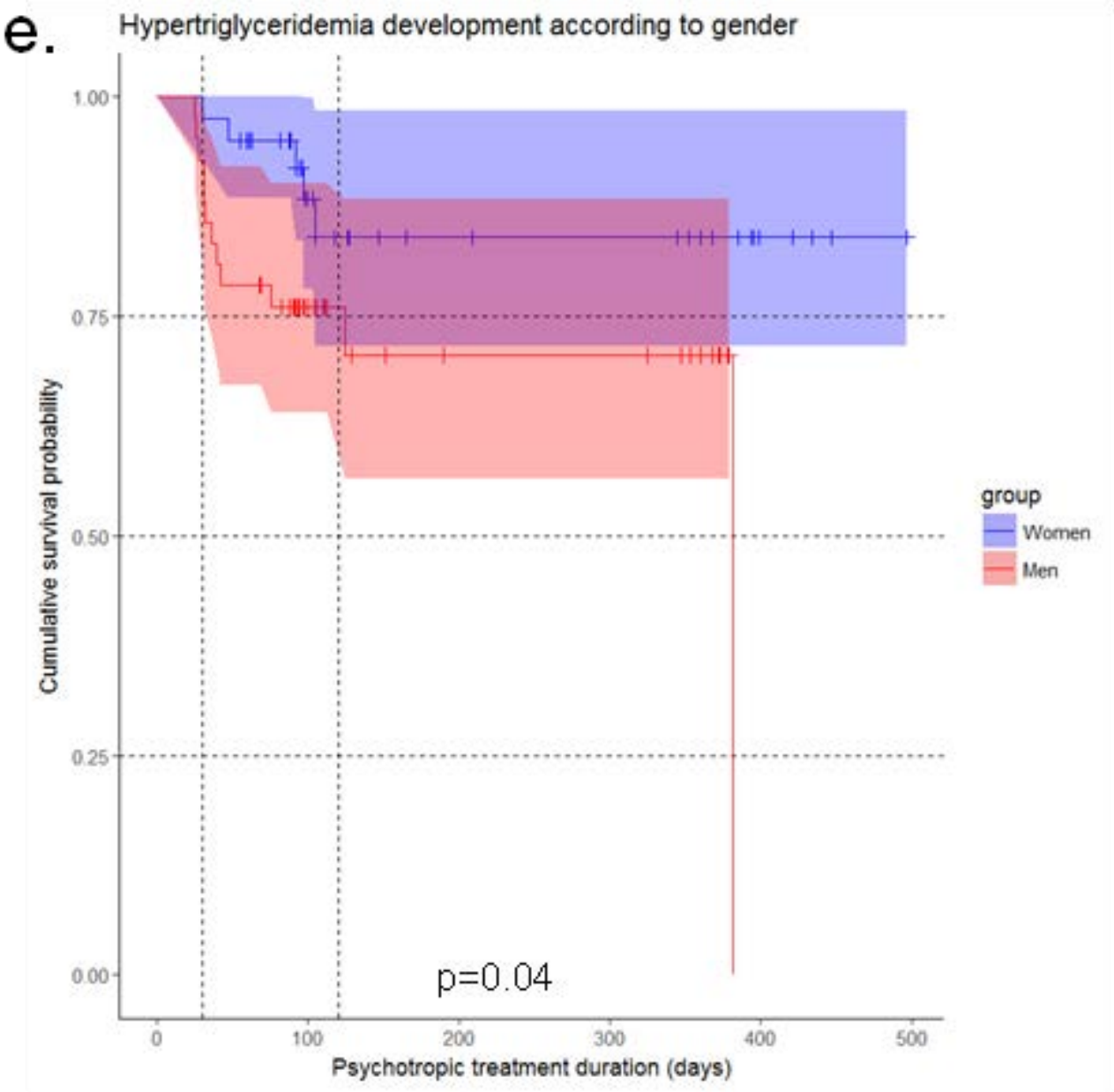
S2 Figure. **Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters**

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.



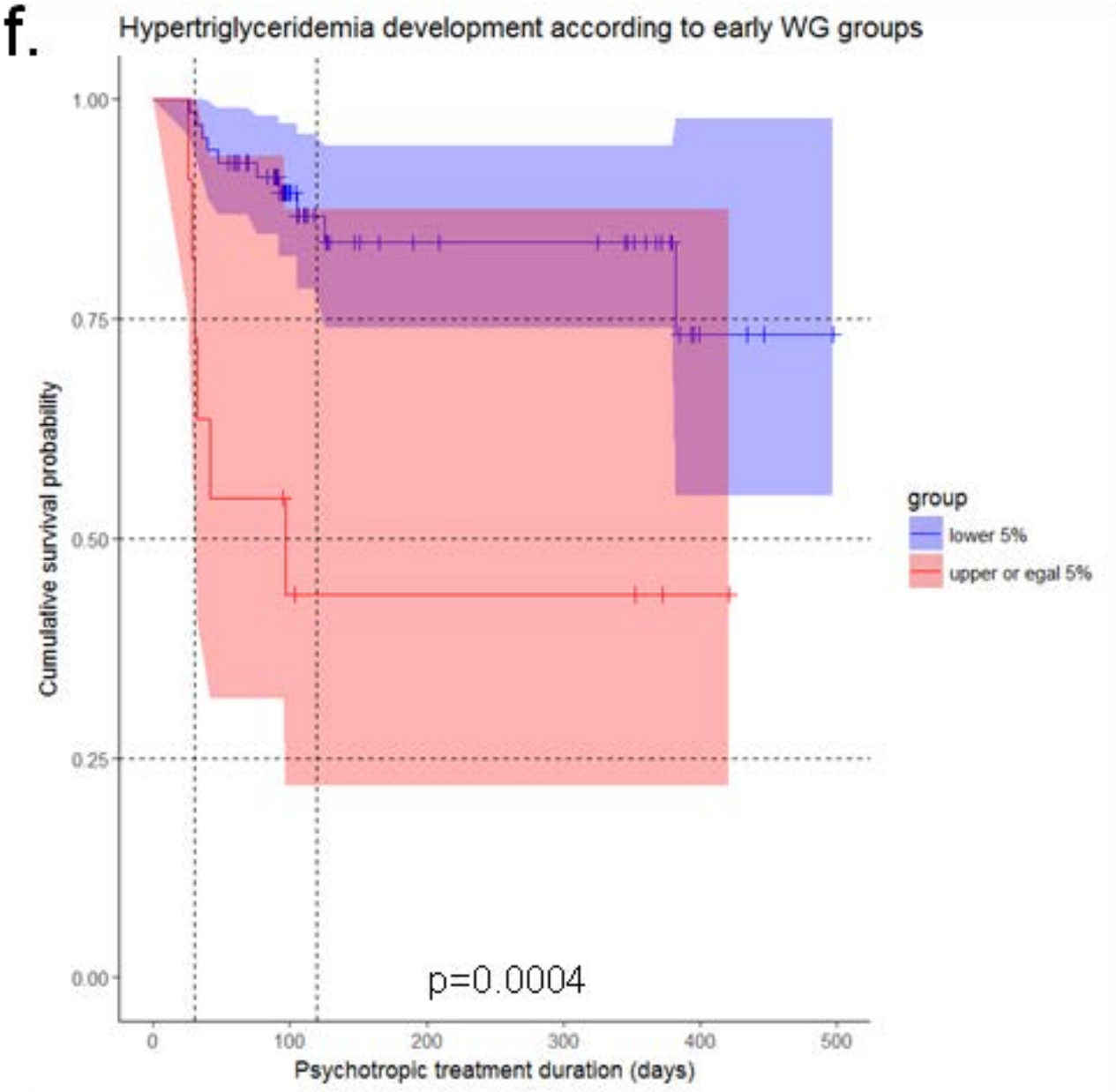
S2 Figure. **Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters**

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



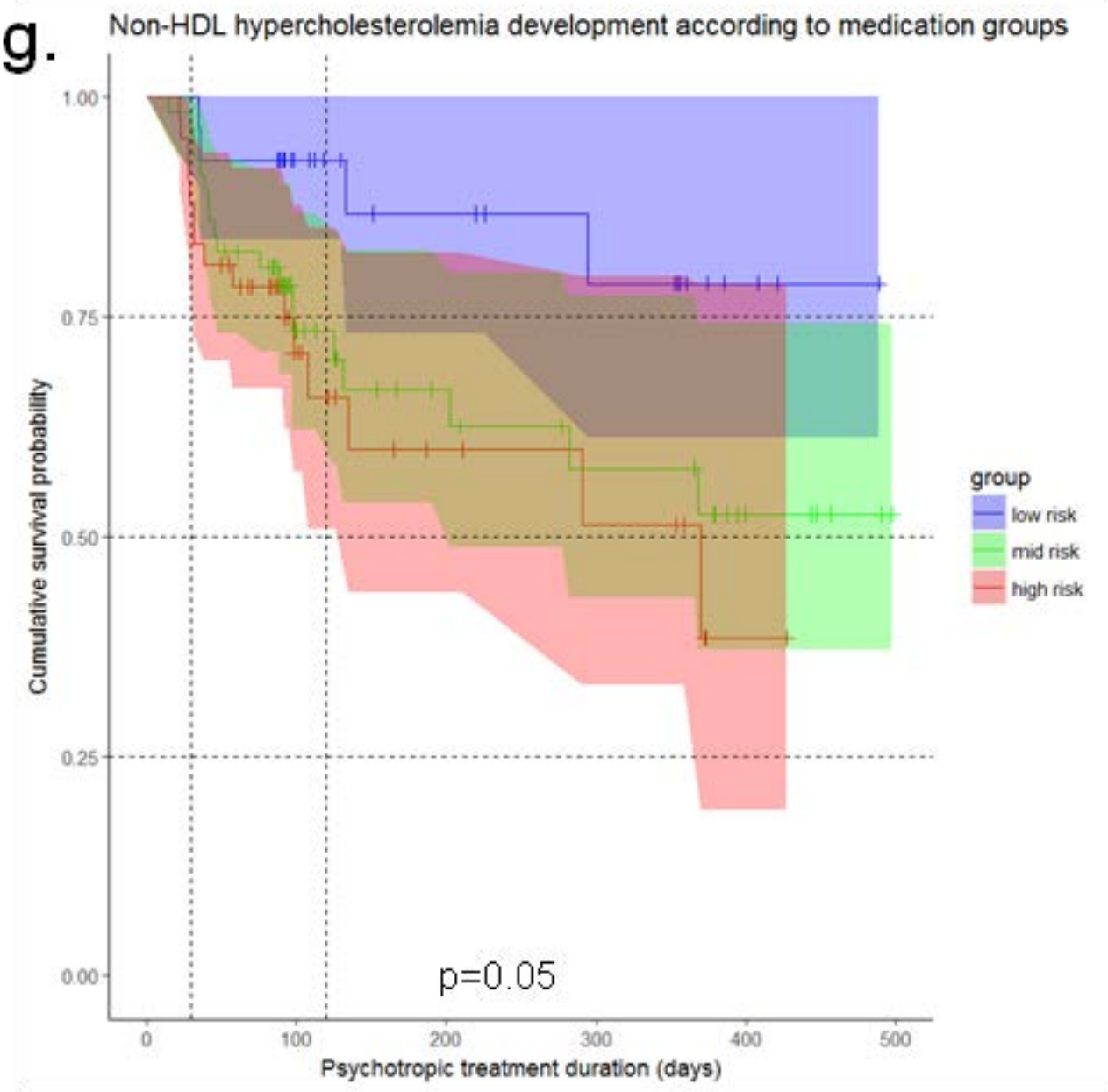
S2 Figure. **Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters**

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



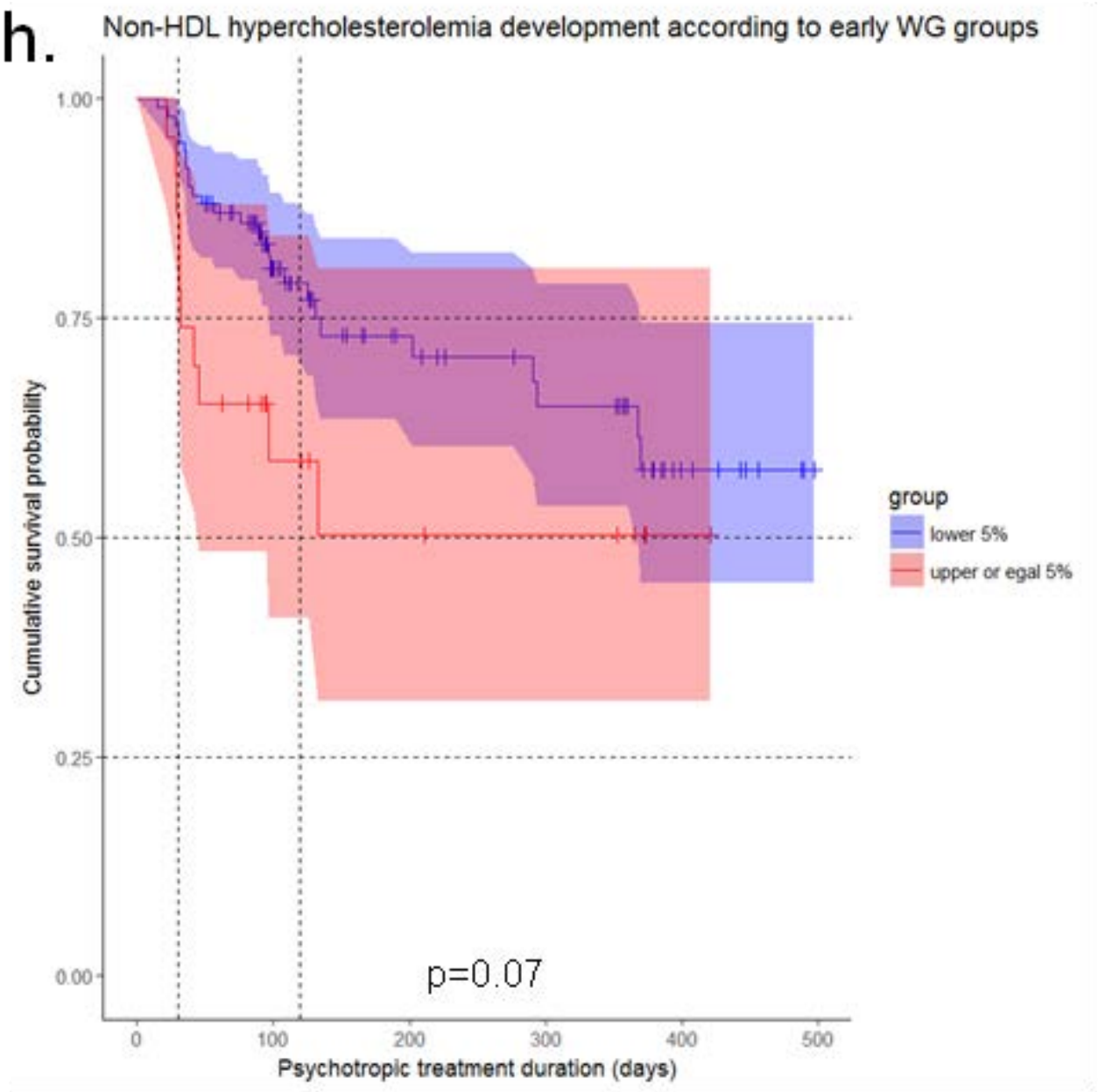
S2 Figure. **Survival curves for new onset dyslipidemia (NOD) by Kaplan-Meier curves according to clinical parameters**

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.

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. 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;130:546-553.

3. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet.* 2014;384:626-635.

4. 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;106:3143-3421.

5. Mancia G, Fagard R, Narkiewicz K, et al. 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). *Journal of hypertension.* 2013;31:1281-1357.

6. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *European heart journal.* 2016;37:2999-3058.

7. Ansermot N, Brawand-Amey M, Kottelat A, Eap CB. Fast quantification of ten psychotropic drugs and metabolites in human plasma by ultra-high performance liquid chromatography tandem mass spectrometry for therapeutic drug monitoring. *Journal of chromatography. A.* 2013;1292:160-172.

8. Choong E, Rudaz S, Kottelat A, Guillarme D, Veuthey JL, Eap CB. Therapeutic drug monitoring of seven psychotropic drugs and four metabolites in human plasma by HPLC-MS. *Journal of pharmaceutical and biomedical analysis.* 2009;50:1000-1008.

9. Gradinaru J, Vullioud A, Eap CB, Ansermot N. Quantification of typical antipsychotics in human plasma by ultra-high performance liquid chromatography tandem mass spectrometry for therapeutic drug monitoring. *Journal of pharmaceutical and biomedical analysis.* 2014;88:36-44.

10. Viswanathan CT, Bansal S, Booth B, et al. Quantitative bioanalytical methods validation and implementation: best practices for chromatographic and ligand binding assays. *Pharmaceutical research.* 2007;24:1962-1973.

11. Hiemke C, Baumann P, Bergemann N, et al. AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011. *Pharmacopsychiatry.* 2011;44:195-235.

12. Pereira MA, Weggemans RM, Jacobs DR, Jr., et al. Within-person variation in serum lipids: implications for clinical trials. *International journal of epidemiology.* 2004;33:534-541.

13. 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;382:951-962.

14. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World psychiatry : official journal of the World Psychiatric Association.* 2015;14:119-136.

15. Vandenberghe F, Gholam-Rezaee M, Saigi-Morgui N, et al. Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment. *The Journal of clinical psychiatry.* 2015;76:e1417-1423.

16. 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;71:1350-1363.

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

DISCUSSION

A substantial inter-individual variation in the therapeutic efficacy and tolerability of psychotropic drugs is observed in psychiatry, which represents a significant challenge for physicians and their patients. Adverse metabolic effects induced by psychotropic drugs are a major source of patients' non adherence (and/or treatment discontinuation), which leads to higher rates of relapse (165, 166). To date, there is still a lack of evidence regarding the consideration of clinical and pharmacogenetic data in psychiatric care, in particular to prevent metabolic side effects induced by psychotropic drugs. The global aim of the present thesis was to improve the current understanding of psychotropic-induced metabolic side effects and to identify the possible clinical and genetic predictors of these adverse effects.

For that purpose, we conducted different projects based on different approaches. Firstly, we examined the influence of tagging SNPs localized in a candidate gene involved in the regulation of food intake, the melanin-concentrating hormone receptor 2 (*MCHR2*), on BMI during treatment with psychotropic drugs. In a second step, we aimed to determine whether population-based genetic variants related to BMI are associated with cardiometabolic phenotype worsening in patients during psychotropic treatment. The two other projects were focused on psychotropic-induced lipid disturbances. Firstly, we investigated whether polygenic risk score combining multiple risk-associated SNPs from two lipid meta-analyses were associated with dyslipidemia-related traits in patients receiving psychotropic drugs. Secondly, in a more clinic-based approach, we investigated the evolution of lipid changes over one year of treatment, and attempted to define how plasma lipid changes during the first month of treatment could predict mid- and long-term plasma lipid changes and new onset dyslipidemia (NOD) in patients taking psychotropic drugs. Of note, we also investigated whether psychotropic drugs could induce methylation changes in candidate genes during the first month of treatment, and to which extent these potential epigenetic modulations were associated with the worsening of cardiometabolic

parameters during psychotropic treatment. In addition, we aimed to use genetic and clinical markers in order to predict early lipid changes during treatment with psychotropic medications.

Since the last decade, the ability to sequence DNA at increasing throughput and decreasing cost has enabled scientists to successfully reveal many genetic variants associated with cardiometabolic parameters in the general population (167) and in patients treated with psychotropic drugs known to induce metabolic disturbances (130, 168). Although GWAS on metabolic traits have been a rich source to determine new pathways and provide new candidate genes, the explained variance of genetics on cardiometabolic phenotypes remains very low (169-173). Thus, it appears that very little of the heritability of cardiometabolic phenotypes has been explained, suggesting that many genetic and epigenetic variants remain to be determined.

In a first step, we conducted a candidate gene approach, i.e. a hypothesis-driven approach. We focused our analysis on *MCHR2*, a receptor involved in the transduction of orexigenic signals, which can be upregulated during treatment with antipsychotics and may probably enhance rewarding aspects of food (69). We determined a significant association between BMI and one variant (i.e. rs7754794) located in the promoter of *MCHR2* and/or of its antisense gene. In addition, this association was also recognized in individuals from the general population suffering from atypical depression, an illness characterized by an improved mood in response to positive events, featuring some symptoms such as an increased appetite, weight gain and hypersomnia (174). It is worth mentioning that no difference of rs7754794 frequency was observed in the atypical depression subgroup of PsyCoLaus as compared to others, suggesting that rs7754794 is not a risk factor for atypical depression but rather for BMI increase during atypical depression. In our research unit, similar hypothesis-driven approaches were used to identify associations between obesity and genetic variants located in other candidate genes (e.g. *HSD11B1*, *PCK1* and *CRTC1* genes (131-133)); (see collaborations in Appendix). Interestingly, the contribution of the latter genetic variants on metabolic phenotypes appeared to be greater in psychiatric patients compared to individuals from the general population, possibly

attributable to the higher prevalence of metabolic abnormalities in the psychiatric population compared to the general population (32), but also to a possible specific synergistic influence of these genetic factors in patients with psychiatric disorders. Thus, it has been hypothesized that psychiatric disorders share common etiological pathways with obesity, suggesting that comorbid obesity and psychiatric diseases have related neurobiological bases (175-177). Another further study on *CRTC1* aimed to investigate whether this gene was associated with major depressive disorder (MDD) and/or with obesity markers in large case-control samples with MDD (178) (see collaborations in Appendix). As for *MCHR2*, *CRTC1* did not seem to play a role in the development of psychiatric diseases, but was rather involved in obesity markers specifically in individuals with MDD (178). By contrast, one example of a shared genetic contributor between metabolic and psychiatric conditions is the well-known gene *FTO*, which was extensively associated with obesity in GWAS (179), and which was also recognized to be associated with major depressive disorder especially in patients suffering from atypical depression, independently of BMI (180-182). To date, data on such shared and/or synergistic genes remain scarce and further genetic studies are warranted to better elucidate the close interaction between psychiatric and metabolic diseases, in particular in diagnostic-stratified studies.

As mentioned above, a growing body of evidence suggests that the influence of genetic factors on metabolic phenotypes in patients suffering from psychiatric diseases seems to be stronger than in healthy controls. On the other hand, some genetic studies have paid attention to the possibility of certain genetic variants to be pleiotropic, meaning that these can be associated with multiple phenotypic traits at once (e.g. obesity, hyperlipidemia, diabetes, hypertension) (169). Given that the power to detect genetic associations with cardiometabolic variables appears particularly high in the psychiatric population (177), we examined whether SNPs previously associated with BMI and other cardiometabolic variables in the general population (170) are associated with the worsening of cardiometabolic phenotypes in a psychiatric population receiving psychotropic treatments known to induce metabolic disturbances. In particular, we aimed to refine underlying mechanisms linking and/or discerning

genetics of BMI with regard to other cardiometabolic comorbidities in the psychiatric population. For that purpose, we used a hierarchical statistical approach to detect SNPs whose impact on cardiometabolic variable deterioration during psychotropic treatment was meaningful, i.e. on TC, HDL, LDL, TG, BMI, waist circumference (WC), fasting glucose (FG), systolic blood pressure (SBP) and diastolic blood pressure (DBP). After some statistical steps fully described in the paper (183), we determined that *SH2B1* rs3888190C>A and *RABEP1* rs1000940A>G were significantly associated with LDL and FG levels, respectively, in two independent psychiatric samples. This study proposed possible mechanisms to explain the novel association of these SNPs with both cardiometabolic variables, which were not observed in population-based samples. The most recent GWAS meta-analysis of BMI including more than 300'000 individuals from the general population observed that although most BMI variants were associated with related cardiometabolic traits in accordance with epidemiological relationships, some BMI-associated variants had effects on other cardiometabolic traits going against biological expectations. To date, cross phenotypic associations going against biological expectations are only poorly understood and many other effects remain to be discovered. In addition, future studies on obesity should preferably focus on body fat percentage rather than on BMI, which is a less accurate marker of overall adiposity (184).

Metabolic diseases arise from a complex interplay between genetic and environmental factors. During the last two decades, many efforts were put into understanding how genetic and environmental factors interact to contribute to the development of cardiometabolic diseases. Recently, epigenetic mechanisms have been proposed to link the genetic background with environmental influences, thus placing significant expectations on their potential to give new insights into the mechanisms underlying cardiometabolic diseases (185). Although different types of epigenetic regulation have been investigated in relation to cardiometabolic diseases (e.g. DNA methylation, histone modification and post-transcriptional silencing mediated by micro-RNAs) (186-188), most efforts have been essentially put on DNA methylation, due in part

to the large number of technical platforms available for analysis (189). A growing number of epigenome-wide studies indicate that BMI and other obesity features are associated with widespread changes in DNA methylation in different tissues (188, 190-193). Besides, environmental factors such as smoking, diet, physical exercise, environmental toxins and certain drugs are known to promote substantial changes in DNA methylation (194-204). In the psychiatric population, DNA methylation changes in different genes and tissues have been recognized in patients treated with psychotropic drugs, including atypical antipsychotics (73-75) and mood stabilizers (76-78), giving insights into possible mechanisms underlying the side effects of these drugs. Recently, some studies observed a relationship between the use of second generation antipsychotics, insulin resistance and global DNA methylation (81, 82). However, to the best of our knowledge, no prospective study has been performed yet in psychiatric patients receiving psychotropic drugs. In the epigenetic project, we aimed to better understand epigenetic mechanisms underlying metabolic adverse effects induced by psychotropic drugs. In particular, methylation analyses were conducted in DNA extracted from blood samples drawn before the initiation of psychotropic drug and after the first month of treatment, in 96 candidate methylation sites, using each patient as his own control. During the first month of psychotropic treatment, significant methylation decreases in 4 methylation sites localized in different candidate genes (i.e. *SP110*, *NR3C2*, *IRS2* and *CRTC1*) were determined. In particular, during the first month of treatment, *CRTC1* CpG319 decrease was associated with BMI increase. However, whether BMI increase resulted from psychotropic-driven methylation decrease or conversely (i.e. methylation decrease resulted from psychotropic-drug induced BMI increase) remains to be determined. Such a causal inference could be conducted in future studies using mendelian randomization, a recently proposed tool which can be used in this sort of analysis (205). Besides, in order to test the validity of our GoldenGate Genotyping VeraCode Technology-derived methylation results, *CRTC1* CpG319 was assessed using another technique considered as the gold-standard for methylation analyses, namely pyrosequencing. Unfortunately, methylation values observed using pyrosequencing were totally inconsistent with

those obtained with the GoldenGate Genotyping VeraCode Technology Assay. Since all quality controls were adequate in results obtained using the GoldenGate VeraCode Technology, one hypothesis that might explain these discrepancies is that the detected signal resulted from a combination of multiple signals in the genome, suggesting that the probe used for these analyses was not specific enough. This hypothesis is in accordance with one study which recognized some limitations of methylation arrays from Illumina, such as a suboptimal probe design (e.g. probes hybridizing to multiple map adresses) (206). In spite of this, in accordance with results observed using the GoldenGate Genotyping VeraCode Technology, results from pyrosequencing analyses also showed a trend of association between the *CRTC1* SNP previously associated BMI (i.e. rs3746266A>G) and *CRTC1* CpG319, located only 10 base pairs apart, in line with the literature showing associations between some methylation sites and certain SNPs in their close proximity (207, 208). It is worth noting that this trend was also observed in samples from adipose tissue, which sounds promising regarding the possible use of blood samples as a peripheral biomarker, at least for the present methylation site. However, as these results are only preliminary, they will be confirmed (or infirmed) in the future by using the Infinium MethylationEPIC Array of Illumina, an assay including more than 850'000 methylation sites. *CRTC1* methylation sites (n=44 in 450K) will be analysed in order to better understand to which extent *CRTC1* is epigenetically modulated following psychotropic treatment and to understand the biological mechanisms underlying this possible influence (funds obtained, study in preparation). Globally, the contribution of epigenetic mechanisms in the development of cardiometabolic diseases is an exciting, yet complex, field of research. A growing number of prospective studies are now emerging, which will help better understand to which extent epigenetic mechanisms are involved in the pathophysiology of cardiometabolic diseases, specifically in patients taking psychotropic treatments known to induce metabolic abnormalities.

Metabolic diseases are polygenic diseases resulting from multiple contributing genetic variants, which have shown minor effects on metabolic phenotypes when considered

individually. In order to grasp the overall picture of the contribution of genetic factors in cardiometabolic phenotype worsening during psychotropic treatments, one approach would entail a combination of all contributing genetic risk factors into one single parameter. Thus, combining data from numerous SNPs in the construction of a polygenic risk score (PRS) would allow a better integration of these numerous nominal effects (139). While several PRS were identified to be associated with obesity, diabetes and dyslipidemia in population-based studies (140-142), associations between PRS and these metabolic conditions among the psychiatric population have never been established. Our research group recently demonstrated that PRS (combining 52 polymorphisms associated with BMI) was shown to be significantly associated with BMI increase in psychiatric patients taking psychotropic treatment (142); see collaborations in Appendix. Similarly, the aim of the third project was to investigate whether PRS combining multiple risk-associated SNPs from two lipid meta-analyses (137, 138) were associated with lipid traits (i.e. HDL, LDL, TC and TG) in patients taking psychotropic drugs known to induce worsening of metabolic parameters. In the present study, we observed that genetic variants from population-based PRS had significant influence on lipid levels in the psychiatric population. Thus, genetics alone explained 4.3%, 3.4%, 3.3% and 4.8% of the total variability of HDL (73 SNPs), LDL (60 SNPs), TC (72 SNPs) and TG (47 SNPs), respectively. Compared to the previously reported explained variability of BMI-associated SNP on BMI (i.e. 2%; see collaborations in Appendix (142), these values are higher, in agreement with previous genetic studies showing a greater contribution of genetics on lipid levels than on BMI (138, 170). However, in the general population, polygenic risk scores constructed using lipid-associated SNPs explained 6.6%, 5.7%, 8.2% and 5.0% for the variance of HDL, LDL, TC and TG respectively (209), which seems higher than in the present psychiatric sample. This difference can be explained by a lower number of patients in our psychiatric sample but also by the use of inappropriate allele estimates. Thus, population-based estimates could either under- or over-represent the influence of some SNPs in the psychiatric population, which may flatten explained variability. As a matter of fact, the psychiatric population displays a greater influence of some

genetic variants on metabolic features in comparison to the general population, possibly because of an intricate interaction between the psychiatric illness and metabolic regulation (178, 210), as well as a higher prevalence of metabolic abnormalities in this specific population (211). As a consequence, a PRS constructed with estimates from psychiatric samples would be more pertinent and would certainly enhance the explained variability of genetics in this high-risk population. Unfortunately, no GWAS on lipid traits has been performed in the psychiatric population yet. Hence, results from this project underline the need to conduct GWAS in psychiatric patients in order to get more accurate estimates for the construction of more adequate polygenic risk scores. Although some questions remain about the eventual clinical utility of polygenic risk scores, new ways to combine polygenic risk scores with other traditional risk factors (e.g. clinical) may prove to be beneficial.

The clinical project of the present thesis aimed to calculate the predictive power of early (i.e. after one month) modifications of lipid levels on further (i.e. after 3 months) changes of lipid levels. In our psychiatric sample, increases of 5% for TC, LDL and TG (and decrease for HDL) were found to be the best predictors for important lipid changes after 3 and 12 months of psychotropic treatment. The negative predictive value observed for TG was in agreement with findings from the only other predictive study previously conducted on lipid levels, which recognized that patients with low triglyceride increase during the first month of treatment (i.e. less than 20 mg/dl (corresponding to 0.22 mmol/l) after 6 to 12 weeks) did not have a substantial triglyceride increase after 24 to 28 weeks of treatment with haloperidol, olanzapine or risperidone (212). Taken together, results from the present study emphasize the importance of metabolic monitoring in patients receiving psychotropic treatments known to induce metabolic disturbances. Because clinicians have been found to have a poor adherence to these guidelines worldwide (213), there is a need for programs to help educate providers and to facilitate monitoring of these cardiometabolic risk factors. To date, no consensus has been established among clinicians with regard to thresholds of lipid increase that would need a reconsideration of

the psychotropic treatment. Nevertheless, recent guidelines from the European Society of Cardiology and European Atherosclerosis Society were proposed for the management of dyslipidemia in patients receiving antipsychotics (214). These recommendations emphasize the importance of starting primary prevention earlier rather than later in psychiatric patients receiving psychotropic medication associated with metabolic disturbances (215). In addition, a study investigating cardiometabolic risks in first-episode schizophrenic patients showed that only a small proportion of patients with dyslipidemia were treated with lipid-lowering agent, underlining poor access to health care and an under-recognition of lipid abnormalities (216), consistent with some other studies from Mitchell and collaborators (20, 213, 217) and with the low proportion (i.e. less than 10%) of patients with hyperlipidemia who receive lipid-lowering drugs in our present psychiatric sample. In the present study, patients with baseline hypercholesterolemia appeared to be less prone to have ≥ 5% early increase of TC, LDL, TG or decrease of HDL during the first month, in comparison to patients who did not have baseline hypercholesterolemia. These results are in agreement with those reported for early WG (i.e. where baseline obese patients were less prone to have a strong and rapid WG during the first month of treatment than leaner patients (218); (see collaborations in Appendix)). In order to better understand to which extent early lipid levels could potentially predict an important WG during the first year of psychotropic treatment, as well as the reverse (i.e. to which extent an early WG could predict important lipid changes during the first year of treatment), further predictive analyses were conducted. These additional analyses showed that patients with early LDL, TC and TG increase of ≥5% had a significantly higher WG over one year of treatment (by approximately 3%; p≤0.007) compared to those who had an early LDL, TC and TG increase of <5% (data not shown). However, the observed difference of WG appears clinically marginal, indicating that, compared to early lipid predictors, the early WG predictor is a better indicator to predict subsequent important WG. Conversely, patients with early WG ≥5% had higher HDL decrease (9%; p=0.004) compared to others during the long term psychotropic treatment (no difference was however observed for TC, LDL and TG increase). The above-mentioned results

are in agreement with the reported kinetics of the different metabolic variables during psychotropic treatment (haloperidol, risperidone or olanzapine) in patients with a first treated psychotic episode (219). The latter study observed that weight and levels of TC, LDL and TG significantly increased during the first year of treatment whereas HDL levels only started to decrease after the first year of treatment (219).

The identification of at-risk patients before the initiation of a psychotropic drug, based on individual susceptibilities, would be even more pertinent for personalized medicine. In the last project, we aimed to combine genetic and clinical risk factors to predict, before initiating the psychotropic treatment, patients who are at high risk for developing important increase of lipid levels and/or dyslipidemia (i.e. patients with ≥5% early TC, LDL and TG increase and HDL decrease). Genetic variants associated with lipid levels in GWAS meta-analyses from the general population were retained in the final predictive model if they contributed to the variance of linear mixed models, using a statistical method described in the project. Preliminary results showed that adding genetic to clinical factors significantly increased the prediction of a ≥5% early TC, LDL and TG increase and HDL decrease by approximately 20%. Analyses are underway to test the present findings for replication in an independent psychiatric sample. Of note, because no GWAS has been performed yet on the genetic determinants of a 5% increase of lipid levels, no estimates were available to construct a polygenic risk score.

The results of the projects presented in the scope of this thesis need to be evaluated with some limitations. First, projects including genetic analyses were restricted to Caucasian patients. Second, effects of environmental changes such as physical exercise or diet habits throughout the treatment, which could have influenced the evolution of metabolic features, were not available and therefore not taken into account. Third, a considerable drop-out rate was observed during the prospective study, reducing the number of available observations after one year of treatment, possibly due to psychiatry-related factors such as treatment switching, poor medication compliance and/or the refusal of outpatients to be followed-up. Fourth, in both cross-

sectional studies (i.e. *Etude Ambulatoire* and *Etude Poids Genève*), initial weights (i.e. before the introduction of the psychotropic treatment) were self-estimated by patients, which may not be accurate. However, it is worth mentioning that, for a subset of patients for whom both self-reported and medical file weights were available, a good concordance between both values was observed (164). In addition, the majority of patients were not drug naïve, and the observed metabolic disturbances may have resulted from past treatments. However, the naturalistic setting of the present studies strengthens the clinical validity of the present findings. In addition, therapeutic drug monitoring was performed to ascertain compliance to exclude false negatives, i.e. patients who did not develop metabolic disturbances because they did not take the drug, which is an important factor to consider in the psychiatric population. Finally, the naturalistic and prospective setting of PsyMetab strengthens the clinical validity of the present findings.

Perspectives

The present work gives new insights into mechanisms underlying psychotropic drug-induced metabolic disturbances and emphasizes the importance of clinical and genetic parameters to predict metabolic side effects in patients receiving these drugs, providing possible steps towards personalized medicine.

In particular, clinically useful values for sensitivity, specificity and accuracy (>70%) were identified using predictive models integrating clinical and/or genetic predictors. For instance, models including both polygenic risk scores and clinical variables indicated that the prediction of HDL hypocholesterolemia was informative and useful enough (220) and that only 24 patients would be needed to be genotyped to avoid HDL hypocholesterolemia for one patient (221). Besides, an early lipid increase during the first month of treatment of ≥ 5% for TC, LDL and TG and an early decrease of ≥ 5% for HDL were identified as best predictors for subsequent important lipid changes after 3 and 12 months of psychotropic treatment. Sensitivities of these early predictors (≥70%) indicated that they allowed the detection of the majority of at-risk

patients. Conversely, the observed high negative predictive values (≥94%) implied that most patients who did not outreach early lipid thresholds did not have neither substantial increase of lipid levels in the longer-term. Finally, models combining clinical and genetic variables to predict early lipid changes of ≥5% displayed high predictive values (i.e. AUC>0.8) and emphasized the additive value of adding genetic in the model, improving accuracy by more than 10%. The aforementioned results seem clinically relevant and should motivate clinicians to consider genetic testing in clinical health care. However, these models should be tested for replication in additional studies with larger sample size before the additive value of including genetic information in predictive models is transposable to routine clinical practice. On the other hand, it must be emphasized that our results show the need to combine clinical with genetic data to increase the accuracy of predictive models.

With improvements in technology, the analysis of multiple genes in a single assay has become more easily available, for considerably lower costs than previously for single gene tests. Thus, costs for genome sequencing have been in continuous free falls since the human genome has been sequenced for the first time in 2003 (which costed roughly $ 2.7 billion and took more than ten years). In 2017, Illumina announced the launch of a new sequencer, called NovaSeq, able to sequence a whole genome for less than $100, within less than one hour. Many scientists have predicted that in the near future, each individual's entire genome will be sequenced, making genetic results available for clinical use and for an optimized health care throughout life (222). Nowadays, the question is therefore shifting from "whether to perform a genetic test" to "how the available genetic results can and should be used for prescribing optimization". Considering the important amount of data we are facing, there is a growing need of consortia to puts efforts into creating evidence-based and publicly available guidelines for prescribers to know how to use genomic data.

Despite an increasing number of tools helping to predict side effects, a trial and error strategy is still commonly used today in clinical practice when prescribing psychotropic drugs. Thus, many barriers hinder the implementation of clinical and pharmacogenetic tools in clinical

settings. For instance, many health care systems do not provide financial reimbursement for preventive medicine or for pre-emptive screening services (223, 224), although the situation has changed recently in Switzerland (225). Although the cost-effectiveness for some drugs has been studied (226), the cost-effectiveness of a panel approach implemented early in life usable for an individual's lifetime has never been established, which impedes reimbursement of systematic pre-emptive genomic testing. In addition, the significant reduction of genotyping costs is counterbalanced by emerging costs associated with genetic result interpretations and their continuous updates, including annotation of additional novel variants (222). Another hurdle of using pharmacogenetic tools in clinical settings is the lack of clinical guidelines for translating genetic variation into actionable recommendations. Finally, other barriers include the willingness of more clinical evidence, the lack of education among clinicians about utility and interpretation of pharmacogenomic tests and logistic barriers (e.g. institutional inertia, automation of clinical decision support in electronic medical record) (227). For the last ten years, many efforts of implementation were made worldwide for improving therapy by integrating pharmacogenetic information into clinical care (228-234). In the near future, genetic tests integrated into comprehensive knowledge of side effects related to psychotropic drugs will hopefully help to intervene earlier to achieve better somatic outcomes.

In parallel, the implementation of metabolic monitoring programs has still to be developed in many institutions. Although the American Diabetes Association and the American Psychiatric Association published a consensus statement including metabolic monitoring guidelines more than ten years ago (235), clinicians have been found to have a poor adherence to them. According to studies conducted between 2000 and 2011 in five countries, only 22% of patients initiating a second-generation antipsychotic received a test for lipid profile (213). Even if local and national guideline implementations helped to significantly increase this disquieting screening rate (up to 37%), rates of testing remained insufficient (213). More recently, another study also concluded that only a minority of psychiatric patients being prescribed psychotropic medications known to induce metabolic side effects was screened for metabolic syndrome in

accordance with best practice recommendations (236). In addition, it has been evaluated that nearly 40% of primary care providers were unaware of consensus guidelines for metabolic monitoring, an alarming rate which should be diminished, partly by putting more efforts into the enforcement of knowledge (237). In our institution, since ten years, many efforts have been made to carry out metabolic monitoring in clinical practice. However, further steps need to be taken in order to improve the early detection of at-risk patients and to define clinical recommendations and procedures for dealing with metabolic disturbances.

With regard to future research projects, an increased number of patients and of observations would enable to examine the evolution of additional pertinent phenotypes during psychotropic treatment. For instance, calculating a cardiovascular risk score (e.g. Framingham risk score (238)), would be useful to determine the likelihood of a patient to develop cardiovascular disease (e.g. coronary heart disease, stroke, peripheral vascular disease, or heart failure) over a fixed time, for example the next 10 years. Because such an algorithm integrates numerous cardiovascular risk factors, i.e. sex, age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking behavior, and diabetes status, such analyses require data fully completed for each of these variables. Furthermore, an increased number of patients would allow performing medication-stratified analyses in order to examine the influence of particular psychotropic drugs on the worsening of metabolic parameters. In the future, many other projects will be conducted in our research group once the number of observations and/or of patients is sufficient.

Finally, complex diseases such as obesity and dyslipidemia arise from a close interplay between genetic and multiple environmental factors. Ongoing and future whole-genome sequencing studies will help to identify additional common and rare variants associated with these diseases. In addition, the influence of other sources of variability including other genetic (e.g. copy number variants) or epigenetic factors (e.g. histone acetylation, DNA methylation and microRNA) should be integrated in future predictive models. Last but not least, multiple “omic” techniques, including transcriptomics, epigenomics, proteomics, metabolomics and/or

microbiomics, also recently emerged as possible predictors of complex diseases (213). Future studies integrating the combination of such variables will need to develop complex statistical algorithms in order to further refine the prediction of metabolic side effects induced by psychotropic drugs.

To conclude, over the last decades, substantial improvements have been achieved in medical science. To date, many efforts remain to be made before personalized medicine can be applied in routine care, in particular for patients suffering from complex diseases. The emergence of new “omic” techniques holds the promise of providing new steps towards personalized medicine.

REFERENCES

1. Lopez-Munoz F, Alamo C, Cuenca E, Shen WW, Clervoy P, Rubio G. History of the discovery and clinical introduction of chlorpromazine. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists. 2005;17(3):113-35.
2. Meltzer HY, Alphs LD, Bastani B, Ramirez LF, Kwon K. Clinical efficacy of clozapine in the treatment of schizophrenia. Pharmacopsychiatry. 1991;24(2):44-5.
3. Stahl SM. Stahl's Essential Psychopharmacology - Neuroscientific Basis and Practical Applications. New York: Cambridge University Press; 2008. 1-1057 p.
4. Tarsy D, Baldessarini RJ. The pathophysiologic basis of tardive dyskinesia. Biological psychiatry. 1977;12(3):431-50.
5. Bostwick JR, Guthrie SK, Ellingrod VL. Antipsychotic-induced hyperprolactinemia. Pharmacotherapy. 2009;29(1):64-73.
6. Kusumi I, Boku S, Takahashi Y. Psychopharmacology of atypical antipsychotic drugs: From the receptor binding profile to neuroprotection and neurogenesis. Psychiatry and clinical neurosciences. 2015;69(5):243-58.
7. Schotte A, Bonaventure P, Janssen PF, Leysen JE. In vitro receptor binding and in vivo receptor occupancy in rat and guinea pig brain: risperidone compared with antipsychotics hitherto used. Japanese journal of pharmacology. 1995;69(4):399-412.
8. Schotte A, Janssen PF, Gommeren W, Luyten WH, Van Gompel P, Lesage AS, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology. 1996;124(1-2):57-73.
9. Horacek J, Bubenikova-Valesova V, Kopecek M, Palenicek T, Dockery C, Mohr P, et al. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. CNS drugs. 2006;20(5):389-409.
10. Abbas AI, Hedlund PB, Huang XP, Tran TB, Meltzer HY, Roth BL. Amisulpride is a potent 5-HT7 antagonist: relevance for antidepressant actions in vivo. Psychopharmacology. 2009;205(1):119-28.
11. Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2003;28(8):1400-11.
12. Gross G, Drescher K. The role of dopamine D(3) receptors in antipsychotic activity and cognitive functions. Handbook of experimental pharmacology. 2012(213):167-210.
13. Roth BL, Craigo SC, Choudhary MS, Uluer A, Monsma FJ, Jr., Shen Y, et al. Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. The Journal of pharmacology and experimental therapeutics. 1994;268(3):1403-10.
14. Schmidt AW, Lebel LA, Howard HR, Jr., Zorn SH. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. European journal of pharmacology. 2001;425(3):197-201.
15. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World psychiatry : official journal of the World Psychiatric Association. 2015;14(2):119-36.
16. 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):334-41.
17. Gracious BL, Cook SR, Meyer AE, Chirieac MC, Malhi N, Fischetti AT, et al. Prevalence of overweight and obesity in adolescents with severe mental illness: a cross-sectional chart review. The Journal of clinical psychiatry. 2010;71(7):949-54.
18. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Archives of general psychiatry. 2010;67(3):220-9.

19. Cerimele JM, Katon WJ. Associations between health risk behaviors and symptoms of schizophrenia and bipolar disorder: a systematic review. General hospital psychiatry. 2013;35(1):16-22.
20. De Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World psychiatry : official journal of the World Psychiatric Association. 2011;10(1):52-77.
21. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373(9657):31-41.
22. Parsons B, Allison DB, Loebel A, Williams K, Giller E, Romano S, et al. Weight effects associated with antipsychotics: a comprehensive database analysis. Schizophrenia research. 2009;110(1-3):103-10.
23. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. PloS one. 2014;9(4):e94112.
24. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951-62.
25. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nature reviews Endocrinology. 2012;8(2):114-26.
26. Hasnain M, Vieweg WV, Hollett B. Weight gain and glucose dysregulation with second-generation antipsychotics and antidepressants: a review for primary care physicians. Postgraduate medicine. 2012;124(4):154-67.
27. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379(9817):721-8.
28. Peselow ED, Dunner DL, Fieve RR, Lautin A. Lithium carbonate and weight gain. Journal of affective disorders. 1980;2(4):303-10.
29. Vendsborg PB, Bech P, Rafaelsen OJ. Lithium treatment and weight gain. Acta psychiatrica Scandinavica. 1976;53(2):139-47.
30. Verrotti A, D'Egidio C, Mohn A, Coppola G, Chiarelli F. Weight gain following treatment with valproic acid: pathogenetic mechanisms and clinical implications. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2011;12(5):e32-43.
31. Laimer M, Kramer-Reinstadler K, Rauchenzauner M, Lechner-Schoner T, Strauss R, Engl J, et al. Effect of mirtazapine treatment on body composition and metabolism. The Journal of clinical psychiatry. 2006;67(3):421-4.
32. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World psychiatry : official journal of the World Psychiatric Association. 2015;14(3):339-47.
33. Pramyothin P, Khaodhiar L. Metabolic syndrome with the atypical antipsychotics. Current opinion in endocrinology, diabetes, and obesity. 2010;17(5):460-6.
34. Chadda RK, Ramshankar P, Deb KS, Sood M. Metabolic syndrome in schizophrenia: Differences between antipsychotic-naive and treated patients. Journal of pharmacology & pharmacotherapeutics. 2013;4(3):176-86.
35. Papanastasiou E. The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. Therapeutic advances in psychopharmacology. 2013;3(1):33-51.
36. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. Schizophrenia bulletin. 2013;39(2):306-18.
37. Olfson M, Marcus SC, Corey-Lisle P, Tuomari AV, Hines P, L'Italien GJ. Hyperlipidemia following treatment with antipsychotic medications. The American journal of psychiatry. 2006;163(10):1821-5.
38. Vancampfort D, Vansteelandt K, Correll CU, Mitchell AJ, De Herdt A, Sienaert P, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. The American journal of psychiatry. 2013;170(3):265-74.

39. Vancampfort D, Correll CU, Wampers M, Sienaert P, Mitchell AJ, De Herdt A, et al. Metabolic syndrome and metabolic abnormalities in patients with major depressive disorder: a meta-analysis of prevalences and moderating variables. Psychological medicine. 2014;44(10):2017-28.
40. McIntyre RS, Soczynska JK, Konarski JZ, Kennedy SH. The effect of antidepressants on lipid homeostasis: a cardiac safety concern? Expert opinion on drug safety. 2006;5(4):523-37.
41. McIntyre RS, McElroy SL, Eudicone JM, Forbes RA, Carlson BX, Baker RA. A 52-week, double-blind evaluation of the metabolic effects of aripiprazole and lithium in bipolar I disorder. The primary care companion for CNS disorders. 2011;13(6).
42. Ezzaher A, Haj Mouhamed D, Mechri A, Neffati F, Douki W, Gaha L, et al. Thyroid function and lipid profile in bipolar I patients. Asian journal of psychiatry. 2011;4(2):139-43.
43. Calandre EP, Rodriquez-Lopez C, Blazquez A, Cano D. Serum lipids, lipoproteins and apolipoproteins A and B in epileptic patients treated with valproic acid, carbamazepine or phenobarbital. Acta neurologica Scandinavica. 1991;83(4):250-3.
44. Elmslie JL, Porter RJ, Joyce PR, Hunt PJ, Shand BI, Scott RS. Comparison of insulin resistance, metabolic syndrome and adiponectin in overweight bipolar patients taking sodium valproate and controls. The Australian and New Zealand journal of psychiatry. 2009;43(1):53-60.
45. Chang HH, Yang YK, Gean PW, Huang HC, Chen PS, Lu RB. The role of valproate in metabolic disturbances in bipolar disorder patients. Journal of affective disorders. 2010;124(3):319-23.
46. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nature reviews Endocrinology. 2011;8(2):114-26.
47. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. Jama. 2009;302(16):1765-73.
48. Cai HL, Tan QY, Jiang P, Dang RL, Xue Y, Tang MM, et al. A potential mechanism underlying atypical antipsychotics-induced lipid disturbances. Translational psychiatry. 2015;5:e661.
49. Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, McEvoy JP, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. The American journal of psychiatry. 2003;160(2):290-6.
50. 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 Arch Psychiatry. 2014;26(6):339-46.
51. Birkenaes AB, Birkeland KI, Engh JA, Faerden A, Jonsdottir H, Ringen PA, et al. Dyslipidemia independent of body mass in antipsychotic-treated patients under real-life conditions. Journal of clinical psychopharmacology. 2008;28(2):132-7.
52. Yood MU, DeLorenze G, Quesenberry CP, Jr., Oliveria SA, Tsai AL, Willey VJ, et al. The incidence of diabetes in atypical antipsychotic users differs according to agent--results from a multisite epidemiologic study. Pharmacoepidemiology and drug safety. 2009;18(9):791-9.
53. Ballon JS, Pajvani U, Freyberg Z, Leibel RL, Lieberman JA. Molecular pathophysiology of metabolic effects of antipsychotic medications. Trends in endocrinology and metabolism: TEM. 2014;25(11):593-600.
54. Albaugh VL, Singareddy R, Mauger D, Lynch CJ. A double blind, placebo-controlled, randomized crossover study of the acute metabolic effects of olanzapine in healthy volunteers. PloS one. 2011;6(8):e22662.
55. Teff KL, Rickels MR, Grudziak J, Fuller C, Nguyen HL, Rickels K. Antipsychotic-induced insulin resistance and postprandial hormonal dysregulation independent of weight gain or psychiatric disease. Diabetes. 2013;62(9):3232-40.
56. Bhattacharjee S, Bhattacharya R, Kelley GA, Sambamoorthi U. Antidepressant use and new-onset diabetes: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2013;29(4):273-84.
57. Chien IC, Wu EL, Lin CH, Chou YJ, Chou P. Prevalence of diabetes in patients with major depressive disorder: a population-based study. Comprehensive psychiatry. 2012;53(5):569-75.

58. Belcastro V, D'Egidio C, Striano P, Verrotti A. Metabolic and endocrine effects of valproic acid chronic treatment. Epilepsy research. 2013;107(1-2):1-8.
59. Cuerda C, Velasco C, Merchan-Naranjo J, Garcia-Peris P, Arango C. The effects of second-generation antipsychotics on food intake, resting energy expenditure and physical activity. European journal of clinical nutrition. 2014;68(2):146-52.
60. Bonhaus DW, Weinhardt KK, Taylor M, DeSouza A, McNeeley PM, Szczepanski K, et al. RS-102221: a novel high affinity and selective, 5-HT2C receptor antagonist. Neuropharmacology. 1997;36(4-5):621-9.
61. Kring SI, Werge T, Holst C, Toubro S, Astrup A, Hansen T, et al. Polymorphisms of serotonin receptor 2A and 2C genes and COMT in relation to obesity and type 2 diabetes. PloS one. 2009;4(8):e6696.
62. Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Muller DJ. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. Molecular psychiatry. 2012;17(3):242-66.
63. Stahl SM, Shayegan DK. The psychopharmacology of ziprasidone: receptor-binding properties and real-world psychiatric practice. The Journal of clinical psychiatry. 2003;64 Suppl 19:6-12.
64. Orthen-Gambill N. Antihistaminic drugs increase feeding, while histidine suppresses feeding in rats. Pharmacology, biochemistry, and behavior. 1988;31(1):81-6.
65. Navarro-Badenes J, Martinez-Mir I, Palop V, Rubio E, Morales-Olivas FJ. Weight gain associated with cinnarizine. The Annals of pharmacotherapy. 1992;26(7-8):928-30.
66. Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2003;28(3):519-26.
67. Deng C. Effects of antipsychotic medications on appetite, weight, and insulin resistance. Endocrinology and metabolism clinics of North America. 2013;42(3):545-63.
68. Balt SL, Galloway GP, Baggott MJ, Schwartz Z, Mendelson J. Mechanisms and genetics of antipsychotic-associated weight gain. Clinical pharmacology and therapeutics. 2011;90(1):179-83.
69. Guesdon B, Denis RG, Richard D. Additive effects of olanzapine and melanin-concentrating hormone agonism on energy balance. Behavioural brain research. 2010;207(1):14-20.
70. Weston-Green K, Huang XF, Deng C. Alterations to melanocortinergic, GABAergic and cannabinoid neurotransmission associated with olanzapine-induced weight gain. PloS one. 2012;7(3):e33548.
71. Stip E, Lungu OV, Anselmo K, Letourneau G, Mendrek A, Stip B, et al. Neural changes associated with appetite information processing in schizophrenic patients after 16 weeks of olanzapine treatment. Translational psychiatry. 2012;2:e128.
72. Potvin S, Zhornitsky S, Stip E. Antipsychotic-induced changes in blood levels of leptin in schizophrenia: a meta-analysis. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2015;60(3 Suppl 2):S26-34.
73. Melka MG, Laufer BI, McDonald P, Castellani CA, Rajakumar N, O'Reilly R, et al. The effects of olanzapine on genome-wide DNA methylation in the hippocampus and cerebellum. Clinical epigenetics. 2014;6(1):1.
74. Dong E, Nelson M, Grayson DR, Costa E, Guidotti A. Clozapine and sulpiride but not haloperidol or olanzapine activate brain DNA demethylation. Proceedings of the National Academy of Sciences of the United States of America. 2008;105(36):13614-9.
75. Sugawara H, Bundo M, Asai T, Sunaga F, Ueda J, Ishigooka J, et al. Effects of quetiapine on DNA methylation in neuroblastoma cells. Progress in neuro-psychopharmacology & biological psychiatry. 2015;56:117-21.
76. Asai T, Bundo M, Sugawara H, Sunaga F, Ueda J, Tanaka G, et al. Effect of mood stabilizers on DNA methylation in human neuroblastoma cells. The international journal of neuropsychopharmacology

/ official scientific journal of the Collegium Internationale Neuropsychopharmacologicum. 2013;16(10):2285-94.
77. D'Addario C, Dell'Osso B, Palazzo MC, Benatti B, Lietti L, Cattaneo E, et al. Selective DNA methylation of BDNF promoter in bipolar disorder: differences among patients with BDI and BDII. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2012;37(7):1647-55.
78. Milutinovic S, D'Alessio AC, Detich N, Szyf M. Valproate induces widespread epigenetic reprogramming which involves demethylation of specific genes. Carcinogenesis. 2007;28(3):560-71.
79. Seo MS, Scarr E, Lai CY, Dean B. Potential molecular and cellular mechanism of psychotropic drugs. Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology. 2014;12(2):94-110.
80. Melas PA, Rogdaki M, Osby U, Schalling M, Lavebratt C, Ekstrom TJ. Epigenetic aberrations in leukocytes of patients with schizophrenia: association of global DNA methylation with antipsychotic drug treatment and disease onset. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2012;26(6):2712-8.
81. Burghardt KJ, Goodrich JM, Dolinoy DC, Ellingrod VL. Gene-specific DNA methylation may mediate atypical antipsychotic-induced insulin resistance. Bipolar disorders. 2016;18(5):423-32.
82. Burghardt KJ, Goodrich JM, Dolinoy DC, Ellingrod VL. DNA methylation, insulin resistance and second-generation antipsychotics in bipolar disorder. Epigenomics. 2015;7(3):343-52.
83. Gardiner E, Carroll A, Tooney PA, Cairns MJ. Antipsychotic drug-associated gene-miRNA interaction in T-lymphocytes. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum. 2014;17(6):929-43.
84. Zhou R, Yuan P, Wang Y, Hunsberger JG, Elkahloun A, Wei Y, et al. Evidence for selective microRNAs and their effectors as common long-term targets for the actions of mood stabilizers. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2009;34(6):1395-405.
85. Chen H, Wang N, Burmeister M, McInnis MG. MicroRNA expression changes in lymphoblastoid cell lines in response to lithium treatment. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum. 2009;12(7):975-81.
86. Hunsberger JG, Fessler EB, Chibane FL, Leng Y, Maric D, Elkahloun AG, et al. Mood stabilizer-regulated miRNAs in neuropsychiatric and neurodegenerative diseases: identifying associations and functions. American journal of translational research. 2013;5(4):450-64.
87. Bocchio-Chiavetto L, Maffioletti E, Bettinsoli P, Giovannini C, Bignotti S, Tardito D, et al. Blood microRNA changes in depressed patients during antidepressant treatment. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2013;23(7):602-11.
88. Teff KL, Rickels K, Alshehabi E, Rickels MR. Metabolic Impairments Precede Changes in Hunger and Food Intake Following Short-Term Administration of Second-Generation Antipsychotics. Journal of clinical psychopharmacology. 2015;35(5):579-82.
89. Newcomer JW, Haupt DW, Fucetola R, Melson AK, Schweiger JA, Cooper BP, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. Archives of general psychiatry. 2002;59(4):337-45.
90. Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. Archives of general psychiatry. 2005;62(1):19-28.
91. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. Trends in molecular medicine. 2011;17(2):97-107.

92. Amemiya-Kudo M, Shimano H, Hasty AH, Yahagi N, Yoshikawa T, Matsuzaka T, et al. Transcriptional activities of nuclear SREBP-1a, -1c, and -2 to different target promoters of lipogenic and cholesterogenic genes. Journal of lipid research. 2002;43(8):1220-35.
93. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. The Journal of clinical investigation. 2002;109(9):1125-31.
94. Oh KJ, Park J, Lee SY, Hwang I, Kim JB, Park TS, et al. Atypical antipsychotic drugs perturb AMPK-dependent regulation of hepatic lipid metabolism. American journal of physiology Endocrinology and metabolism. 2011;300(4):E624-32.
95. Lauressergues E, Staels B, Valeille K, Majd Z, Hum DW, Duriez P, et al. Antipsychotic drug action on SREBPs-related lipogenesis and cholesterogenesis in primary rat hepatocytes. Naunyn-Schmiedeberg's archives of pharmacology. 2010;381(5):427-39.
96. Ferno J, Raeder MB, Vik-Mo AO, Skrede S, Glambek M, Tronstad KJ, et al. Antipsychotic drugs activate SREBP-regulated expression of lipid biosynthetic genes in cultured human glioma cells: a novel mechanism of action? The pharmacogenomics journal. 2005;5(5):298-304.
97. Polymeropoulos MH, Licamele L, Volpi S, Mack K, Mitkus SN, Carstea ED, et al. Common effect of antipsychotics on the biosynthesis and regulation of fatty acids and cholesterol supports a key role of lipid homeostasis in schizophrenia. Schizophrenia research. 2009;108(1-3):134-42.
98. Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Serum leptin and triglyceride levels in patients on treatment with atypical antipsychotics. The Journal of clinical psychiatry. 2003;64(5):598-604.
99. Yang Z, Yin JY, Gong ZC, Huang Q, Chen H, Zhang W, et al. Evidence for an effect of clozapine on the regulation of fat-cell derived factors. Clinica chimica acta; international journal of clinical chemistry. 2009;408(1-2):98-104.
100. Adachi H, Yanai H, Hirowatari Y. The Underlying Mechanisms for Olanzapine-induced Hypertriglyceridemia. Journal of clinical medicine research. 2012;4(3):206-8.
101. Yan H, Chen JD, Zheng XY. Potential mechanisms of atypical antipsychotic-induced hypertriglyceridemia. Psychopharmacology. 2013;229(1):1-7.
102. Horie S, Suga T. Enhancement of peroxisomal beta-oxidation in the liver of rats and mice treated with valproic acid. Biochemical pharmacology. 1985;34(9):1357-62.
103. Holt RI, Mitchell AJ. Diabetes mellitus and severe mental illness: mechanisms and clinical implications. Nature reviews Endocrinology. 2015;11(2):79-89.
104. Al-Zoairy R, Ress C, Tschoner A, Kaser S, Ebenbichler C. The effects of psychotropic drugs on the regulation of glucose metabolism. Current diabetes reviews. 2013;9(5):362-70.
105. Starrenburg FC, Bogers JP. How can antipsychotics cause Diabetes Mellitus? Insights based on receptor-binding profiles, humoral factors and transporter proteins. European psychiatry : the journal of the Association of European Psychiatrists. 2009;24(3):164-70.
106. Miron IC, Baroana VC, Popescu F, Ionica F. Pharmacological mechanisms underlying the association of antipsychotics with metabolic disorders. Current health sciences journal. 2014/05/03 ed2014. p. 12-7.
107. Coccurello R, Moles A. Potential mechanisms of atypical antipsychotic-induced metabolic derangement: clues for understanding obesity and novel drug design. Pharmacology & therapeutics. 2010;127(3):210-51.
108. Strassnig M, Miewald J, Keshavan M, Ganguli R. Weight gain in newly diagnosed first-episode psychosis patients and healthy comparisons: one-year analysis. Schizophrenia research. 2007;93(1-3):90-8.
109. Vandenberghe F, Gholam-Rezaee M, Saigi-Morgui N, Delacretaz A, Choong E, Solida-Tozzi A, et al. Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment. The Journal of clinical psychiatry. 2015;76(11):e1417-23.
110. Hiemke C, Shams M. Phenotyping and genotyping of drug metabolism to guide pharmacotherapy in psychiatry. Current drug delivery. 2013;10(1):46-53.

111. Vehof J, Burger H, Wilffert B, Al Hadithy A, Alizadeh BZ, Snieder H. Clinical response to antipsychotic drug treatment: association study of polymorphisms in six candidate genes. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2012;22(9):625-31.
112. Eum S, Lee AM, Bishop JR. Pharmacogenetic tests for antipsychotic medications: clinical implications and considerations. Dialogues in clinical neuroscience. 2016;18(3):323-37.
113. Eap CB. Personalized prescribing: a new medical model for clinical implementation of psychotropic drugs. Dialogues in clinical neuroscience. 2016;18(3):313-22.
114. Fleeman N, Dundar Y, Dickson R, Jorgensen A, Pushpakom S, McLeod C, et al. Cytochrome P450 testing for prescribing antipsychotics in adults with schizophrenia: systematic review and meta-analyses. The pharmacogenomics journal. 2011;11(1):1-14.
115. Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. The Journal of clinical psychiatry. 2009;70(7):1041-50.
116. de Leon J, Diaz FJ, Josiassen RC, Cooper TB, Simpson GM. Weight gain during a double-blind multidosage clozapine study. Journal of clinical psychopharmacology. 2007;27(1):22-7.
117. Frankenburg FR, Zanarini MC, Kando J, Centorrino F. Clozapine and body mass change. Biological psychiatry. 1998;43(7):520-4.
118. Beasley CM, Jr., Hamilton SH, Crawford AM, Dellva MA, Tollefson GD, Tran PV, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 1997;7(2):125-37.
119. Kinon BJ, Volavka J, Stauffer V, Edwards SE, Liu-Seifert H, Chen L, et al. Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. Journal of clinical psychopharmacology. 2008;28(4):392-400.
120. Rojo LE, Gaspar PA, Silva H, Risco L, Arena P, Cubillos-Robles K, et al. Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology. Pharmacological research. 2015;101:74-85.
121. Lindenmayer JP, Liu-Seifert H, Kulkarni PM, Kinon BJ, Stauffer V, Edwards SE, et al. Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. The Journal of clinical psychiatry. 2009;70(7):990-6.
122. Lau SL, Muir C, Assur Y, Beach R, Tran B, Bartrop R, et al. Predicting Weight Gain in Patients Treated With Clozapine: The Role of Sex, Body Mass Index, and Smoking. Journal of clinical psychopharmacology. 2016;36(2):120-4.
123. Jones B, Basson BR, Walker DJ, Crawford AM, Kinon BJ. Weight change and atypical antipsychotic treatment in patients with schizophrenia. The Journal of clinical psychiatry. 2001;62 Suppl 2:41-4.
124. Hennen J, Perlis RH, Sachs G, Tohen M, Baldessarini RJ. Weight gain during treatment of bipolar I patients with olanzapine. The Journal of clinical psychiatry. 2004;65(12):1679-87.
125. Lee E, Leung CM, Wong E. Atypical antipsychotics and weight gain in Chinese patients: a comparison of olanzapine and risperidone. The Journal of clinical psychiatry. 2004;65(6):864-6.
126. Mitchell M, Riesenberg R, Bari MA, Marquez E, Kurtz D, Falk D, et al. A double-blind, randomized trial to evaluate the pharmacokinetics and tolerability of 30 or 40 mg/d oral olanzapine relative to 20 mg/d oral olanzapine in stable psychiatric subjects. Clinical therapeutics. 2006;28(6):881-92.
127. Brecher M, Rak IW, Melvin K, Jones AM. The long-term effect of quetiapine (Seroquel TM) monotherapy on weight in patients with schizophrenia. International journal of psychiatry in clinical practice. 2000;4(4):287-91.
128. Melkersson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. The Journal of clinical psychiatry. 1999;60(11):783-91.

129. Melkersson KI, Dahl ML. Relationship between levels of insulin or triglycerides and serum concentrations of the atypical antipsychotics clozapine and olanzapine in patients on treatment with therapeutic doses. Psychopharmacology. 2003;170(2):157-66.
130. MacNeil RR, Muller DJ. Genetics of Common Antipsychotic-Induced Adverse Effects. Molecular neuropsychiatry. 2016;2(2):61-78.
131. Quteineh L, Vandenberghe F, Saigi Morgui N, Delacretaz A, Choong E, Gholam-Rezaee M, et al. Impact of HSD11B1 polymorphisms on BMI and components of the metabolic syndrome in patients receiving psychotropic treatments. Pharmacogenetics and genomics. 2015;25(5):246-58.
132. Choong E, Quteineh L, Cardinaux JR, Gholam-Rezaee M, Vandenberghe F, Dobrinas M, et al. Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and the general adult population. JAMA psychiatry. 2013;70(10):1011-9.
133. Saigi-Morgui N, Vandenberghe F, Delacretaz A, Quteineh L, Choong E, Gholamrezaee M, et al. Association of PCK1 with Body Mass Index and Other Metabolic Features in Patients With Psychotropic Treatments. Journal of clinical psychopharmacology. 2015;35(5):544-52.
134. Gregoor JG, Mulder H, Cohen D, van Megen HJ, Egberts TC, Heerdink ER, et al. Combined HTR2C-LEP genotype as a determinant of obesity in patients using antipsychotic medication. Journal of clinical psychopharmacology. 2010;30(6):702-5.
135. Ellingrod VL, Taylor SF, Dalack G, Grove TB, Bly MJ, Brook RD, et al. Risk factors associated with metabolic syndrome in bipolar and schizophrenia subjects treated with antipsychotics: the role of folate pharmacogenetics. Journal of clinical psychopharmacology. 2012;32(2):261-5.
136. Zhang JP, Lencz T, Zhang RX, Nitta M, Maayan L, John M, et al. Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis. Schizophrenia bulletin. 2016;42(6):1418-37.
137. Surakka I, Horikoshi M, Magi R, Sarin AP, Mahajan A, Lagou V, et al. The impact of low-frequency and rare variants on lipid levels. Nature genetics. 2015;47(6):589-97.
138. Global Lipids Genetics C, Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, et al. Discovery and refinement of loci associated with lipid levels. Nature genetics. 2013;45(11):1274-83.
139. Belsky DW, Moffitt TE, Sugden K, Williams B, Houts R, McCarthy J, et al. Development and evaluation of a genetic risk score for obesity. Biodemography and social biology. 2013;59(1):85-100.
140. Hung CF, Breen G, Czamara D, Corre T, Wolf C, Kloiber S, et al. A genetic risk score combining 32 SNPs is associated with body mass index and improves obesity prediction in people with major depressive disorder. BMC medicine. 2015;13:86.
141. Lin X, Song K, Lim N, Yuan X, Johnson T, Abderrahmani A, et al. Risk prediction of prevalent diabetes in a Swiss population using a weighted genetic score--the CoLaus Study. Diabetologia. 2009;52(4):600-8.
142. Saigi-Morgui N, Vandenberghe F, Delacretaz A, Quteineh L, Gholamrezaee M, Aubry JM, et al. Association of genetic risk scores with body mass index in Swiss psychiatric cohorts. Pharmacogenetics and genomics. 2016;26(5):208-17.
143. Smemo S, Tena JJ, Kim KH, Gamazon ER, Sakabe NJ, Gomez-Marin C, et al. Obesity-associated variants within FTO form long-range functional connections with IRX3. Nature. 2014;507(7492):371-5.
144. Pomerantz MM, Ahmadiyeh N, Jia L, Herman P, Verzi MP, Doddapaneni H, et al. The 8q24 cancer risk variant rs6983267 shows long-range interaction with MYC in colorectal cancer. Nature genetics. 2009;41(8):882-4.
145. Mansego ML, Milagro FI, Zulet MA, Martinez JA. SH2B1 CpG-SNP is associated with body weight reduction in obese subjects following a dietary restriction program. Annals of nutrition & metabolism. 2015;66(1):1-9.
146. Razin A, Cedar H. DNA methylation and gene expression. Microbiological reviews. 1991;55(3):451-8.

147. Grundberg E, Meduri E, Sandling JK, Hedman AK, Keildson S, Buil A, et al. Global analysis of DNA methylation variation in adipose tissue from twins reveals links to disease-associated variants in distal regulatory elements. American journal of human genetics. 2013;93(5):876-90.
148. Drong AW, Nicholson G, Hedman AK, Meduri E, Grundberg E, Small KS, et al. The presence of methylation quantitative trait loci indicates a direct genetic influence on the level of DNA methylation in adipose tissue. PloS one. 2013;8(2):e55923.
149. Davies MN, Volta M, Pidsley R, Lunnon K, Dixit A, Lovestone S, et al. Functional annotation of the human brain methylome identifies tissue-specific epigenetic variation across brain and blood. Genome biology. 2012;13(6):R43.
150. Smith AK, Kilaru V, Kocak M, Almli LM, Mercer KB, Ressler KJ, et al. Methylation quantitative trait loci (meQTLs) are consistently detected across ancestry, developmental stage, and tissue type. BMC genomics. 2014;15:145.
151. van Eijk KR, de Jong S, Boks MP, Langeveld T, Colas F, Veldink JH, et al. Genetic analysis of DNA methylation and gene expression levels in whole blood of healthy human subjects. BMC genomics. 2012;13:636.
152. Dick KJ, Nelson CP, Tsaprouni L, Sandling JK, Aissi D, Wahl S, et al. DNA methylation and body-mass index: a genome-wide analysis. Lancet. 2014;383(9933):1990-8.
153. Almen MS, Nilsson EK, Jacobsson JA, Kalnina I, Klovins J, Fredriksson R, et al. Genome-wide analysis reveals DNA methylation markers that vary with both age and obesity. Gene. 2014;548(1):61-7.
154. Foley DL, Morley KI. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. Archives of general psychiatry. 2011;68(6):609-16.
155. Manu P, Dima L, Shulman M, Vancampfort D, De Hert M, Correll CU. Weight gain and obesity in schizophrenia: epidemiology, pathobiology, and management. Acta psychiatrica Scandinavica. 2015;132(2):97-108.
156. Cooper SJ, Reynolds GP, Barnes T, England E, Haddad PM, Heald A, et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. Journal of psychopharmacology (Oxford, England). 2016;30(8):717-48.
157. 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(171):1994-9.
158. Alvarez-Jimenez M, Hetrick SE, Gonzalez-Blanch C, Gleeson JF, McGorry PD. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. The British journal of psychiatry : the journal of mental science. 2008;193(2):101-7.
159. Caemmerer J, Correll CU, Maayan L. Acute and maintenance effects of non-pharmacologic interventions for antipsychotic associated weight gain and metabolic abnormalities: a meta-analytic comparison of randomized controlled trials. Schizophrenia research. 2012;140(1-3):159-68.
160. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2010;35(7):1520-30.
161. Maayan L, Correll CU. Management of antipsychotic-related weight gain. Expert review of neurotherapeutics. 2010;10(7):1175-200.
162. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. European psychiatry : the journal of the Association of European Psychiatrists. 2010;25 Suppl 2:S12-21.
163. Wu RR, Zhang FY, Gao KM, Ou JJ, Shao P, Jin H, et al. Metformin treatment of antipsychotic-induced dyslipidemia: an analysis of two randomized, placebo-controlled trials. Molecular psychiatry. 2016;21(11):1537-44.

164. Choong E, Bondolfi G, Etter M, Jermann F, Aubry JM, Bartolomei J, et al. Psychotropic drug-induced weight gain and other metabolic complications in a Swiss psychiatric population. Journal of psychiatric research. 2012;46(4):540-8.
165. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. The Journal of clinical psychiatry. 2006;67(3):453-60.
166. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry research. 2010;176(2-3):109-13.
167. Waalen J. The genetics of human obesity. Translational research : the journal of laboratory and clinical medicine. 2014;164(4):293-301.
168. Garrido-Cardenas JA, Garcia-Maroto F, Alvarez-Bermejo JA, Manzano-Agugliaro F. DNA Sequencing Sensors: An Overview. Sensors (Basel, Switzerland). 2017;17(3).
169. Rankinen T, Sarzynski MA, Ghosh S, Bouchard C. Are there genetic paths common to obesity, cardiovascular disease outcomes, and cardiovascular risk factors? Circulation research. 2015;116(5):909-22.
170. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015;518(7538):197-206.
171. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. Nature genetics. 2013;45(1):25-33.
172. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011;478(7367):103-9.
173. Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir V, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nature genetics. 2012;44(9):981-90.
174. Lamers F, de Jonge P, Nolen WA, Smit JH, Zitman FG, Beekman AT, et al. Identifying depressive subtypes in a large cohort study: results from the Netherlands Study of Depression and Anxiety (NESDA). The Journal of clinical psychiatry. 2010;71(12):1582-9.
175. Farmer A, Korszun A, Owen MJ, Craddock N, Jones L, Jones I, et al. Medical disorders in people with recurrent depression. The British journal of psychiatry : the journal of mental science. 2008;192(5):351-5.
176. Forty L, Ulanova A, Jones L, Jones I, Gordon-Smith K, Fraser C, et al. Comorbid medical illness in bipolar disorder. The British journal of psychiatry : the journal of mental science. 2014;205(6):465-72.
177. Lopresti AL, Drummond PD. Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment. Progress in neuro-psychopharmacology & biological psychiatry. 2013;45:92-9.
178. Quteineh L, Preisig M, Rivera M, Milaneschi Y, Castelao E, Gholam-Rezaee M, et al. Association of CRTC1 polymorphisms with obesity markers in subjects from the general population with lifetime depression. Journal of affective disorders. 2016;198:43-9.
179. Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. Nature reviews Endocrinology. 2014;10(1):51-61.
180. Rivera M, Cohen-Woods S, Kapur K, Breen G, Ng MY, Butler AW, et al. Depressive disorder moderates the effect of the FTO gene on body mass index. Molecular psychiatry. 2012;17(6):604-11.
181. Samaan Z, Anand SS, Zhang X, Desai D, Rivera M, Pare G, et al. The protective effect of the obesity-associated rs9939609 A variant in fat mass- and obesity-associated gene on depression. Molecular psychiatry. 2013;18(12):1281-6.
182. Milaneschi Y, Lamers F, Mbarek H, Hottenga JJ, Boomsma DI, Penninx BW. The effect of FTO rs9939609 on major depression differs across MDD subtypes. Molecular psychiatry. 2014.

183. Delacretaz A, Zdralovic A, Vandenberghe F, Saigi-Morgui N, Glatard A, Quteineh L, et al. Association of variants in SH2B1 and RABEP1 with worsening of low-density lipoprotein and glucose parameters in patients treated with psychotropic drugs. Gene. 2017.
184. Lu Y, Day FR, Gustafsson S, Buchkovich ML, Na J, Bataille V, et al. New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk. Nature communications. 2016;7:10495.
185. Baccarelli A, Rienstra M, Benjamin EJ. Cardiovascular epigenetics: basic concepts and results from animal and human studies. Circulation Cardiovascular genetics. 2010;3(6):567-73.
186. Barringhaus KG, Zamore PD. MicroRNAs: regulating a change of heart. Circulation. 2009;119(16):2217-24.
187. Pons D, de Vries FR, van den Elsen PJ, Heijmans BT, Quax PH, Jukema JW. Epigenetic histone acetylation modifiers in vascular remodelling: new targets for therapy in cardiovascular disease. European heart journal. 2009;30(3):266-77.
188. Zhong J, Agha G, Baccarelli AA. The Role of DNA Methylation in Cardiovascular Risk and Disease: Methodological Aspects, Study Design, and Data Analysis for Epidemiological Studies. Circulation research. 2016;118(1):119-31.
189. Bakulski KM, Fallin MD. Epigenetic epidemiology: promises for public health research. Environmental and molecular mutagenesis. 2014;55(3):171-83.
190. Wilson LE, Harlid S, Xu Z, Sandler DP, Taylor JA. An epigenome-wide study of body mass index and DNA methylation in blood using participants from the Sister Study cohort. International journal of obesity. 2017;41(1):194-9.
191. Mendelson MM, Marioni RE, Joehanes R, Liu C, Hedman AK, Aslibekyan S, et al. Association of Body Mass Index with DNA Methylation and Gene Expression in Blood Cells and Relations to Cardiometabolic Disease: A Mendelian Randomization Approach. PLoS medicine. 2017;14(1):e1002215.
192. Main AM, Gillberg L, Jacobsen AL, Nilsson E, Gjesing AP, Hansen T, et al. DNA methylation and gene expression of HIF3A: cross-tissue validation and associations with BMI and insulin resistance. Clinical epigenetics. 2016;8:89.
193. Wahl S, Drong A, Lehne B, Loh M, Scott WR, Kunze S, et al. Epigenome-wide association study of body mass index, and the adverse outcomes of adiposity. Nature. 2017;541(7635):81-6.
194. Breitling LP, Yang R, Korn B, Burwinkel B, Brenner H. Tobacco-smoking-related differential DNA methylation: 27K discovery and replication. American journal of human genetics. 2011;88(4):450-7.
195. Joubert BR, Haberg SE, Nilsen RM, Wang X, Vollset SE, Murphy SK, et al. 450K epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. Environmental health perspectives. 2012;120(10):1425-31.
196. Allione A, Marcon F, Fiorito G, Guarrera S, Siniscalchi E, Zijno A, et al. Novel epigenetic changes unveiled by monozygotic twins discordant for smoking habits. PloS one. 2015;10(6):e0128265.
197. Wan ES, Qiu W, Baccarelli A, Carey VJ, Bacherman H, Rennard SI, et al. Cigarette smoking behaviors and time since quitting are associated with differential DNA methylation across the human genome. Human molecular genetics. 2012;21(13):3073-82.
198. Lim U, Song MA. Dietary and lifestyle factors of DNA methylation. Methods in molecular biology (Clifton, NJ). 2012;863:359-76.
199. Roseboom T, de Rooij S, Painter R. The Dutch famine and its long-term consequences for adult health. Early human development. 2006;82(8):485-91.
200. Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. Human molecular genetics. 2009;18(21):4046-53.
201. Ronn T, Volkov P, Davegardh C, Dayeh T, Hall E, Olsson AH, et al. A six months exercise intervention influences the genome-wide DNA methylation pattern in human adipose tissue. PLoS genetics. 2013;9(6):e1003572.

202. Marsit CJ. Influence of environmental exposure on human epigenetic regulation. The Journal of experimental biology. 2015;218(Pt 1):71-9.
203. Baccarelli A, Ghosh S. Environmental exposures, epigenetics and cardiovascular disease. Current opinion in clinical nutrition and metabolic care. 2012;15(4):323-9.
204. Du Y, Xu X, Chu M, Guo Y, Wang J. Air particulate matter and cardiovascular disease: the epidemiological, biomedical and clinical evidence. Journal of thoracic disease. 2016;8(1):E8-e19.
205. Relton CL, Davey Smith G. Two-step epigenetic Mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. International journal of epidemiology. 2012;41(1):161-76.
206. Daca-Roszak P, Pfeifer A, Zebracka-Gala J, Rusinek D, Szybinska A, Jarzab B, et al. Impact of SNPs on methylation readouts by Illumina Infinium HumanMethylation450 BeadChip Array: implications for comparative population studies. BMC genomics. 2015;16:1003.
207. Dayeh TA, Olsson AH, Volkov P, Almgren P, Ronn T, Ling C. Identification of CpG-SNPs associated with type 2 diabetes and differential DNA methylation in human pancreatic islets. Diabetologia. 2013;56(5):1036-46.
208. Chen X, Chen X, Xu Y, Yang W, Wu N, Ye H, et al. Association of six CpG-SNPs in the inflammation-related genes with coronary heart disease. Hum Genomics. 2016;10 Suppl 2:21.
209. Justesen JM, Allin KH, Sandholt CH, Borglykke A, Krarup NT, Grarup N, et al. Interactions of Lipid Genetic Risk Scores With Estimates of Metabolic Health in a Danish Population. Circulation Cardiovascular genetics. 2015;8(3):465-72.
210. Delacretaz A, Preisig M, Vandenberghe F, Saigi Morgui N, Quteineh L, Choong E, et al. Influence of MCHR2 and MCHR2-AS1 Genetic Polymorphisms on Body Mass Index in Psychiatric Patients and In Population-Based Subjects with Present or Past Atypical Depression. PloS one. 2015;10(10):e0139155.
211. Toalson P, Ahmed S, Hardy T, Kabinoff G. The Metabolic Syndrome in Patients With Severe Mental Illnesses. Primary care companion to the Journal of clinical psychiatry. 2004;6(4):152-8.
212. Hoffmann VP, Case M, Stauffer VL, Jacobson JG, Conley RR. Predictive value of early changes in triglycerides and weight for longer-term changes in metabolic measures during olanzapine, ziprasidone or aripiprazole treatment for schizophrenia and schizoaffective disorder post hoc analyses of 3 randomized, controlled clinical trials. Journal of clinical psychopharmacology. 2010;30(6):656-60.
213. Mitchell AJ, Delaffon V, Vancampfort D, Correll CU, De Hert M. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. Psychological medicine. 2012;42(1):125-47.
214. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. European heart journal. 2016;37(39):2999-3058.
215. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). European psychiatry : the journal of the Association of European Psychiatrists. 2009;24(6):412-24.
216. Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. JAMA psychiatry. 2014;71(12):1350-63.
217. Mitchell AJ, Lord O, Malone D. Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis. The British journal of psychiatry : the journal of mental science. 2012;201(6):435-43.
218. Allison DB, Loebel AD, Lombardo I, Romano SJ, Siu CO. Understanding the relationship between baseline BMI and subsequent weight change in antipsychotic trials: effect modification or regression to the mean? Psychiatry research. 2009;170(2-3):172-6.
219. Perez-Iglesias R, Martinez-Garcia O, Pardo-Garcia G, Amado JA, Garcia-Unzueta MT, Tabares-Seisdedos R, et al. Course of weight gain and metabolic abnormalities in first treated episode of

psychosis: the first year is a critical period for development of cardiovascular risk factors. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum. 2014;17(1):41-51.
220. Janssens AC, Moonesinghe R, Yang Q, Steyerberg EW, van Duijn CM, Khoury MJ. The impact of genotype frequencies on the clinical validity of genomic profiling for predicting common chronic diseases. Genetics in medicine : official journal of the American College of Medical Genetics. 2007;9(8):528-35.
221. Muller B, Wilcke A, Boulesteix AL, Brauer J, Passarge E, Boltze J, et al. Improved prediction of complex diseases by common genetic markers: state of the art and further perspectives. Human genetics. 2016;135(3):259-72.
222. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015;526(7573):343-50.
223. Schroeder SA, Frist W. Phasing out fee-for-service payment. The New England journal of medicine. 2013;368(21):2029-32.
224. Levy KD, Decker BS, Carpenter JS, Flockhart DA, Dexter PR, Desta Z, et al. Prerequisites to implementing a pharmacogenomics program in a large health-care system. Clinical pharmacology and therapeutics. 2014;96(3):307-9.
225. Ordonnance du DFI sur les prestations dans l'assurance obligatoire des soins en cas de maladie (Ordonnance sur les prestations de l'assurance des soins, OPAS); Liste des analyses. 2017;Art.28.
226. Verbelen M, Weale ME, Lewis CM. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? The pharmacogenomics journal. 2017.
227. Turner RM, Pirmohamed M. Cardiovascular pharmacogenomics: expectations and practical benefits. Clinical pharmacology and therapeutics. 2014;95(3):281-93.
228. Gottesman O, Scott SA, Ellis SB, Overby CL, Ludtke A, Hulot JS, et al. The CLIPMERGE PGx Program: clinical implementation of personalized medicine through electronic health records and genomics-pharmacogenomics. Clinical pharmacology and therapeutics. 2013;94(2):214-7.
229. Johnson JA, Burkley BM, Langaee TY, Clare-Salzler MJ, Klein TE, Altman RB. Implementing personalized medicine: development of a cost-effective customized pharmacogenetics genotyping array. Clinical pharmacology and therapeutics. 2012;92(4):437-9.
230. Oetjens MT, Denny JC, Ritchie MD, Gillani NB, Richardson DM, Restrepo NA, et al. Assessment of a pharmacogenomic marker panel in a polypharmacy population identified from electronic medical records. Pharmacogenomics. 2013;14(7):735-44.
231. Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clinical pharmacology and therapeutics. 2011;89(5):662-73.
232. Manolio TA, Abramowicz M, Al-Mulla F, Anderson W, Balling R, Berger AC, et al. Global implementation of genomic medicine: We are not alone. Science translational medicine. 2015;7(290):290ps13.
233. Luzum JA, Pakyz RE, Elsey AR, Haidar CE, Peterson JF, Whirl-Carrillo M, et al. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: Outcomes and Metrics of Pharmacogenetic Implementations Across Diverse Healthcare Systems. Clinical pharmacology and therapeutics. 2017;102(3):502-10.
234. Rasmussen-Torvik LJ, Stallings SC, Gordon AS, Almoguera B, Basford MA, Bielinski SJ, et al. Design and anticipated outcomes of the eMERGE-PGx project: a multicenter pilot for preemptive pharmacogenomics in electronic health record systems. Clinical pharmacology and therapeutics. 2014;96(4):482-9.
235. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes care. 2004;27(2):596-601.
236. Barnes TR, Bhatti SF, Adroer R, Paton C. Screening for the metabolic side effects of antipsychotic medication: findings of a 6-year quality improvement programme in the UK. BMJ Open. 2015;5(10):e007633.

237. Mangurian C, Giwa F, Shumway M, Fuentes-Afflick E, Perez-Stable EJ, Dilley JW, et al. Primary care providers' views on metabolic monitoring of outpatients taking antipsychotic medication. Psychiatric services (Washington, DC). 2013;64(6):597-9.
238. D'Agostino RB, Sr., Pencina MJ, Massaro JM, Coady S. Cardiovascular Disease Risk Assessment: Insights from Framingham. Global heart. 2013;8(1):11-23.

APPENDIX

Co-authorship publications

Impact of *HSD11B1* polymorphisms on BMI and components of the metabolic syndrome in patients receiving psychotropic treatments

Lina Quteineh[a], Frederik Vandenberghe[a], Nuria Saigi Morgui[a], Aurélie Delacrétaz[a], Eva Choong[a], Mehdi Gholam-Rezaee[b], Pierre Magistretti[e,l], Guido Bondolfi[j], Armin Von Gunten[c], Martin Preisig[b], Enrique Castelao[b], Peter Vollenweider[f], Gerard Waeber[f], Murielle Bochud[g], Zoltán Kutalik[g,h,i], Philippe Conus[d] and Chin B. Eap[a,k]

Background Metabolic syndrome (MetS) associated with psychiatric disorders and psychotropic treatments represents a major health issue. 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme that catalyzes tissue regeneration of active cortisol from cortisone. Elevated enzymatic activity of 11β-HSD1 may lead to the development of MetS.

Methods We investigated the association between seven *HSD11B1* gene (encoding 11β-HSD1) polymorphisms and BMI and MetS components in a psychiatric sample treated with potential weight gain-inducing psychotropic drugs ($n = 478$). The polymorphisms that survived Bonferroni correction were analyzed in two independent psychiatric samples ($n_{R1} = 168$, $n_{R2} = 188$) and in several large population-based samples ($n_1 = 5338$; $n_2 = 123\,865$; $n_3 > 100\,000$).

Results *HSD11B1 rs846910-A*, *rs375319-A*, and *rs4844488-G* allele carriers were found to be associated with lower BMI, waist circumference, and diastolic blood pressure compared with the reference genotype ($P_{corrected} < 0.05$). These associations were exclusively detected in women ($n = 257$) with more than 3.1 kg/m^2, 7.5 cm, and 4.2 mmHg lower BMI, waist circumference, and diastolic blood pressure, respectively, in *rs846910-A*, *rs375319-A*, and *rs4844488-G* allele carriers compared with noncarriers ($P_{corrected} < 0.05$). Conversely, carriers of the *rs846906-T* allele had significantly higher waist circumference and triglycerides and lower high-density lipoprotein-cholesterol exclusively in men ($P_{corrected} = 0.028$). The *rs846906-T* allele was also associated with a higher risk of MetS at 3 months of follow-up (odds ratio: 3.31, 95% confidence interval: 1.53–7.17, $P_{corrected} = 0.014$). No association was observed between *HSD11B1* polymorphisms and BMI and MetS components in the population-based samples.

Conclusions Our results indicate that *HSD11B1* polymorphisms may contribute toward the development of MetS in psychiatric patients treated with potential weight gain-inducing psychotropic drugs, but do not play a significant role in the general population. *Pharmacogenetics and Genomics* 25:246–258 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Pharmacogenetics and Genomics 2015, **25**:246–258

Keywords: body mass index, metabolic syndrome, pharmacogenetics, psychotropic drugs

[a]Unit of Pharmacogenetics and Clinical Psychopharmacology, Department of Psychiatry, Centre for Psychiatric Neuroscience, [b]Department of Psychiatry, Centre of Psychiatric Epidemiology and Psychopathology, [c]Department of Psychiatry, Service of Old Age Psychiatry, [d]Department of Psychiatry, Service of General Psychiatry, Lausanne University Hospital, Prilly, [e]Laboratory of Neuroenergetics and Cellular Dynamics, Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne, [f]Department of Medicine, [g]Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital, [h]Department of Medical Genetics, University of Lausanne, [i]Swiss Institute of Bioinformatics, Lausanne, [j]Department of Mental Health and Psychiatry, University Hospital of Geneva, [k]School of Pharmaceutical Sciences, University of Geneve, University of Lausanne, Geneva, Switzerland and [l]Faculty of Biological and Environmental Science and Engineering, King Abdullah University of Science and Technology, Thuwal, Saudi Arabia

Correspondence to Chin B. Eap, PhD, Hôpital de Cery, 1008 Prilly, Lausanne, Switzerland
Tel: +41 21 314 26 04; fax: +41 21 314 24 44; e-mail: chin.eap@chuv.ch

Received 22 October 2014 **Accepted** 6 February 2015

Introduction

Weight gain and obesity are major health problems associated with psychiatric disorders and/or with psychotropic drug treatments, and in particular, atypical antipsychotics (AP) and some mood stabilizers (MS) [1,2]. This may have major clinical consequences considering that obesity can lead to the development of other components of the metabolic syndrome (MetS) such as dyslipidemia, hypertension, and type 2 diabetes [1], which may ultimately lead to the development of cardiovascular diseases (CVDs), reducing patients' quality of life and increasing mortality in psychiatric populations [3]. Indeed, schizophrenic patients are reported to have excess risk of mortality and 20% shorter life span compared with the general population,

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (*www.pharmacogeneticsandgenomics.com*).

1744-6872 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/FPC.0000000000000131

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

with CVDs being the leading cause of death [4]. Meta-analyses also showed nearly two times increased risk of mortality and CVDs in depressive patients [5] and regular follow-up of all components of the MetS is therefore strongly recommended in psychiatric patients receiving psychotropic drug treatments [6].

Heritability has been shown to influence individual susceptibility to overweight or obesity, both in the general population [7,8] and in psychiatric patients treated with weight-inducing psychotropic drugs [9–11]. Genome-wide association studies (GWAS) carried out to date only explain a small fraction of BMI heritability [8] and more obesity susceptibility genes remain to be discovered. Whereas genome-wide association study meta-analyses have been very useful, other approaches are also needed to further understand the biology of human obesity.

The 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) has been associated with the MetS in the general population (reviewed in Wamil and Seckl [12]). This microsomal enzyme catalyzes tissue regeneration of active cortisol from the inactive form cortisone and is highly expressed in metabolic tissues such as liver and adipose tissue and also in the central nervous system, where it amplifies the action of endogenous cortisol, which binds to glucocorticosteroids receptors [13]. Although not all patients with MetS have increased levels of cortisol [14], it is well known that increased plasma cortisol levels (as in Cushing's syndrome) are associated with visceral obesity and with other features of the MetS. Thus, increased enzymatic activity of 11β-HSD1 may also lead to the development of MetS. Indeed, mice with transgenic overexpression of 11β-HSD1 in liver or adipose tissue are hyperphagic, obese, and show other features of the MetS, especially under a high-fat diet [15,16], whereas inhibition of 11β-HSD1 ameliorates the features of MetS in obese mice [17,18]. In obese humans, there is an association between 11β-HSD1 activity in abdominal subcutaneous fat/adipose tissue and central obesity [19,20].

Human population-based studies suggest that polymorphisms within the *HSD11B1* gene, which encodes 11β-HSD1, are associated with MetS and/or its different components [21–25]. Two single nucleotide polymorphisms (SNPs), *HSD11B1 rs846910G>A* in the 5′-flanking region and *rs12086634T>G* in the third intron, were associated independently with type 2 diabetes [21], hypertension [22,23], waist circumference (WC) [23], and the MetS overall [23], but not with BMI [21,22,26–28]. Other SNPs within the *HSD11B1* showed inconsistent results with the MetS [26,28–30]. Importantly, no pharmacogenetic studies, to our knowledge, have investigated the association between *HSD11B1* SNPs and obesity or MetS components in psychiatric samples treated with psychotropic weight gain-inducing drugs.

We aimed to study the association of seven *HSD11B1* variants (*rs12565406G>T*, *rs10863782G>A*, *rs846910G>A*, *rs3753519G>A*, *rs12086634T>G*, *rs4844488A>G*, and *rs846906C>T*) with BMI, MetS, and its different components in psychiatric patients taking potential weight gain-inducing psychotropic drugs, a population known to have the higher prevalence of obesity, and hence MetS, compared with the general population.

Materials and methods

The association of *HSD11B1* variants with BMI, MetS, and its different components as defined by the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) [31] including WC, systolic and diastolic blood pressure (SBP and DBP), fasting glucose, triglycerides, and high-density lipoprotein-cholesterol (HDL-C) was investigated in the main study sample. A full description of this sample has been published elsewhere [32]. Briefly, 478 White psychiatric patients with newly prescribed aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, lithium, valproate, and/or mirtazapine were recruited prospectively since 2007 from all psychiatric wards of the Lausanne University Hospital. Sixty-two percent had already received other psychotropic treatments and were included after having switched medication. No wash-out period was required. Body weight, WC, blood pressure, and the other components of the MetS were prospectively recorded at several time points during the first 12 months of psychotropic treatment according to published recommended monitoring guidelines (i.e. before starting the current psychotropic drugs, and then at months 1, 2, 3, 6, 9, and 12) [6]. The newly introduced psychotropic drug was considered the main psychotropic medication and any other potential weight gain-inducing drugs of interest, including typical and atypical AP and MS, were classified as comedications possibly causing weight gain. The study was approved by the Psychiatry Ethics Committee of Lausanne University hospital and written informed consent was provided by all participants or by their legal representatives.

Replication samples

We attempted to replicate the results in two independent samples of White psychiatric patients [32]. The first replication sample was from a retrospective study carried out in outpatient psychiatric centers of Geneva University Hospital from 2006 to 2008. A total of 168 patients treated for more than 3 months with clozapine, olanzapine, quetiapine, risperidone, lithium, and/or valproate were included. Seventy-two percent had already received other psychotropic treatments before the current treatment. The second replication sample was also recruited from a retrospective study carried out since 2010 in two outpatient psychiatric centers of Lausanne (Lausanne University Hospital and a private psychiatric center). A total of 188 patients treated with aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole lithium, and/or valproate were included. Fifty-two percent of the

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

studied sample had already received another psychotropic drug before the current treatment. For both samples, only BMI was available at different time-points during treatment; body weight and height were measured in all patients at inclusion, whereas their baseline weight before the initiation of the current treatment and/or at different times during treatment was obtained from the medical file or was self-reported (baseline weight was self-reported in 76% of the cases). As shown previously in our replication samples [32], self-reported weight was found to be a very reliable estimate of measured weight obtained from the medical files. Both studies consisted of one single visit performed during the usual clinical psychiatric follow-up. The medication with the longest treatment duration was entered in the model as the main psychotropic medication. Both studies were approved by their respective ethical committees and written informed consent was provided by all participants or by their legal representatives.

Population-based samples

Cohorte Lausannoise (CoLaus and PsyCoLaus)

Participants aged 35–75 years in this population-based study (CoLaus) were recruited between June 2003 and May 2006 as described previously [33]. The assessment included cardiovascular risk factors such as the BMI, fat mass, WC, blood pressure, blood glucose, triglycerides, and HDL-C. In addition, all Whites (91% of the sample) underwent a genetic exam ($n = 5338$). All participants of CoLaus in the age range of 35–66 years were asked to also participate in a psychiatric evaluation (PsyCoLaus) based essentially on a semistructured diagnostic interview [34]. Combined genetic and psychiatric data were available for 2990 participants. Genotyping for the CoLaus/PsyCoLaus participants was performed using the Affymetrix GeneChipR Human Mapping 500K array set.

Genetic Investigation of ANtropometric Traits (GIANT) consortium

The GIANT consortium carried out a meta-analysis of GWAS data with a discovery set of 123 865 individuals of European ancestry from 46 studies for height [35], BMI [8], and waist-to hip ratio [36].

Genome-wide associations scans for total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and triglycerides

Data on lipid traits have been downloaded from the 'Genome Wide Associations Scans for Total Cholesterol, HDL-C, LDL-C and triglycerides' website [37,38], which is a meta-analysis of 46 lipid GWASs. These studies together comprise around 100 000 individuals of European descent (maximum sample size 100 184 for total cholesterol, 95 454 for LDL-C, 99 900 for HDL-C, and 96 598 for triglycerides), ascertained in the USA, Europe, or Australia.

Of note, CoLaus is part of both GIANT and 'Genome Wide Associations Scans for Total Cholesterol, HDL-C, LDL-C and triglycerides'.

Selection and genotyping of *HSD11B1* polymorphisms

Genomic DNA of psychiatric patients' was extracted from whole blood. Selection and genotyping of *HSD11B1* SNPs were carried out in two steps: first *rs846910G>A*, *rs12086634T>G* polymorphisms, which were investigated previously in the general population, were selected and genotyped using the TaqMan allelic discrimination assay (ABI PRISM 7000 Sequence Detection System; Applied Biosystems, Rotkreuz, Switzerland). TaqMan SNP Genotyping Assays ID: C___8887157_10 and ID: C__22275467_10 were used for *rs846910G>A* and *rs12086634T>G* SNPs, respectively. All reagents were obtained from Applied Biosystems, and genotyping was performed according to the manufacturer's protocol. In a second step, selection of tagging SNPs within the *HSD11B1* gene using the hapMap Genome Browser (release 28) and analyzed by haploview [39] was applied. Eight tagging SNPs (*rs12565406G>T*, *rs10863782G>A*, *rs846910G>A*, *rs3753519G>A*, *rs12086634T>G*, *rs11119328C>A*, *rs4844488A>G*, and *rs846906C>T*) were found by limiting the search to SNPs with a minor allele frequency more than 5% in the White population and an r^2 cutoff of 0.8, covering 100% of genetic variations within the *HSD11B1* gene in the HapMap Genome Browser and 87% of *HSD11B1* genetic variations in the 1000genome database [40]. Of note, both *rs846910G>A* and *rs12086634T>G* were among the tagging SNPs. These eight SNPs were customized and added to the Illumina 200K cardiometabochip [41]. All the SNPs were tested for Hardy–Weinberg equilibrium and linkage disequilibrium (LD), the latter measured by both D' and r^2. It is worth mentioning that genotypes for *rs846910G>A* and *rs12086634T>G* performed using the TaqMan method were identical to those genotyped using the cardiometabochip. For technical reasons, *HSD11B1 rs11119328* SNP could not be genotyped in the cardiometabochip; therefore, seven *HSD11B1* SNPs were finally analyzed (covering 86% of genetic variations within the *HSD11B1* gene in the HapMap Genome Browser).

Gene expression analysis

The functional effect of the two promoter SNPs (*rs846910G>A* and *rs3753519G>A*) on *HSD11B1* gene expression was investigated in a peripheral model using peripheral blood mononuclear cells (details in Supplementary data, Supplemental digital content 1, *http://links.lww.com/FPC/A815*).

Statistical analysis

Psychiatric samples

The impact of *HSD11B1* SNPs on BMI, MetS, and its components was investigated in the main psychiatric

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

follow-up study, in which multiple observations for each clinical variable for each patient at different time-points were measured. Because of the nonlinearity of our models and the absence of any linear transformation, these associations were assessed by fitting a Generalized Additive Mixed Model (GAMM) [42,43] to allow a smooth trend for the response in time on the basis of multiple observations for each patient (using a thin plate regression spline basis) adjusting for age, sex, smoking status, current psychotropic drug, and comedications possibly causing weight gain for BMI and WC analyses (lists of these comedications have been published in Choong *et al.* [32]), adjusted for antihypertensive drug intake for blood pressure analyses, antidiabetics for glucose analyses, and hypolipidemic drug intake for triglycerides and HDL-C analyses. A random effect at the participant level was also introduced to take the dependence structure of the observed data into account. GAMMs were fitted using the mgcv package of R (settings were fixed at package defaults). To be more conservative, the uncertainty of estimated parameters was assessed by 1000 bootstraps [44] at the participant level and the results were similar to those obtained by 10 000 bootstraps. Whenever the *P*-value for the 1000 bootstrap was lower than 0.001 ($P < 0.001$), 10 000 bootstrap analysis was carried out. If the *P*-value for the 10 000 bootstrap was lower than 0.0001 ($P < 0.0001$), 100 000 bootstrap was applied. The model is fitted on all observations of patients; thus, model coefficients provide information on both the direction and the magnitude of the overall association between BMI and different components of the MetS and the genotypes for the specific period of treatment studied. The psychotropic drugs were classified according to their therapeutic class (AP vs. MS vs. mirtazapine) [45]. Similar GAMM models were applied to test the association between *HSD11B1* SNPs and BMI in the replication samples and in the combined sample.

Because of the small number of individuals homozygous for *HSD11B1* variant alleles, the associations were analyzed using a dominant model. Stratified sex analyses were carried out systematically when analyzing the effect of *HSD11B1* polymorphisms on BMI or MetS components. The *P*-values of these models were adjusted for multiple comparisons using Bonferroni correction; for each outcome tested in the main study sample, the *P*-values were corrected by the seven studied *HSD11B1* SNPs. Both the empirical *P*-values for the GAMM models and the adjusted *P*-values are cited in the Tables and Supplementary Tables (*http://links.lww.com/FPC/A818*, *http://links.lww.com/FPC/A819*, *http://links.lww.com/FPC/A820*, *http://links.lww.com/FPC/A821*, *http://links.lww.com/FPC/A822*, *http://links.lww.com/FPC/A826*).

The χ^2-test was used to assess the risk of MetS as a whole between *HSD11B1* genotypes at baseline, 3, and 12 months of follow-up. Logistic regression was then applied adjusting for age and sex.

All the analyses were carried out using Stata 12 (StataCorp, College Station, Texas, USA) and R version 2.13.0 software (*http://www.R-project.org*). Haploview 4.2 (Daly Lab at the Broad Institute, Cambridge, Massachusetts, USA) [39] was used to define haplotype blocks and LD between different *HSD11B1* SNPs (D' and r^2).

Population-based studies

The associations of *HSD11B1* SNPs with adiposity traits (BMI, weight, WC, and fat mass), blood pressure, and glucose and lipid traits were analyzed using multivariate linear regression with allele dosage in which potential confounding factors such as age, sex, and smoking status were added as covariates in the CoLaus study. In addition, to determine whether the SNPs of interest were differentially associated with the components of the MetS in patients with and without major depressive disorder (MDD), we tested the two-way interactions between each *HSD11B1* SNP and MDD in the PsyCoLaus subsample. BMI, WC, and waist-to hip ratio were the only adiposity traits analyzed by the GIANT Consortium. Triglycerides and HDL-C were analyzed in the 'Genome Wide Associations Scans for Total Cholesterol, HDL-C, LDL-C and triglycerides' study. In both meta-analysis GWAS studies, we determined the association *P*-values for the four SNPs. For the GIANT study, sex-specific BMI associations were also available [46]. As the three population-based samples have large samples sizes and to measure the influence of each copy of the protective/risk variant allele, the association between *HSD11B1* SNPs and metabolic traits were tested in an additive model.

Results

Table 1 shows the clinical characteristics of the White samples of the main study ($n = 478$) and the two replication studies ($n_1 = 168$ and $n_2 = 188$). The prevalence of obesity was higher in the replication studies compared with the main study, which could be explained by the very long treatment duration in the former studies (Table 1). MetS was detected in almost 17% of the main psychiatric sample at baseline, and 27 and 27.5% at 3 and 12 months of the follow-up, respectively.

Table 2 shows the analyzed *HSD11B1* SNPs, their positions, and minor allele frequencies observed in the main psychiatric study sample ($n = 478$). None of the SNPs deviates from Hardy–Weinberg equilibrium and the minor allele frequencies in the psychiatric sample was comparable with those reported in HapMap for Whites (Table 2). Haploview analyses defined two haplotype blocks formed from *rs12565406–rs10863782* and *rs846910–rs3753519* SNPs (Supplementary Fig. 1, Supplemental digital content 2, *http://links.lww.com/FPC/A816*). Only *rs10863782* and *rs3753519* SNPs were in considerable LD ($r^2 = 0.58$) (Supplementary Fig. 1b, Supplemental digital content 2, *http://links.lww.com/FPC/A816*).

Genotype frequencies in the main psychiatric sample, the replication samples, and the combined sample are shown in Supplementary Table 1 (Supplemental digital content 3, *http://links.lww.com/FPC/A817*).

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

Table 1 Characteristics of the three psychiatric study samples: main study and replication studies

Characteristics	Psychiatric study sample ($n=478$)	First replication sample ($n=168$)	Second replication sample ($n=188$)
Men (%)	43.7	52.9	62.2
Age [median (range)] years	50 (12–97)	42.2 (19.5–64)	42.3 (19–69)
Diagnosis (%)			
Psychotic disorders	28.7	27.4	42.0
Mood disorders	35.4	49.4	29.8
Schizoaffective disorder	6.5	15.5	11.7
Other diagnosis	19.2	7.1	13.3
Unknown diagnosis	10.2	0.6	3.2
BMI			
Initial BMI [median (range)] (kg/m^2)[a]	23.5 (13.3–44.5)	25.2 (15.4–45.5)	24.4 (15.5–46.2)
25 ≥ initial BMI < 30 (%)[a]	22.7	36.7	31.7
Initial BMI ≥ 30 (%)[a]	15.7	15.1	15
Current BMI [median (range)] (kg/m^2)	24.2 (15.2–50.2)	28.0 (16.2–42.3)	26.5 (16.8–43.9)
25 ≥ current BMI < 30 (%)	25.6	29.8	33.5
Current BMI ≥ 30 (%)	18.7	39.9	27.6
Smoker (%)	42.0	59.5	76.4
Prescribed psychotropic drug			
Amisulpride (%)	8.2	0	10.7
Aripirazole (%)	8.8	0	7.5
Clozapine (%)	7.3	14.3	9.1
Olanzapine (%)	10.5	16.1	12.3
Quetiapine (%)	32.2	18.4	22.4
Risperidone (%)	15.9	17.3	17.6
Lithium (%)	6.9	20.2	11.8
Valproate (%)	4.8	13.7	8.6
Mirtazapine (%)	5.4	0	0
Treatment duration, [median (range)] (months)	6.0 (1.0–12.0)	27.4 (2.9–332.6)	35.7 (1.0–390.3)
Comedication possibly causing weight gain (%)	48.3	29.2	26.1

[a]Before the current psychotropic treatment.

Table 2 Genomic positions, minor allele frequencies, and deviation from Hardy–Weinberg equilibrium of *HSD11B1* single nucleotide polymorphisms in the main psychiatric study

HSD11B1 SNP	Alleles W/m	Position	MAF	HWE	MAF HapMap
rs12565406	G/T	209861086	0.088	0.33	0.085
rs10863782	G/A	209872590	0.175	0.65	0.164
rs846910	G/A	209875254	0.058	0.23	0.077
rs3753519	G/A	209875515	0.110	0.56	0.097
rs12086634	T/G	209880259	0.178	0.73	0.206
rs4844488	A/G	209885509	0.040	0.77	0.075
rs846906	C/T	209887718	0.151	0.76	0.136

HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequencies.

HSD11B1 polymorphisms in the main psychiatric study sample

Only complete observations and data on the tested variables were included in the GAMM model (different sample sizes were obtained for each clinical variable). Carriers of the variant *rs846910-A*, *rs375319-A*, and *rs4844488-G* alleles showed 2.3, 2.3, and 2.2 kg/m^2 lower BMI values, respectively, compared with patients with the wild-type genotypes [$n=450$, Bonferroni-corrected P-values ($P_{corrected}$) = 0.0014, < 0.00007, and 0.007, respectively] (Table 3). This association was exclusively detected in women ($n=257$), with more than 3.1 kg/m^2 lower BMI in *HSD11B1 rs846910-A*, *rs375319-A*, and *rs4844488-G* carriers compared with noncarriers ($P_{corrected} < 0.00007$, < 0.00007, and 0.04, respectively, explaining 3.6, 4.8, and 1.5% of BMI variance in women), whereas no association was observed among men ($n=193$, $P_{corrected} > 0.05$) (Table 3). No significant association was observed between *HSD11B1 rs12086634T>G*, *rs10863782G>A*, *rs12565406G>T*, and *rs846906C>T* SNPs and BMI, also when analyzing men and women separately ($P_{corrected} > 0.05$).

Because of sex differences of WC, the GAMM was applied for each sex separately. Similar to the findings for BMI, women ($n=255$) had 8.2 cm ($P_{corrected} = 0.00007$), 8.1 cm ($P_{corrected} < 0.00007$), and 7.5 cm ($P_{corrected} = 0.028$) lower WC among carriers of the *HSD11B1 rs846910-A*, *rs375319-A*, and *rs4844488-G* alleles, respectively, compared with noncarriers, explaining 2.8, 5.1, and 1.7% of the variance in WC (Table 4). No association was observed between these three SNPs and WC in men. Interestingly, for the *rs846906C>T* SNP, only men carrying the *T*-allele showed 4.7 cm higher WC compared with noncarriers ($n=204$, $P_{corrected} = 0.014$), explaining 2.3% of the variance in WC. No significant association was observed between *HSD11B1 rs12086634T>G*, *rs10863782G>A* and *rs12565406G>T* and WC in both sexes ($P_{corrected} > 0.05$).

No significant association was observed between *HSD11B1* SNPs and SBP in the main psychiatric group ($n=386$, $P_{corrected} > 0.05$) or on analyzing the men and women subgroups (Supplementary Table 2, Supplemental digital content 4, *http://links.lww.com/FPC/A818*). However, *rs846910G>A*, *rs375319G>A*, and *rs4844488A>G* were associated significantly with DBP. Among women ($n=219$), carriers of the *rs846910-A*, *rs375319-A*, and *rs4844488-G* alleles had 4.7 mmHg ($P_{corrected} = 0.028$), 4.2 mmHg ($P_{corrected} = 0.004$), and 7.0 mmHg ($P_{corrected} = 0.001$) lower DBP compared with noncarriers, explaining 1.3, 1.9, and 2.2% of the variance in DBP for each SNP, respectively (Supplementary Table 3, Supplemental digital content 5, *http://links.lww.com/FPC/A819*).

No significant association was observed between *HSD11B1* SNPs and fasting blood glucose in the main psychiatric group ($n=294$, $P_{corrected} > 0.05$) or on analyzing subgroups of men and women (Supplementary Table 4, Supplemental digital content 6, *http://links.lww.com/FPC/A820*). However, lipid analyses showed a significant association between *rs846906C>T* and triglycerides in the entire sample, with *T*-allele carriers having 0.29 mmol/l higher triglyceride levels compared with noncarriers ($n=312$, $P_{corrected} = 0.007$, explained variance = 1.9%). This association was exclusively observed in men, among whom carriers of the *T*-allele had 0.53 mmol/l higher triglyceride levels compared with

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

Table 3 Associations between *HSD11B1* single nucleotide polymorphisms in a dominant model and body mass index during follow-up in the main psychiatric study

	Main psychiatric sample				Men				Women			
BMI	*n*	*β* (95% CI)	*P*-value ($P_{corrected}$)	E. var.	*n*	*β* (95% CI)	*P*-value ($P_{corrected}$)	E. var.	*n*	*β* (95% CI)	*P*-value ($P_{corrected}$)	E. var.
rs12565406	450				193				257			
GG		Reference				Reference				Reference		
GT/TT		−0.855 (−1.71 to 0.03)	0.03 (>0.05)			−0.62 (−1.52 to 0.35)	0.16 (>0.05)			−1.01 (−2.36 to 0.72)	0.07 (>0.05)	
rs10863782	450				193				257			
GG		Reference				Reference				Reference		
GA/AA		−0.97 (−1.80 to −0.20)	0.02 (>0.05)			−0.54 (−1.49 to 0.26)	0.12 (>0.05)			−1.33 (−2.19 to −0.49)	0.01 (>0.05)	
rs846910	450				193				257			
GG		Reference				Reference				Reference		
GA/AA		−2.28 (−3.49 to −1.12)	**0.0002 (0.0014)**[§]	1.68		−0.18 (−1.70 to 1.55)	0.44 (>0.05)			−3.94 (−5.77 to −2.37)	**<0.00001 (<0.00007)**[§]	3.64
rs3753519	450				193				257			
GG		Reference				Reference				Reference		
GA/AA		−2.27 (−3.08 to −1.59)	**<0.00001 (<0.00007)**[§]	2.91		−0.92 (−2.02 to −0.02)	0.03 (>0.05)			−3.29 (−4.61 to −2.23)	**<0.00001 (<0.00007)**[§]	4.79
rs12086634	450				193				257			
TT		Reference				Reference				Reference		
TG/GG		−0.16 (−0.98 to 0.74)	0.46 (>0.05)			0.06 (−1.17 to 0.96)	0.46 (>0.05)			−0.22 (−1.34 to 0.95)	0.42 (>0.05)	
rs4844488	450				193				257			
AA		Reference				Reference				Reference		
AG/GG		−2.24 (−3.67 to −0.76)	**0.001 (0.007)**	1.17		−1.38 (−2.75 to 0.24)	0.06 (>0.05)			−3.11 (−5.76 to −1.24)	**0.006 (0.042)**	1.53
rs846906	450				193				257			
CC		Reference				Reference				Reference		
CT/TT		0.75 (−0.03 to 1.55)	0.03 (>0.05)			1.35 (0.22–2.43)	0.01 (>0.05)			0.30 (−0.80 to 1.55)	0.20 (>0.05)	

Results were obtained by fitting Generalized Additive Mixed Models for patients, controlling for age, sex (whenever appropriate), smoking status, current psychotropic drug, and comedications possibly causing weight gain. *P*-values that survived Bonferroni correction are presented in bold.
CI, confidence interval; *E. Var.*, explained variance by the polymorphism (%), only calculated for tests that survived Bonferroni correction; $P_{corrected}$, Bonferroni-corrected *P*-value.
[§]100 000 bootstraps were used for this analysis. One thousand bootstraps were performed for the rest of the analyses.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

Table 4 Associations between *HSD11B1* single nucleotide polymorphisms in a dominant model and waist circumference during follow-up in the main psychiatric study

	Main psychiatric sample				Men				Women			
Waist circumference	*n*	*β* (95% CI)	*P*-value ($P_{corrected}$)	E. var.	*n*	*β* (95% CI)	*P*-value ($P_{corrected}$)	E. var.	*n*	*β* (95% CI)	*P*-value ($P_{corrected}$)	E. var.
rs12565406					204				255			
GG		NA				Reference				Reference		
GT/TT						−1.51 (−4.03 to 2.30)	0.18 (>0.05)			−1.56 (−4.72-2.36)	0.20 (>0.05)	
rs10863782					204				255			
GG		NA				Reference				Reference		
GA/AA						−1.61 (−3.91 to 1.91)	0.19 (>0.05)			−3.59 (−6.05 to −1.07)	0.01 (>0.05)	
rs846910					204				255			
GG		NA				Reference				Reference		
GA/AA						−2.33 (−6.34 to 3.12)	0.27 (>0.05)			−8.22 (−11.84 to −4.63)	**0.00001 (0.00007)**[§]	2.82
rs3753519					204				255			
GG		NA				Reference				Reference		
GA/AA						−2.99 (−5.85 to 1.48)	0.11 (>0.05)			−8.05 (−11.11 to −4.75)	**<0.00001 (<0.00007)**[§]	5.09
rs12086634					204				255			
TT		NA				Reference				Reference		
TG/GG						−0.78 (−5.61 to 1.90)	0.25 (>0.05)			−0.29 (−2.96 to 2.82)	0.43 (>0.05)	
rs4844488					204				255			
AA		NA				Reference				Reference		
AG/GG						−4.83 (−9.75 to 0.91)	0.07 (>0.05)			−7.49 (−12.66 to −2.06)	**0.004 (0.028)**	1.66
rs846906					204				255			
CC		NA				Reference				Reference		
CT/TT						4.69 (1.88–8.68)	**0.002 (0.014)**	2.34		0.31 (−3.32 to 3.23)	0.39 (>0.05)	

Results were obtained by fitting Generalized Additive Mixed Models for patients, controlling for age, smoking status, current psychotropic drug, and comedications possibly causing weight-gain.
P-values that survived Bonferroni correction are presented in bold.
CI, confidence interval; E. var., explained variance by the polymorphism (%), only calculated for tests that survived Bonferroni correction; NA, non-applicable; $P_{corrected}$, Bonferroni-corrected *P*-value.
[§]100 000 bootstraps were used for this analysis. One thousand bootstraps were performed for the rest of the analyses.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

Table 5 Associations between *HSD11B1* single nucleotide polymorphisms in a dominant model and body mass index during follow-up in the three combined psychiatric study samples

	Combined psychiatric samples				Men			Women			
BMI	*n*	β (95% CI)	*P*-value	E. var.	*n*	β (95% CI)	*P*-value	E. var.	*n*	β (95% CI)	*P*-value	E. var.
rs846910	802				396				406			
GG		Reference				Reference				Reference		
GA/AA		−1.42 (−2.22 to −0.56)	**0.001**	0.59		−0.25 (−1.19 to 0.65)	0.36			−2.45 (−3.66 to −1.33)	**<0.0001**[§]	1.49
rs3753519	802				396				406			
GG		Reference				Reference				Reference		
GA/AA		−1.87 (−2.46 to −1.15)	**<0.0001**[§]	1.89		−1.13 (−1.91 to −0.50)	**0.002**	0.85		−2.57 (−3.32 to −1.63)	**<0.0001**[§]	3.00
rs4844488	802				396				406			
AA		Reference				Reference				Reference		
AG/GG		−0.87 (−1.89 to 0.29)	0.08			−0.97 (−2.15 to −0.05)	**0.02**	0.34		−0.78 (−2.25 to 0.82)	0.25	

Results were obtained by fitting Generalized Additive Mixed Models for patients, controlling for age, sex (whenever appropriate), smoking status, current psychotropic drug, and comedications possibly causing weight gain.
Significant *P*-values are presented in bold.
CI, confidence interval; E. Var., explained variance by the polymorphism (%), only calculated for significant tests.
[§]10 000 bootstraps were used for this analysis. 1000 bootstraps were performed for the rest of the analyses.

noncarriers ($n = 128$, $P_{corrected} = 0.028$), explaining 5.4% of variance in triglycerides (Supplementary Table 5, Supplemental digital content 7, *http://links.lww.com/FPC/A821*). No significant association was observed between the other *HSD11B1* SNPs and triglycerides, either for women or for men ($P_{corrected} > 0.05$). Because of differences in HDL-C levels between men and women, the GAMM model was used for each sex separately (Supplementary Table 6, Supplemental digital content 8, *http://links.lww.com/FPC/A822*). Interestingly, men carrying the *T*-allele of *rs846906C > T* showed 0.14 mmol/l lower HDL-C levels compared with noncarriers ($n = 126$, $P_{corrected} = 0.006$), explaining 3.4% of the variance in HDL-C. No significant association was observed between the other *HSD11B1* SNPs and HDL-C ($P_{corrected} > 0.05$).

HSD11B1 polymorphisms in the psychiatric replication studies

Only BMI data were available for the two psychiatric replication samples. The three *HSD11B1* SNPs *rs846910G > A*, *rs3753519G > A*, and *rs4844488A > G* that survived Bonferroni correction for BMI were analyzed in the replication samples (Supplementary Table 7, Supplemental digital content 9, *http://links.lww.com/FPC/A823*). For the rs*3753519G > A*, a significant association was only found in the second replication sample ($n = 184$), in which carriers of the *A*-allele had 1.3 kg/m^2 lower BMI compared with noncarriers (95% confidence interval: −2.28 to −0.31, $P = 0.01$) (Supplementary Table 7, Supplemental digital content 9, *http://links.lww.com/FPC/A823*).

No association was observed between *HSD11B1 rs846910G > A* or *rs4844488A > G* SNPs and BMI in the two replication samples. The lower frequency of female participants in both replication samples (Table 1) did not explain the lack of association between these two SNPs and BMI, given that there was also no such association among women in these samples.

On combining the three psychiatric samples, a significant association was observed between *HSD11B1 rs846910G > A* and BMI in the entire sample ($n = 802$, $P = 0.001$) and in women ($n = 406$, $P < 0.0001$) (Table 5). Significant associations were also found for *rs3753519G > A* in the entire sample, as well as in men and women, whereas *rs4844488A > G* was no longer associated with BMI after adding the replication samples to the main study sample (Table 5).

We further studied the effect of *HSD11B1* SNPs on BMI between different psychotropic drugs. *HSD11B1* SNPs were mostly associated with BMI in the subgroup of patients treated with olanzapine/clozapine or with risperidone/quetiapine. No influence of *HSD11B1* SNPs was found in the subgroup of patients treated with MS (more details in Supplementary Table 8, Supplemental digital content 10, *http://links.lww.com/FPC/A824*).

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

HSD11B1 haplotype blocks and combinations

A haplotype block was created from *HSD11B1 rs846910* and *rs3753519*. A small increase in the effect was observed in patients carrying the variant alleles of the two SNPs compared with the other genotypes and also compared with the carriers of the variant allele of each SNP separately. More details in Supplementary Table 9, Supplemental digital content 11 (*http://links.lww.com/FPC/A825*).

HSD11B1 single nucleotide polymorphisms in newly diagnosed patients

The effect of *HSD11B1* SNPs on BMI or MetS components (mainly WC and DBP) was more pronounced in a subgroup of patients from the main psychiatric study sample who were newly diagnosed with a psychiatric disorder. Details in Supplementary Tables 10, Supplemental digital content 12 (*http://links.lww.com/FPC/A826*) and 11, Supplemental digital content 12 (*http://links.lww.com/FPC/A826*).

HSD11B1 polymorphisms and the risk of metabolic syndrome

The risk of Mets as a whole was assessed between different *HSD11B1* genotypes at three time-points: at baseline, and at 3 and 12 months of follow-up (Table 6). *rs846906C>T* was associated with a higher risk of MetS at 3 months of follow-up (21 and 43% for *rs846906-CC* and *T*-allele carriers, respectively, odds ratio: 3.31, 95% confidence interval: 1.53–7.17, $P_{corrected}=0.014$). The same association was observed for this SNP and MetS at 12 months of follow-up, but did not survive Bonferroni correction (Table 6). None of the other *HSD11B1* SNPs were associated with the MetS. The same results were also obtained applying the criteria of the International Diabetes Federation consensus [47] (data not shown).

HSD11B1 polymorphisms in the population-based samples

No significant associations were observed between *HSD11B1* SNPs that survived Bonferroni corrections (*rs846910G>A*, *rs3753519G>A*, *rs4844488A>G*, and *rs846906C>T*) and BMI or MetS components in the CoLaus sample, including sex analyses (Supplementary Table 12 Supplemental digital content 13, *http://links.lww.com/FPC/A827*). Moreover, in PsyCoLaus, there were no two-way interactions between *HSD11B1* SNPs and MDD for the risk of the MetS or its components, that is there was no evidence for differential associations between these SNPs and MetS components according to the patients' depression status. *HSD11B1* SNPs were not associated with obesity traits in the GIANT study sample or with lipid traits in the 'Genome Wide Associations Scans for Total Cholesterol, HDL-C, LDL-C and triglycerides' study. Moreover, GIANT's sex-specific meta-analyses ($N_{men}=60\,586$ and $N_{women}=73\,137$) [46] do not show significant associations between the four *HSD11B1* SNPs and BMI (Supplementary Table 13, Supplemental digital content 14, *http://links.lww.com/FPC/A828*). Interestingly, even if the results were not significant, the direction of the association was similar to the psychiatric samples in most of the population-based analyses.

Gene expression analyses and *HSD11B1* polymorphism

No influence of *rs846910G>A* and *rs3753519G>A* was observed on *HSD11B1* gene expression. Details including discussion are available in Supplementary data and Supplementary Figs 2–4 (Supplemental digital content 1, *http://links.lww.com/FPC/A815*).

Discussion

Several conflicting results have been found between *HSD11B1* SNPs and MetS in the general population. However, these studies were carried out in relatively small samples with different ethnicities. The present study aimed to test whether common SNPs within the *HSD11B1* gene are associated with BMI and the MetS in a sample of psychiatric patients receiving potential weight gain-inducing psychotropic drugs, which has, to our knowledge, never been investigated. In addition, we extended our analyses to several large community samples to elucidate the real impact of *HSD11B1* SNPs in nonclinical individuals. Carriers of the variant alleles of three *HSD11B1* SNPs (*rs846910-A*, *rs3753519-A*, *and rs4844488-G*) showed lower BMI, WC, and DBP compared with the wild-type genotypes in the main psychiatric study sample. These associations were exclusively observed in women. A small increase in the effect on BMI and/or MetS components was also observed by combining two SNPs, *rs846910G>A*, and *rs3753519G>A*. In addition, men carrying the variant allele of *rs846906C>T* showed higher WC, higher triglycerides, and lower HDL-C blood levels compared with wild-type genotype. *HSD11B1* SNPs were investigated previously in population-based samples and related to the MetS, but with contradictory results. In American Indians, the variant *rs846910-A* allele was associated with diabetes mellitus ($n=706$) [21] and higher blood pressure ($n=918$) [22]. In contrast, in a study in Bosnian patients ($n=86$), the *rs846910-A* allele showed a protective effect against high blood pressure [48]. This SNP also showed a protective effect in 248 White families ascertained through a proband with hypertension ($n>800$) as it was associated with lower left ventricular mass, an independent risk factor for cardiovascular mortality [25]. In a sample of 600 women, patients who were heterozygous for *rs846910-A* and homozygous for *rs12086634T* had a higher risk of MetS; however, no data were presented for the influence of *rs846910* SNP solely with the MetS [23]. Finally, this SNP was not associated with obesity or other metabolic traits in other studies ($n=448$, 534, 1880) [27,28,49]. These contradictory results could be explained by differences in methodology and tested samples as well as differences in the outcome in each study. *Rs3753519G>A* was investigated in only one study and *rs3753519-A* was associated strongly with obesity in

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

Table 6 Association between *HSD11B1* genotypes and the metabolic syndrome as defined by the National Cholesterol Education Program's Adult Treatment Panel III report in the main psychiatric sample

	At baseline			3 months			12 months		
	n (%)	OR (95% CI)	*P*-value ($P_{corrected}$)	*n* (%)	OR (95% CI)	*P*-value ($P_{corrected}$)	*n* (%)	OR (95% CI)	*P*-value ($P_{corrected}$)
rs12565406									
GG	23/135 (17)	Reference		37/137 (27)	Reference		23/87 (26)	Reference	
GT/TT	4/26 (15)	1.34 (0.39–4.602)	0.64 (>0.05)	7/26 (27)	1.18 (0.44–3.14)	0.75 (>0.05)	7/22 (32)	1.25 (0.44–3.53)	0.68 (>0.05)
rs10863782									
GG	20/111 (18)	Reference		31/116 (27)	Reference		19/75 (25)	Reference	
GA/AA	7/50 (14)	1.16 (0.42–3.19)	0.78 (>0.05)	13/47 (28)	1.11 (0.50–2.44)	0.79 (>0.05)	11/34 (32)	1.36 (0.55–3.37)	0.51 (>0.05)
rs846910									
GG	26/145 (18)	Reference		41/147 (28)	Reference		27/100 (27)	Reference	
GA/AA	1/16 (6)	0.46 (0.06–3.88)	0.48 (>0.05)	3/16 (19)	0.69 (0.18–2.66)	0.59 (>0.05)	3/9 (33)	1.32 (0.30–5.74)	0.71 (>0.05)
rs3753519									
GG	24/129 (19)	Reference		40/138 (29)	Reference		23/84 (27)	Reference	
GA/AA	3/32 (9)	0.61 (0.16–2.26)	0.46 (>0.05)	4/25 (16)	0.52 (0.16–1.68)	0.28 (>0.05)	7/25 (28)	1.02 (0.37–2.80)	0.96 (>0.05)
rs12086634									
TT	16/107 (15)	Reference		29/119 (24)	Reference		20/72 (28)	Reference	
TG/GG	11/54 (20)	1.47 (0.61–3.58)	0.39 (>0.05)	15/44 (34)	1.38 (0.63–3.03)	0.42 (>0.05)	10/37 (27)	0.88 (0.35–2.19)	0.78 (>0.05)
rs4844488									
AA	27/152 (18)	Reference		43/157 (27)	Reference		28/102 (27)	Reference	
AG/GG	0/9 (0)	NA		1/6 (17)	0.44 (0.05–4.27)	0.48 (>0.05)	2/7 (29)	0.90 (0.16–5.09)	0.91 (>0.05)
rs846906									
CC	18/117 (15)	Reference		24/117 (21)	Reference		17/79 (22)	Reference	
CT/TT	9/44 (20)	1.59 (0.62–4.09)	0.34 (>0.05)	20/46 (43)	3.31 (1.53–7.18)	**0.002 (0.014)**	13/30 (43)	3.17 (1.25–8.06)	**0.02 (>0.05)**

Odds ratios (OR) and *P*-values were adjusted for age and sex.
P-values that survived Bonferroni correction are presented in bold.
The NCEP ATP III panel defined metabolic syndrome as the presence of three or more of the following risk determinants: (a) increased waist circumference (>102 cm for men, >88 cm for women); (b) increased triglycerides (≥150 mg/dl) or treatment with hypolipidemic agents; (c) low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women); (d) hypertension (≥130/≥85 mmHg) or treatment with antihypertensive; and (e) impaired fasting glucose (≥110 mg/dl) or treatment with antidiabetics.

children (n=534) [28]. The results on obesity are inconsistent with our results in which carriers of the *rs3753519-A* allele showed a protective effect against obesity and was associated with lower blood pressure. In addition, unlike our results, other SNPs within the *HSD11B1* gene such as *rs846910*, *rs4844488*, and *rs846906* were not associated with obesity in the former study [28]. This discrepancy could be explained by the fact that the former study was carried out in healthy children, whereas ours included mostly adult psychiatric patients treated with potential weight gain-inducing drugs. *HSD11B1 rs4844488* was analyzed in few studies, and no significant association was found between this SNP and BMI and/or MetS components [25,28,50]. Finally, in our study, *HSD11B1 rs846906C>T* was the only SNP associated with increased WC, triglycerides and decreased HDL-C, and exclusively in men. In addition, the *rs846906C>T* was associated with an increased risk of MetS at 3 months of follow-up. Only a few publications have analyzed this intronic SNP and no association was found with the tested phenotypes [25,28,51,52].

In the present study, three *HSD11B1* SNPs were associated strongly with BMI and MetS components in the subgroup of psychiatric women taking psychotropic drugs. The adipose tissue is a well-known source of estrogen production through aromatization of androgens [53,54]. A direct relationship between aromatase activity and body weight was also proposed [55,56]. In addition, a dual relationship in the production of estrogen and cortisol in the adipose tissue was suggested [56], in which estrogen may increase cortisone to cortisol conversion mediated by 11β-HSD1 and cortisol may increase aromatase activity, producing more estrogen in the tissues [57]. However, we cannot explain the findings between *rs846906C>T* and lipid traits and WC in men.

The association between *HSD11B1* SNPs and BMI was mainly observed in the main psychiatric study and was only partially observed in the replication samples. The main psychiatric sample has a shorter treatment duration, includes relatively newly treated patients, and has lower initial BMI compared with the replication samples, which have a longer treatment duration and a longer history of psychiatric disorder (Table 1). Interestingly, when investigating specifically the subgroup of newly diagnosed patients with psychiatric illness at the same year of study inclusion and started psychotropic treatment within the first year following the first psychiatric diagnosis, a stronger association was observed between *HSD11B1* SNPs and BMI or MetS components during the follow-up, suggesting a role of *HSD11B1* SNPs early in the psychiatric disorder and/or during the psychotropic medication. The effect of these SNPs might disappear after years of psychiatric illness and/or treatment with psychotropic drugs, with the majority of patients being overweight or obese.

In the present paper, we observed a significant association between the *HSD11B1* SNPs and BMI or MetS components in the clinical, but not in the population-based samples. Previous data suggest a role of glucocorticoids

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

and the hypothalamic–pituitary–adrenal (HPA) axis in the development of psychosis and/or depression. Animal studies showed an influence of 11ß-HSD1 on the regulation of the HPA axis [58,59]. In humans, 11ß-HSD1 was found to be expressed in the hypothalamus, suggesting not only a role in the modulation of glucocorticoids feedback of the HPA axis but also a possible regulatory effect on metabolism and appetite [60]. In addition, *HSD11B1 rs11119328* SNP was found to be associated with increased susceptibility to depression and with increased late-night cortisol levels and in postmenopausal women with higher androstenedione levels [52]. Altogether, these data suggest a possible role of the 11ß-HSD1 in the development of psychiatric disorders. Given the low proportion of patients with severe psychiatric disorders and psychotropic medication in the community, the discrepant results according to the recruitment source suggest that the effect of the *HSD11B1* gene on BMI and MetS is restricted to severe psychiatric disorders and/or patients treated with AP or MS. This hypothesis is in line with our recent study showing a stronger association between polymorphisms within the *cAMP-regulated transcriptional coactivator 1* (*CRTC1*) gene and obesity markers (BMI and fat mass) in psychiatry compared with population-based samples, even though the former sample size is much smaller than the latter [32]. The *CRTC1* genetic polymorphism explains up to 9% of BMI variance in young psychiatric women [32]. Another example is the *fat mass and obesity associated* (*FTO*) gene in which polymorphisms within this gene showed significant associations with obesity in two cohorts of depressive patients, but not in healthy controls [61]. SNPs in the *melanocortin 4 receptor* (*MC4R*) gene were also associated significantly with weight gain in four independent small psychiatric populations [11] and showed a small effect in the population-based samples [8]. Altogether, these data suggest that psychiatric disorders and/or psychotropic treatments seem to unravel the importance of selected genes involved in obesity and the effect of these polymorphisms could be observed even in small psychiatric sample sizes compared with the population-based samples.

Several limitations of this study need to be acknowledged. Hormonal measurements were not available for our samples; thus, the interaction between estrogen and *HSD11B1* variants could not be explored. This study was restricted to patients of White origin and the results cannot be generalized to other ethnic groups. Finally, our gene expression analysis did not show a functional activity of the two SNPs and further studies, in particular, with adipocytes and/or peripheral blood mononuclear cells from psychiatric patients, are needed to elucidate the biochemical mechanisms underlying the associations observed.

In conclusion, this is the first pharmacogenetic study relating genetic polymorphisms within *HSD11B1* and BMI and/or MetS and its components in psychiatric patients. Previous studies failed to associate *HSD11B1* SNPs with BMI and/or WC in different population-based samples and showed many conflicting results for the other MetS traits. In the present psychiatric sample treated with potential weight gain-inducing psychotropic drugs, *HSD11B1* SNPs were significantly associated with BMI and metabolic traits, especially in women and in newly drug-treated patients. In addition, in several very large population-based samples, we could not show an impact of *HSD11B1* SNPs on BMI and MetS traits, showing that these SNPs do not play an important role in the general population. Further studies are needed to determine the mechanism by which *HSD11B1* SNPs influence obesity and other metabolic disturbances in psychiatric patients treated with psychotropic drugs.

Acknowledgements

The authors thank Dr S. Crettol, C. Brogli, V. Hodel (logistical assistance), E. Retamales (bibliographical help), A. C. Aubert, M. Brocard, N. Cochard, M. Delessert, A. Kottelat, M. Brawand, K. Powell Golay, S. Jacquet, and M. Jonzier (sample analysis). They thank the GIANT consortium for access to their BMI association result in 123 807 individuals.

This work has been funded in part by the Swiss National Research Foundation (CBE and PC: 324730_144064). C.B.E. has received research support from Takeda and from the Roche Organ Transplantation Research Foundation in the past 3 years. M.B. is supported by the Swiss School of Public Health Plus (SSPH+). P.V. and G.W. received an unrestricted grant from GlaxoSmithKline to build the CoLaus study. The CoLaus/PsyCoLaus study received financial contributions from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (105993, 118308, 122661, 139468). Z.K. received support from the Leenaards Foundation and the Swiss National Science Foundation (31003A-143914).

Conflicts of interest

C.B.E. has received honoraria for conferences or teaching CME courses from Advisis, Astra Zeneca, Essex Chemie, Lundbeck, MSD, Sandoz, Servier, and Vifor-Pharma in the past 3 years. A.V.G. has received honoraria for a conference or workshop participation from Vifor and Bayer Sheringer in the past 3 years. G.W. has received honoraria from Lilly, Novartis, GSK, and MSD for talks. M.P. has received honoraria for conferences or teaching CME courses from Astra Zeneca, Lundbeck, Servier SA, and swissprofessionalmedia AG in the past 3 years. For the remaining authors there are no conflicts of interest.

References

1 Yumru M, Savas HA, Kurt E, Kaya MC, Selek S, Savas E, *et al.* Atypical antipsychotics related metabolic syndrome in bipolar patients. *J Affect Disord* 2007; **98**:247–252.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

2 Berkowitz RI, Fabricatore AN. Obesity, psychiatric status, and psychiatric medications. *Psychiatr Clin North Am* 2011; **34**:747–764.
3 Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, *et al.* Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; **24**:683–689.
4 Brown S. Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry* 1997; **171**:502–508.
5 Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. *Br J Psychiatry* 2013; **202**:22–27.
6 American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; **27**:596–601.
7 Dubois L, Ohm Kyvik K, Girard M, Tatone-Tokuda F, Pérusse D, Hjelmborg J, *et al.* Genetic and environmental contributions to weight, height, and BMI from birth to 19 years of age: an international study of over 12,000 twin pairs. *PLoS One* 2012; **7**:e30153.
8 Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, *et al.* Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010; **42**:937–948.
9 Ryan MC, Flanagan S, Kinsella U, Keeling F, Thakore JH. The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naive patients with schizophrenia. *Life Sci* 2004; **74**:1999–2008.
10 Correll CU, Malhotra AK. Pharmacogenetics of antipsychotic-induced weight gain. *Psychopharmacology (Berl)* 2004; **174**:477–489.
11 Malhotra AK, Correll CU, Chowdhury NI, Müller DJ, Gregersen PK, Lee AT, *et al.* Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug-induced weight gain. *Arch Gen Psychiatry* 2012; **69**:904–912.
12 Wamil M, Seckl JR. Inhibition of 11beta-hydroxysteroid dehydrogenase type 1 as a promising therapeutic target. *Drug Discov Today* 2007; **12**:504–520.
13 Tomlinson JW, Walker EA, Bujalska IJ, Draper N, Lavery GG, Cooper MS, *et al.* 11beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. *Endocr Rev* 2004; **25**:831–866.
14 Walker BR, Soderberg S, Lindahl B, Olsson T. Independent effects of obesity and cortisol in predicting cardiovascular risk factors in men and women. *J Intern Med* 2000; **247**:198–204.
15 Masuzaki H, Paterson J, Shinyama H, Morton NM, Mullins JJ, Seckl JR, Flier JS. A transgenic model of visceral obesity and the metabolic syndrome. *Science* 2001; **294**:2166–2170.
16 Paterson JM, Morton NM, Fievet C, Kenyon CJ, Holmes MC, Staels B, *et al.* Metabolic syndrome without obesity: hepatic overexpression of 11beta-hydroxysteroid dehydrogenase type 1 in transgenic mice. *Proc Natl Acad Sci U S A* 2004; **101**:7088–7093.
17 Morton NM, Holmes MC, Fiévet C, Staels B, Tailleux A, Mullins JJ, Seckl JR. Improved lipid and lipoprotein profile, hepatic insulin sensitivity, and glucose tolerance in 11beta-hydroxysteroid dehydrogenase type 1 null mice. *J Biol Chem* 2001; **276**:41293–41300.
18 Wang SJ, Birtles S, de Schoolmeester J, Swales J, Moody G, Hislop D, *et al.* Inhibition of 11beta-hydroxysteroid dehydrogenase type 1 reduces food intake and weight gain but maintains energy expenditure in diet-induced obese mice. *Diabetologia* 2006; **49**:1333–1337.
19 Desbriere R, Vuaroqueaux V, Achard V, Boullu-Ciocca S, Labuhn M, Dutour A, Grino M. 11beta-hydroxysteroid dehydrogenase type 1 mRNA is increased in both visceral and subcutaneous adipose tissue of obese patients. *Obesity (Silver Spring)* 2006; **14**:794–798.
20 Paulsen SK, Pedersen SB, Fisker S, Richelsen B. 11Beta-HSD type 1 expression in human adipose tissue: impact of gender, obesity, and fat localization. *Obesity (Silver Spring)* 2007; **15**:1954–1960.
21 Nair S, Lee YH, Lindsay RS, Walker BR, Tataranni PA, Bogardus C, *et al.* 11beta-hydroxysteroid dehydrogenase type 1: genetic polymorphisms are associated with Type 2 diabetes in Pima Indians independently of obesity and expression in adipocyte and muscle. *Diabetologia* 2004; **47**:1088–1095.
22 Franks PW, Knowler WC, Nair S, Koska J, Lee YH, Lindsay RS, *et al.* Interaction between an 11beta HSD1 gene variant and birth era modifies the risk of hypertension in Pima Indians. *Hypertension* 2004; **44**:681–688.
23 Gambineri A, Tomassoni F, Munarini A, Stimson RH, Mioni R, Pagotto U, *et al.* A combination of polymorphisms in HSD11B1 associates with in vivo 11{beta}-HSD1 activity and metabolic syndrome in women with and without polycystic ovary syndrome. *Eur J Endocrinol* 2011; **165**:283–292.
24 Gambineri A, Vicennati V, Genghini S, Tomassoni F, Pagotto U, Pasquali R, Walker BR. Genetic variation in 11beta-hydroxysteroid dehydrogenase type 1 predicts adrenal hyperandrogenism among lean women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2006; **91**:2295–2302.
25 Rahman TJ, Mayosi BM, Hall D, Avery PJ, Stewart PM, Connell JM, *et al.* Common variation at the 11-beta hydroxysteroid dehydrogenase type 1 gene is associated with left ventricular mass. *Circ Cardiovasc Genet* 2011; **4**:156–162.
26 Moon SS, Lee YS, Kim JG, Kim SW, Jeong JY, Jeon EJ, *et al.* Relationship of 11beta-hydroxysteroid dehydrogenase type 1 and hexose-6-phosphate dehydrogenase gene polymorphisms with metabolic syndrome and type 2 diabetes. *Endocr J* 2011; **58**:949–959.
27 Duran-Gonzalez J, Ortiz I, Gonzales E, Ruiz N, Ortiz M, Gonzalez A, *et al.* Association study of candidate gene polymorphisms and obesity in a young Mexican-American population from South Texas. *Arch Med Res* 2011; **42**:523–531.
28 Olza J, Gil-Campos M, Leis R, Ruperez AI, Tojo R, Canete R, *et al.* A gene variant of 11beta-hydroxysteroid dehydrogenase type 1 is associated with obesity in children. *Int J Obes* 2012; **36**:1558–1563.
29 Smit P, Dekker MJ, de Jong FJ, van den Beld AW, Koper JW, Pols HA, *et al.* Lack of Association of the 11beta-hydroxysteroid dehydrogenase type 1 gene 83,557insA and hexose-6-phosphate dehydrogenase gene R453Q polymorphisms with body composition, adrenal androgen production, blood pressure, glucose metabolism, and dementia. *J Clin Endocrinol Metab* 2007; **92**:359–362.
30 Ku YH, Koo BK, Kwak SH, Cho YM, Shin HD, Lee HK, *et al.* Regulatory effect of common promoter polymorphisms on the expression of the 11beta-hydroxysteroid dehydrogenase type 1 gene. *Horm Res* 2009; **72**:25–32.
31 Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. American Heart Association, *et al.* Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; **109**:433–438.
32 Choong E, Quteineh L, Cardinaux JR, Gholam-Rezaee M, Vandenberghe F, Dobrinas M, *et al.* Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and the general adult population. *JAMA Psychiatry* 2013; **70**:1011–1019.
33 Firmann M, Mayor V, Vidal PM, Bochud M, Pécoud A, Hayoz D, *et al.* The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord* 2008; **8**:6.
34 Preisig M, Waeber G, Vollenweider P, Bovet P, Rothen S, Vandeleur C, *et al.* The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. *BMC Psychiatry* 2009; **9**:9.
35 Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, *et al.* Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* 2010; **467**:832–838.
36 Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V, *et al.* Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet* 2010; **42**:949–960.
37 Genome wide associations scans for total cholesterol, HDL-C, LDL-C and triglycerides. Available at: *http://www.sph.umich.edu/csg/abecasis/public/lipids2010/*. [Accessed 14 January 2014].
38 Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, *et al.* Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* 2010; **466**:707–713.
39 Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 2005; **21**:263–265.
40 Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, *et al.* 1000 Genomes Project Consortium. An integrated map of genetic variation from 1,092 human genomes. *Nature* 2012; **491**:56–65.
41 Voight BF, Kang HM, Ding J, Palmer CD, Sidore C, Chines PS, *et al.* The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. *PLoS Genet* 2012; **8**:e1002793.
42 Lin X, Zhang D. Inference in generalized additive mixed models by using smoothing splines. *J R Statist Soc B* 1999; **61**:381–400.
43 Wood SN. GAMMs with R. In: Carlin BP, Chatfield C, Tanner M, Zidek J, editors. *Generalized additive models – an introduction with R Broken*. Boca Raton, Florida, USA: Chapman & Hall/CRC; 2006. pp. 319–324.
44 Davison AC, Hinkley DV. *Bootstrap methods and their application*. Cambridge, NY: Cambridge University Press; 1997.
45 Morant J. Swiss Drug Compendium, Vol 31e. Basel, Switzerland: Documed S. A; 2010. p. 3-A 5257.
46 Randall JC, Winkler TW, Kutalik Z, Berndt SI, Jackson AU, Monda KL, *et al.* Sex-stratified genome-wide association studies including 270,000 individuals show sexual dimorphism in genetic loci for anthropometric traits. *PLoS Genet* 2013; **9**:e1003500.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

47 The IDF consensus woldwide definition of the metabolic syndrome. 2009. Available at: *http://www.idf.org*. [Accessed January 2014].
48 Dujic T, Bego T, Mlinar B, Semiz S, Malenica M, Prnjavorac B, *et al.* Association between 11beta-hydroxysteroid dehydrogenase type 1 gene polymorphisms and metabolic syndrome in Bosnian population. *Biochem Med (Zagreb)* 2012; **22**:76–85.
49 Iwai N, Tago N, Yasui N, Kokubo Y, Inamoto N, Tomoike H, Shioji K. Genetic analysis of 22 candidate genes for hypertension in the Japanese population. *J Hypertens* 2004; **22**:1119–1126.
50 Feldman K, Szappanos A, Butz H, Grolmusz V, Majnik J, Likó I, *et al.* The rs4844880 polymorphism in the promoter region of the HSD11B1 gene associates with bone mineral density in healthy and postmenopausal osteoporotic women. *Steroids* 2012; **77**:1345–1351.
51 Chua AK, Azziz R, Goodarzi MO. Association study of CYP17 and HSD11B1 in polycystic ovary syndrome utilizing comprehensive gene coverage. *Mol Hum Reprod* 2012; **18**:320–324.
52 Dekker MJ, Tiemeier H, Luijendijk HJ, Kuningas M, Hofman A, de Jong FH, *et al.* The effect of common genetic variation in 11beta-hydroxysteroid dehydrogenase type 1 on hypothalamic-pituitary-adrenal axis activity and incident depression. *J Clin Endocrinol Metab* 2012; **97**:E233–E237.
53 Longcope C, Pratt JH, Schneider SH, Fineberg SE. Aromatization of androgens by muscle and adipose tissue in vivo. *J Clin Endocrinol Metab* 1978; **46**:146–152.
54 Perel E, Killinger DW. The interconversion and aromatization of androgens by human adipose tissue. *J Steroid Biochem* 1979; **10**:623–627.
55 Edman CD, MacDonald PC. Effect of obesity on conversion of plasma androstenedione to estrone in ovulatory and anovulator young women. *Am J Obstet Gynecol* 1978; **130**:456–461.
56 Mattsson C, Olsson T. Estrogens and glucocorticoid hormones in adipose tissue metabolism. *Curr Med Chem* 2007; **14**:2918–2924.
57 Yang K, Khalil MW, Strutt BJ, Killinger DW. 11 beta-hydroxysteroid dehydrogenase 1 activity and gene expression in human adipose stromal cells: effect on aromatase activity. *J Steroid Biochem Mol Biol* 1997; **60**:247–253.
58 Harris HJ, Kotelevtsev Y, Mullins JJ, Seckl JR, Holmes MC. Intracellular regeneration of glucocorticoids by 11beta-hydroxysteroid dehydrogenase (11beta-HSD)-1 plays a key role in regulation of the hypothalamic-pituitary-adrenal axis: analysis of 11beta-HSD-1-deficient mice. *Endocrinology* 2001; **142**:114–120.
59 Paterson JM, Holmes MC, Kenyon CJ, Carter R, Mullins JJ, Seckl JR. Liver-selective transgene rescue of hypothalamic-pituitary-adrenal axis dysfunction in 11beta-hydroxysteroid dehydrogenase type 1-deficient mice. *Endocrinology* 2007; **148**:961–966.
60 Bisschop PH, Dekker MJ, Osterthun W, Kwakkel J, Anink JJ, Boelen A, *et al.* Expression of 11beta-hydroxysteroid dehydrogenase type 1 in the human hypothalamus. *J Neuroendocrinol* 2013; **25**:425–432.
61 Rivera M, Cohen-Woods S, Kapur K, Breen G, Ng MY, Butler AW, *et al.* Depressive disorder moderates the effect of the FTO gene on body mass index. *Mol Psychiatry* 2012; **17**:604–611.

Copyright © 2015 Wolters Kluwer Health, Inc. Unauthorized reproduction of the article is prohibited.

Association of *PCK1* with Body Mass Index and Other Metabolic Features in Patients With Psychotropic Treatments

Núria Saigi-Morgui, PharmD, MPH, Frederik Vandenberghe, PharmD, MSc,* Aurélie Delacrétaz, MSc,* Lina Quteineh, MD, PhD,* Eva Choong, PhD,* Mehdi Gholamrezaee, PhD,† Pierre Magistretti, MD, PhD,‡§ Jean-Michel Aubry, MD,‖ Armin von Gunten, MPhil, MD,¶ Martin Preisig, MD, MPH,† Enrique Castelao, MSc,† Peter Vollenweider, MD,# Gerard Waeber, MD,# Zoltán Kutalik, PhD,**†† Philippe Conus, MD,‡‡ and Chin B. Eap, PhD*§§*

Abstract: Weight gain is a major health problem among psychiatric populations. It implicates several receptors and hormones involved in energy balance and metabolism. Phosphoenolpyruvate carboxykinase 1 is a rate-controlling enzyme involved in gluconeogenesis, glyceroneogenesis and cataplerosis and has been related to obesity and diabetes phenotypes in animals and humans. The aim of this study was to investigate the association of *phosphoenolpyruvate carboxykinase 1* polymorphisms with metabolic traits in psychiatric patients treated with psychotropic drugs inducing weight gain and in general population samples. One polymorphism (*rs11552145G > A*) significantly associated with body mass index in the psychiatric discovery sample (n = 478) was replicated in 2 other psychiatric samples ($n_1 = 168$, $n_2 = 188$), with *AA*-genotype carriers having lower body mass index as compared to *G-allele* carriers. Stronger associations were found among women younger than 45 years carrying *AA*-genotype as compared to *G-allele* carriers (−2.25 kg/m^2, n = 151, $P = 0.009$) and in the discovery sample (−2.20 kg/m^2, n = 423, $P = 0.0004$). In the discovery sample for which metabolic parameters were available, *AA*-genotype showed lower waist circumference (−6.86 cm, $P = 0.008$) and triglycerides levels (−5.58 mg/100 mL, $P < 0.002$) when compared to *G-allele* carriers. Finally, waist-to-hip ratio was associated with *rs6070157* (proxy of *rs11552145*, $r^2 = 0.99$) in a population-based sample (N = 123,865, $P = 0.022$). Our results suggest an association of *rs11552145G > A* polymorphism with metabolic-related traits, especially in psychiatric populations and in women younger than 45 years.

Key Words: metabolic syndrome, body mass index, psychotropic drugs, pharmacogenetics

(*J Clin Psychopharmacol* 2015;35: 544–552)

From the *Unit of Pharmacogenetics and Clinical Psychopharmacology, Department of Psychiatry, Centre for Psychiatric Neuroscience, †Department of Psychiatry, Centre of Psychiatric Epidemiology and Psychopathology, ‡Department of Psychiatry, Centre for Psychiatric Neuroscience, Lausanne University Hospital, Prilly, Switzerland; §Laboratory of Neuroenergetics and Cellular Dynamics, Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne, Lausanne; ‖Department of Mental Health and Psychiatry, University Hospital of Geneva, Geneva; ¶Service of Old Age Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly; #Department of Medicine, Lausanne University Hospital; **Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital; ††Swiss Institute of Bioinformatics, Lausanne; ‡‡Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly; and §§School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland.

Received January 16, 2015; accepted after revision June 26, 2015.

Reprints: Chin B. Eap, PhD, Unit of Pharmacogenetics and Clinical Psychopharmacology, Department of Psychiatry, Lausanne University Hospital, 1008 Prilly, Switzerland (e-mail: chin.eap@chuv.ch).

Funding: This work has been funded in part by the Swiss National Research Foundation (CBE and PC: 320030–120686 and 324730_144064). P.V. and G.W. received an unrestricted grant form GlaxoSmithKline to build the CoLaus study. The CoLaus/PsyCoLaus study is supported by financial contributions from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 3200B0–105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468 and 33CS30-148401). Z.K. received support from the Leenaards Foundation and the Swiss National Science Foundation (31003A-143914). The funding sources had no role in the writing of the manuscript or in the decision to submit it for publication.

Supplemental digital contents are available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000000388

Weight gain is a known side effect of psychotropic drugs, such as antipsychotics, mood stabilizers, and antidepressants.[1] Psychotropic-induced weight gain can lead to many metabolic complications (eg, increase in triglycerides [TG], cholesterol [CHOL], waist circumference [WC]) and is related to comorbidities, such as diabetes, hypertension, and other cardiovascular diseases.[2] Psychiatric populations have a 10- to 25-year reduction in life expectancy due to comorbidities and to the psychiatric illness itself, corresponding to a 2- to 3-fold increased mortality rate when compared to healthy populations.[3] Obesity is attributed to the psychiatric illness, to behavioral and environmental factors (ie, diet, exercise, smoking), as well as genetic factors.[4] Besides, an interaction between genetic factors and psychotropic drug-inducing weight gain has been described implicating several receptors (eg, serotonin and dopamine receptors) and hormones (eg, leptin) involved in energy balance or metabolism pathways.[5,6]

The *Phosphoenolpyruvate carboxykinase* (*PCK*) gene codes for an enzyme involved in the gluconeogenesis[7] and is found in 2 forms, PCK1 (cytosolic) and PCK2 (mitochondrial). Both enzymes are expressed equally in the liver but their expression may vary depending on the tissue.[7,8] The PCK catalyzes the conversion from oxalacetate into phosphoenolpyruvate (a rate-controlling step of gluconeogenesis) and is also involved in glyceroneogenesis and cataplerosis.[7] Of note, *PCK* is a downstream gene of the *CREB-regulated transcription coactivator 1* (*CRTC1*) which is implicated in hypothalamic control of food intake,[9,10] and we recently found in general and psychiatric populations that carriers of a variant allele of a *CRTC1* polymorphism appear to be protected against weight gain especially in women younger than 45 years.[11]

Rodents who overexpress *PCK1* and *PCK2* were obese, hyperglycemic, and insulin-resistant,[12,13] whereas mice that underexpress *PCK1* and *PCK2* developed a lipodistrophy type of metabolic syndrome.[14] This is in line with the positive correlation found between PCK1 mRNA expression levels and body mass index (BMI), body fat percentage, TG, and CHOL levels in subcutaneous adipose tissue of nonmenopausal women.[15] In humans, regions near *PCK1* locus have been related to obesity or fat mass,[16,17] and several positive associations have been reported between *PCK1* polymorphisms and type 2 diabetes mellitus (T2DM)[18–20] although these results could not always be replicated.[21] Other studies conducted in the general population showed no significant association between *PCK1* polymorphisms and

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

BMI, WC or physical activity.[22] A case-control study in a diabetic versus non diabetic population also found that nondiabetic homozygous for the minor allele of a *PCK1* polymorphism (*+4824 T > C*) had increased levels of high-density lipoproteins (HDL) and lower TG levels when compared to wild type.[23] Thus, growing evidence supports that *PCK* contributes to obesity and metabolic syndrome in the general population but, to our knowledge, no studies have yet been conducted in psychiatric populations which are at high risk for developing obesity and metabolic syndrome. The aim of the present study was to analyze whether *PCK1* polymorphisms were associated with BMI and other metabolic traits (ie, WC, blood glucose levels [BGL], low-density lipoprotein [LDL], HDL, CHOL, and TG in 3 independent psychiatric populations treated with drugs inducing weight gain and in 3 large general population cohorts. As a secondary aim, we wanted to explore how *PCK1* and *CRTC1* polymorphisms are associated with BMI in a combined analysis.

MATERIALS AND METHODS

Psychiatric Sample Description

The first psychiatric sample (discovery sample) was recruited during a longitudinal follow-up study on metabolic syndrome at the Lausanne Psychiatric University Hospital (started in 2007, ongoing). Four hundred seventy-eight white patients switching or starting a treatment with drugs known to potentially induce weight gain (aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, mirtazapine, lithium, and/or valproate) were included. Weight, height, and other clinical variables were reported at baseline and at 1, 2, 3, 6, 9, and 12 months after starting the treatment according to published monitoring guidelines of weight and metabolic syndrome parameters.[24] Most patients had already received other psychotropic treatment before the current treatment. Fasting BGL and lipid levels (ie, CHOL, TG, LDL, HDL) were analyzed on a routine basis on blood samples using a Modular P apparatus (Roche Diagnostics, Switzerland). For patients for whom drug plasma determinations were available, we conducted preliminary analysis on the influence of compliance on the observed associations. For this purpose, we defined an arbitrary threshold at 10% of the minimal therapeutic drug plasma concentration[25] (ie, 2, 35, 10, 2, 15, 10, 2 ng/mL, 0.05 mmol/L, 5 mg/L for olanzapine, clozapine, quetiapine, risperidone + hydroxy-risperidone, aripiprazole, amisulpride, paliperidone, lithium, and valproate) to ensure psychotropic drug intake. Similar results to those described in the present article were obtained (data not shown). Thus, to increase the power of the study, the whole cohort was used for statistical analysis. Two other psychiatric samples were used as replication samples. A retrospective study (replication sample 1) was conducted in an outpatient setting in Geneva University Hospital in 2007. One hundred sixty-eight white patients treated for at least 3 months with olanzapine, clozapine, quetiapine, risperidone, lithium, and/or valproate were recruited. Another retrospective outpatient study in Lausanne, replication sample 2 (started in 2010, ongoing) included 188 white patients mostly treated for more than 1 year with aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, mirtazapine, lithium, and/or valproate. For both replication samples, questionnaires were filled during one of the patient routine follow-ups and weight, height, WC, and treatment duration were reported among other clinical variables. Weight before starting psychotropic treatment was self-reported or extracted from medical files. As shown previously,[11] self-reported weight was found to be a reliable estimate of the measured weight extracted from medical files.

In all samples, patients with previous treatments were included after having switched medication. The latest introduced psychotropic medication was considered as the main psychotropic treatment. Weight (patients with light clothes and without shoes) was measured in kilograms to the nearest kg. Height was measured using a height gauge to the nearest cm. The WC was measured to the nearest centimeter. The BMI for all individuals was obtained by dividing weight (in kg) by squared height (in m^2).

Written informed consent was provided by all individuals or by their legal representatives, and the studies were approved by the ethics committee of the corresponding centers. Further details of the 3 psychiatric cohorts have already been described elsewhere.[11,26] Of note, the present study refers to the same 3 psychiatric populations than in our previous article,[11] but with a larger number of patients included in the discovery cohort and in the replication sample 2 (inclusions ongoing).

Population-Based Samples

Significant results were tested for replication in 3 population based samples: participants in CoLaus (n = 5338) were recruited between June 2003 and May 2006 in the Lausanne area as described previously.[27] The Genetic Investigation of Anthropometric Traits Consortium (GIANT) performed a meta-analysis of genomewide association study data with a discovery set of 123,865 individuals of European ancestry from 46 studies for height,[28] BMI,[4] and waist-to-hip ratio (WHR).[29] Finally, the second set of association summary statistics for general populations (Global Lipids Genetics Consortium) was downloaded from "Genome Wide Associations Scans for Total Cholesterol, HDL-C, LDL-C and triglycerides" website[30] and contains data related to lipid traits (n = 100,184). Of note, CoLaus is part of both GIANT and Global Lipids Genetics Consortium.

SNP Selection and Genotyping

In a first step, the best replicated and studied *PCK1* polymorphism in the literature (ie, *rs2071023*) was manually genotyped using TaqMan allelic discrimination assay (ABI PRISM 7000 Sequence Detection System; Applied Biosystems, Rotkreuz, Switzerland, TaqMan SNP genotyping assays ID: C 2508731 1). Additionally, 3 SNPS which were available in the CardioMetaboChip were also considered for analysis (ie, *rs11552145, rs707555*, and *rs8123020*). The CardioMetaboChip is a custom Illumina iSelect genotyping array designed to test DNA variation of 200,000 SNPs from regions identified by large scale meta-analyses of genomewide association studies (GWAS) for metabolic and cardiovascular traits. Quality control excluded samples from the analysis if sex was inconsistent with genetic data from X-linked markers, genotype call rate less than 0.96, Gene Call score less than 0.15. GenomeStudio Data Analysis Software was used to export results generated by Illumina CardioMetaboChip. In total, 4 SNPs were considered for analyses with minor allele frequency (MAF) higher than 0.10 (Supplementary Table S-1, Supplemental Digital Content 1, http://links.lww.com/JCP/A313). All of them were in Hardy Weinberg Equilibrium (Supplementary Table S-2, Supplemental Digital Content 2, http://links.lww.com/JCP/A314). Finally, looking at HapMap Genome Browser (release 27, MAF > 0.10, cutoff of r^2 set at 0.8),[31] we found that several *PCK1* tagging SNPs were in linkage disequilibrium with our four selected SNPs (see details in Supplementary Figure S-1, Supplemental Digital Content 3, http://links.lww.com/JCP/A315).

DNA was extracted from blood samples as described by the manufacturer's protocol using Flexigene DNA kit and QIAamp DNA Blood Mini QIAcube Kit (Qiagen AG, Switzerland) for 834 Caucasian patients from the three psychiatric cohorts. Genotyping

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

of the *rs3746266A > G* SNP from *CRTC1* was performed using TaqMan allelic discrimination assay (ABI PRISM 7000 Sequence Detection System; Applied Biosystems) and according to the manufacturer's protocol as described elsewhere.[11] Genotyping of the CoLaus subjects was performed using the Affymetrix GeneChip Human Mapping 500 K array set as previously described.[27]

Variables of the Study

The main outcome analyzed in the three psychiatric samples was the BMI (kg/m^2) used as a continuous variable. Other outcomes studied were WC (cm), LDL, HDL, TG, CHOL and BGL (mg/100 mL). *PCK1* genotypes were grouped and analyzed in recessive (for *rs11552145, rs707555 and rs8123020*) and dominant (for *rs2071023*) models according to their association with BMI showed in preliminary analyses. Other covariates were extracted from medical files or during the interview and included demographic data (ie, sex, age, and ethnicity) as well as history of treatment (type of psychotropic drug and treatment duration). To preserve homogeneity of the samples, only patients treated up to 24 months were taken into account in combined (ie, discovery plus replication) psychiatric sample analyses.

Statistical Analysis

Psychiatric Samples

Hardy Weinberg Equilibrium was determined for each polymorphism by a χ^2 test. Statistical analyses were done using STATA 12.1 (StataCorp, College Station TX) and R version 2.11.1 software.[32] *P* values less than 0.05 were considered as statistically significant, and when necessary, Bonferroni correction for multiple tests was applied. Eventually, differences in sample size might be due to missing genotypes and/or covariates. First, exploratory analyses were conducted to explore differences in BMI between genetic groups in the 3 psychiatric samples using Mann-Whitney *U* nonparametric test. To fit a longitudinal model on the BMI trend, due to complex and nonlinear BMI evolution in time and presence of multiple observations per individual which introduces interdependence among observations, a Generalized Additive Mixed Model was used to assess the association of genetic polymorphism with BMI adjusted by sex, age, treatment and treatment duration. This allowed a smooth trend for the response in time based on multiple observations for each patient (using a thin plate regression spline basis). A random effect at the subject level was also introduced to take the dependence structure of observed data into account.[33] The Generalized Additive Mixed Models were fitted using the mgcv package of R (settings were fixed at package defaults). To be more conservative, the uncertainty of estimated parameters was assessed by 1000 bootstraps on individuals. For those *P* values lower than 0.001, 10,000 bootstraps were performed whenever possible. Multivariate analysis used the same methodology as previously described for the upstream *CRTC1* gene:[11] It was first conducted in the discovery sample, and the significant results were tested for replication in the 2 replication samples. In fitted longitudinal models, stratification by sex, and in some cases by age, was applied when analyzing all samples together. Also, analyses on WC and on other metabolic traits (ie, BGL and lipid levels) were conducted in the discovery sample (data available only in this sample) and only for *rs11552145* and *rs2071023* polymorphisms. Because of some missing data and the relatively low number of variant alleles of *rs707555* and *rs8123020*, analysis could not be conducted for these polymorphisms. Finally, it should be mentioned that preliminary analysis on *PCK1* haplotypes and BMI for the 3 SNPs that formed a haplotype block (ie, *rs11552145, rs707555* and *rs8123020*) showed no significant results (results not shown).

Population-Based Samples

Significant results from *PCK1* polymorphisms in the discovery sample (ie, *rs6070157*, proxy of *rs11552145*; $r^2 = 0.99$ and *rs2071023*) were further tested for replication in the three population samples (CoLaus, GIANT, and Global Lipids Genetics Consortium).

The associations of *PCK1* polymorphisms with adiposity markers, such as BMI, WC, fat mass, and lipid factors, were analyzed using multiple linear regression with additive model in which potential confounding factors, such as age, sex, and smoking status, were added as covariates in the CoLaus study. For anthropometric traits (BMI, WHR), we performed lookups from the summary statistics of the GIANT consortium. For lipid traits (ie, TG, HDL, CHOL), we looked up association results from the Global Lipid Consortium.[30]

RESULTS

Supplementary Table S-3, Supplemental Digital Content 4, http://links.lww.com/JCP/A316 shows the characteristics of the 3 psychiatric samples. The discovery sample included patients with the shortest treatment duration (median of 6 months versus 27.4 and 36 months in the replications 1 and 2, respectively, $P = 0.0001$), as well as the lowest BMI (current median BMI of 25 versus 28 and 27 kg/m^2 for replications 1 and 2, respectively, $P = 0.0001$) and the lowest prevalence of obesity (BMI ≥ 30 kg/m^2) (18% versus 40% and 27%, respectively, $P < 0.001$).

Association of *PCK1* Polymorphisms With BMI in Psychiatric Populations

Supplementary Table S-2, Supplemental Digital Content 2, http://links.lww.com/JCP/A314 shows *PCK1* genotype distribution among the 3 psychiatric samples. No significant associations were found between *PCK1* polymorphisms and baseline BMI when exploratory analyses were conducted (Supplementary Table S-4, Supplemental Digital Content 5, http://links.lww.com/JCP/A317). However, a trend and a significant association were found between *rs11552145* and *rs2071023* and current BMI (BMI at the last follow-up assessment) in the discovery (*P*-corrected 0.08 and 0.018, respectively) and in the combined sample (*P*-corrected 0.01 and 0.003, respectively). Figure 1 shows the association of PCK1 *rs11552145* polymorphism with BMI.

Multivariate analyses were first conducted in the discovery sample for the 4 SNPs (Table 1). Carriers of *rs11552145-AA* genotype had, on average, 2.20 lower BMI units when compared to carriers of *G-allele* ($P = 0.0004$). Similar results were found for *rs2071023-CC* genotype which had 1.27 lower BMI units when compared to *G-allele* carriers ($P = 0.004$). Significant results were replicated for *rs11552145* and BMI when combining the 2 replication samples. *AA* carriers had 1.42 lower BMI units when compared to *G-allele* carriers ($P = 0.009$). When combining the 3 samples, similar results were found for both *rs11552145* and *rs2071023* (estimates, −1.89 and −1.11 kg/m^2; and $P < 0.001$ and $P < 0.001$, respectively). Explained variances in the combined sample for *rs11552145* and *rs2071023* were 0.65% and 0.85%, respectively. For both *rs11552145* and *rs2071023*, further analyses stratified by sex and age were conducted in the 3 samples combined. *rs2071023* was associated with BMI only in women, whereas for *rs11552145* an association was found in both sexes, but a stronger association was found among women younger than 45 years, where *rs11552145 AA*-carriers had 2.25 lower BMI units when compared to *G-allele* carriers (*P* value of 0.009, explained variance 0.77%). No significant results were found for the other 2 SNPs *rs8123020* and *rs707555*.

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

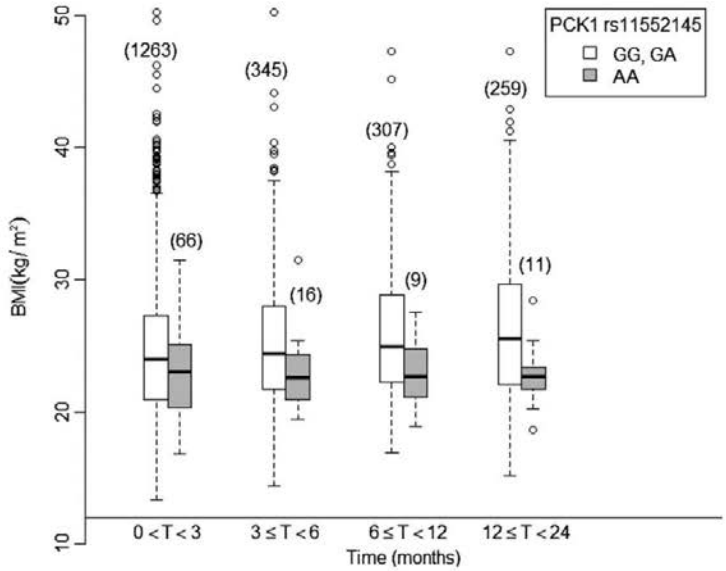


FIGURE 1. BMI in relation to *rs11552145 G > A* genotypes in the combined sample presented at different time periods of the current psychotropic treatment. Boxplots show median values of BMI for each time of the treatment duration (solid horizontal line), 25th and 75th percentile values (box outline), the lowest and upper value within 1.5 interquartile range (whiskers) and outlier values (open circles).

PCK1 Polymorphisms and Metabolic Parameters in Psychiatric Populations

The association of *rs11552145* and *rs2071023* with other metabolic parameters (ie, WC, BGL, CHOL, HDL, LDL, and TG) was analyzed in the discovery sample (Table 2). In agreement with results on BMI, both carriers of *rs11552145-AA* genotype and *rs2071023-CC* genotype had significantly lower WC (−6.86 and −3.45 cm, *P* values of 0.008 and 0.004, respectively). In addition, *rs11552145-AA* genotype carriers had lower TG levels when compared to *G-allele* carriers (−27.59 mg/100 mL, $P < 0.002$).

Association of *CRTC1* and *PCK1* with BMI

Since *PCK1* is a downstream gene of *CRTC1*, we wanted to further analyze the association of both *CRTC1 rs3746266A > G* previously associated with BMI[11] and *PCK1 rs11552145G > A* with BMI over treatment duration (Fig. 2). In the combined analysis, *CRTC1 G-allele* and *PCK1 AA* genotype were pooled together since carriers of these alleles showed lower BMI units when compared to others when analyzed individually. Thus, in the multivariate analysis adjusted by age, sex, treatment, and treatment duration (n = 610), those carriers of *AA* genotype for *CRTC1* and *PCK1* or carriers of *G-allele* of *CRTC1* and *PCK1* had 0.79 less units of BMI when compared to the reference group ($P = 0.009$). Similarly, carriers of *PCK1 AA* genotype and *CRTC1 G-allele* had 2.43 less units of BMI compared to the reference group ($P < 0.001$).

Functional Relevance of *PCK1* Polymorphisms

We explored further the functional relevance of *PCK1* polymorphisms. For *rs11552145* and *rs707555*, the 2 variants in coding regions, PolyPhen-2[34] predicted both mutations to be benign. Further analysis on gene expression platform (GTEX portal[35]) showed significant differences in *rs11552145* expression in subcutaneous adipose tissue with homozygous carriers of the variant allele having lower expression ($P = 0.03$). No differences were found for *rs707555*, *rs8123020* or *rs2071023*.

PCK1 Polymorphisms in Population-Based Samples

The association of *rs6070157* (proxy of *rs11552145*, $r^2 = 0.97$) and *rs2071023* with BMI and other metabolic features was further analyzed for replication in 3 population-based samples (GIANT, CoLaus, and Global Lipids Genetics Consortium). Significant associations were found between the 2 *PCK1* polymorphisms and the WHR in the GIANT cohort (N = 123,865) for women and for both sexes combined. In addition, significant associations were found for *rs2071023* with HDL and TGL in the Global Lipids Genetics Consortium (N = 100,184; *P* values of 0.003 and 0.03, respectively) (Table 3).

DISCUSSION

Growing evidence supports that *PCK* can contribute to obesity and metabolic syndrome both in animal models and in the general population.[12–14,16,17] The main results from this study suggest that carriers of *PCK1 rs11552145-AA* genotype have lower BMI when compared to *G-allele* carriers in psychiatric patients treated with weight gain inducing drugs, this association being found in the discovery sample and in the replication samples analyzed together. Moreover, low WC and TG levels were associated with *rs11552145-AA* in the discovery sample, and low BMI and WC were found as well for *rs2071023-CC* genotype. To our knowledge, this is the first study carried out in psychiatric patients and the first one to find a positive association between *PCK1* polymorphisms and BMI.

In addition, as a proof of concept, a positive association was found in the general population (GIANT cohort) with WHR and *rs6070157* (proxy of *rs11552145*, $r^2 = 0.99$) and *rs2071023*, again suggesting an association of the polymorphisms with obesity traits, although the value was much weaker than in

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 1. Multivariate Analysis of *PCK1* Polymorphisms and BMI

		rs11552145			*rs2071023*			*rs707555*			*rs8123020*		
Sample	**n**	**BMI Difference (kg/m^2) Between AA and G-allele Carriers (95% CI)**	***P***	**E var, %**	**BMI Difference (kg/m^2) Between CC and G-allele Carriers (95% CI)**	***P***	**E var, %**	**BMI Difference (kg/m^2) Between GG and C-allele Carriers (95% CI)**	***P***	**E var, %**	**BMI Difference (kg/m^2) Between TT and C-allele Carriers (95% CI)**	***P***	**E var, %**
Discovery Sample*	423	−2.20 (−3.35 to −1.12)	**0.0004**†	0.84	−1.27 (−2.09 to −0.49)	**0.004**†	1.24	−0.38 (−3.26 to 2.21)	1.00†		−0.83 (−2.46 to 0.82)	0.5‡	
Replication 1	168	−1.82 (−4.24 to 0.45)	0.07		−0.73 (−1.97 to 0.61)	0.1							
Replication 2	183	−0.64 (−2.72 to 1.22)	0.2		−0.18 (−1.40 to 1.04)	0.4							
Replication 1 and Replication 2‡	337	−1.42 (−2.69 to (−)0.25)	**0.009**	0.49	−0.53 (−1.40 to 0.41)	0.1							
Combined sample‡	760	−1.89 (−2.67 to (−)1.09)	**<0.001**	0.65	−1.11 (−1.71 to −0.52)	**<0.001**	0.85						
Combined sample men‡	377	−1.98 (−3.18 to (−)0.85)	**0.001**	1.01	−0.63 (−1.49 to 0.23)	*0.08*							
Combined sample women‡	383	−1.70 (−2.79 to (−)0.62)	**0.002**	0.35	−1.58 (−2.41 to −0.72)	**0.0001**	1.55						
Combined sample women <45 y‡	151	−2.25 (−4.18 to (−)0.45)	**0.009**	0.77	−1.48 (−2.74 to −0.11)	**0.01**	0.57						
Combined sample women ≥ 45 y‡	235	−1.54 (−3.59 to 0.86)	*0.06*		−1.68 (−2.74 to −0.60)	**0.002**	1.63						

*bootstrap at 10 000. Only significant results in discovery sample were further tested for replication.

†*P*-corrected value for discovery sample.

‡Patients treated for up to 24 months.

E var (%): explained variance by the polymorphism, only calculated for significant tests.

Adjusted by: age, sex, treatment (antipsychotic or mood stabilizer) and treatment duration. Bootstrap at 1000.

95% CI indicates 95% confidence interval. Values in bold are significant.

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 2. Association of *PCK1* Polymorphisms With Other Metabolic Phenotypes in the Discovery Sample

rs11552145	n	Difference Between AA and G-allele Carriers (95% CI)	*P**	E.var (%)
WC, cm	408	−6.86 (−11.07 to (−)2.59)	**0.008**	1.04
HDL,† mg/100 mL	305	5.85 (−1.95 to 14.04)	0.13	
TG,† mg/100 mL	305	−27.59 (−39.16 to (−)14.24)	**<0.002**	0.90
LDL,† mg/100 mL	299	−10.14 (−19.89 to 2.34)	0.12	
CHOL,† mg/100 mL	307	−10.53 (−28.08 to 8.19)	0.28	
BGL,† mg/100 mL	289	−3.6 (−8.28 to 0.36)	0.09	
rs2071023	**n**	**Difference between CC and G-allele carriers (95% CI)**	***P****	**E.var (%)**
WC, cm	409	−3.45 (−5.74 to −1.18)	**0.004**	1.14
HDL,† mg/100 mL	305	1.95 (−0.39 to 4.29)	0.12	
TG,† mg/100 mL	305	−8.01 (−19.58 to 3.56)	0.64	
LDL,† mg/100 mL	299	−2.34 (−10.14 to 5.07)	0.54	
CHOL,† mg/100 mL	307	−3.12 (−11.7 to 5.07)	0.32	
BGL,† mg/100 mL	289	2.52 (−2.16 to 5.94)	0.42	

*P-corrected value for discovery sample.

†Fasting patients

E. var (%): explained variance by the polymorphism (%) calculated only for significant tests.

Adjusted by: BMI, age, sex, treatment (antipsychotic or mood stabilizer) and treatment duration. Bootstrap at 1000. Values in bold are significant.

psychiatric samples and being of no clinical significance in the general population. This goes in the same line of what we found in previous results,[11] because psychiatric populations are at high risk of obesity and/or metabolic syndrome. PCK1 function has been previously associated in animal models with glucose and lipid homeostasis and also with weight gain.[36] In humans, the main investigated polymorphism is the *-232C/G* (*rs2071023*) which is located in the promoter region of *PCK1*. This polymorphism has been previously associated with T2DM and gestational diabetes mellitus but with conflicting results in different

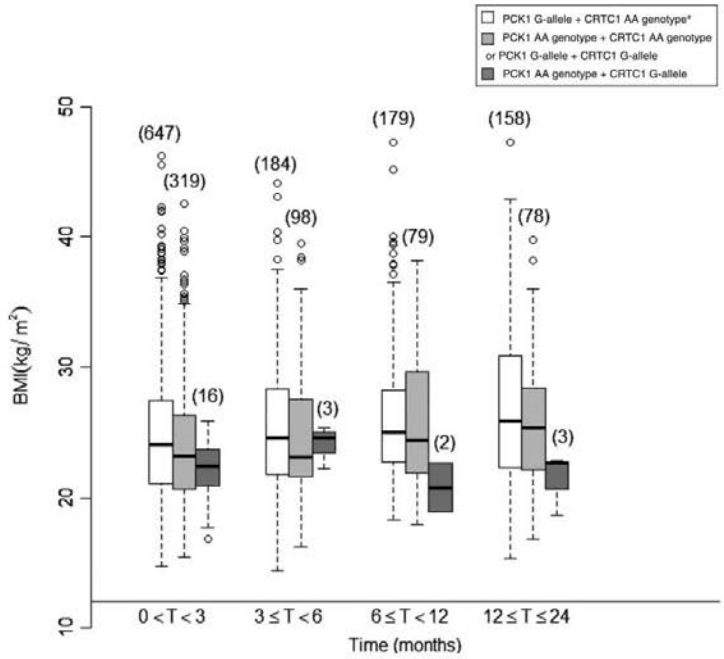


FIGURE 2. Association of *PCK1 rs11552145* and *CRTC1 rs3746266* genotypes with BMI over the time in all samples. * Reference group. Boxplots show median values of BMI for each time of the treatment duration (solid horizontal line), 25th and 75th percentile values (box outline), the lowest and upper value within 1.5 interquartile range (whiskers) and outlier values (open circles).

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 3. Association of *PCK1* Polymorphisms With Metabolic Traits in Population-Based Samples

	CoLaus (n = 5338)		GIANT (n = 123,865)		Global Lipids Genetics Consortium (n = 100,184)	
***rs6070157* (proxy of *rs11552145*, $r^2 = 0.99$)**	**β (SE)**	***P***	**β (SE)**	***P***	**β (SE)**	***P***
Anthropometric traits						
BMI, kg/m^2	−0.0016 (0.0258)	0.95	0.0025 (0.0053)	0.63	N.A.	N.A.
WC, cm	−0.0026 (0.0258)	0.92	N.A.	N.A.	N.A.	N.A.
WHR	−0.0123 (0.0258)	0.63	−0.0163 (0.0071)	**0.02**	N.A.	N.A.
Men	0.0086 (0.038)	0.82	0.0151 (0.0096)	0.11	N.A.	N.A.
Women	−0.0308 (0.035)	0.39	−0.0202 (0.0089)	**0.02**	N.A.	N.A.
Lipids						
HDL, mg/100 mL	0.38 (0.37)	0.30	N.A.	N.A.	0.16 (0.12)	0.20
CHOL, mg/100 mL	−0.14 (1.02)	0.89	N.A.	N.A.	0.05 (0.12)	0.69
TG, mg/100 mL	−3.25 (2.57)	0.21	N.A.	N.A.	−0.10 (−0.28)	0.73
LDL, mg/100 mL	−0.41 (0.90)	0.65	N.A.	N.A.	N.A.	N.A.
BGL, mg/100 mL	0.85 (0.55)	0.12	N.A.	N.A.	−0.06 (−0.08)	0.50
rs2071023	**β (SE)**	***P***	**β (SE)**	***P***	**β (SE)**	***P***
Anthropometric traits						
BMI, kg/m^2	−0.0196 (0.0198)	0.32	−0.0028 (0.0043)	0.2	vN.A.	N.A.
WC, cm	−0.0087 (0.0198)	0.66	N.A.	N.A.	N.A.	N.A.
WHR	0.0026 (0.0198)	0.90	−0.0195 (0.0057)	**0.001**	N.A.	N.A.
Men	−0.0145 (0.029)	0.61	−0.0013 (0.0077)	0.87	N.A.	N.A.
Women	0.0184 (0.028)	0.50	−0.0154 (0.0071)	**0.03**	N.A.	N.A.
Lipids						
HDL, mg/100 mL	−0.54 (0.28)	0.06	N.A.	N.A.	0.28 (0.12)	**0.003**
CHOL, mg/100 mL	−0.99 (0.78)	0.20	N.A.	N.A.	0.078 (0.12)	0.54
TG, mg/100 mL	1.11 (1.98)	0.57	N.A.	N.A.	−0.61 (−0.28)	**0.03**
LDL, mg/100 mL	−0.58 (0.69)	0.41	N.A.	N.A.	N.A.	N.A.
BGL, mg/100 mL	−0.35 (0.42)	0.41	N.A.	N.A.	−0.09 (−0.07)	0.16

N.A. indicates data not available. Values in bold are significant.

ethnicities. Positive associations were found among South Asian and Japanese populations[20,37] concluding that carriers of the minor allele (*GG*) were at risk of developing T2DM, whereas no significant findings were found in German or Danish Caucasian populations.[18,21] Finally, a case series study conducted in 3 Maltese women found that those who developed gestational diabetes mellitus carried the homozygous variant allele, but these results must be replicated in larger cohorts.[38] In the present study, no association was found between *rs2071023* and BGL, although the diabetes phenotype was not assessed. Additionally, and consistent with our results, another *PCK1* polymorphism (*rs707555*) showed no significant association with anthropometric traits such as WC, weight, and fat mass or BMI.[22,39]

Analyses were conducted in the combined discovery and replication samples for treatment duration up to 24 months. Different effect sizes, detected in the discovery versus the replication samples, could be explained by lower prevalence of obesity at baseline and shorter treatment durations in the discovery sample (Supplementary Table S-3, Supplemental Digital Content 4, http://links.lww.com/JCP/A316), because both baseline BMI and treatment duration are moderators of weight gain.[40] However, to exclude a winner's curse event, these results need to be replicated in other short treatment duration samples.

Of note, in the present study as in previous genetic studies, genetically explained variances of BMI are quite low, suggesting that BMI and metabolic features are influenced by multiple genetic factors as previously described in the literature.[4] However, in the present study, *rs11552145* was strongly associated with BMI in the subgroup of women younger than 45 years, and the observed difference in BMI between genotypes is of clinical significance. This result is in agreement with our previous study showing that the association between a polymorphism of *CRTC1* (an upstream gene of *PCK1*) and BMI was higher in women younger than 45 years as compared to nongender stratified sample.[11] In addition, a positive correlation was found between PCK1 mRNA expression levels and BMI in a study conducted with nonmenopausal women.[15] Other pharmacogenetic studies also highlighted the importance of stratifying by sex.[41,42] This finding could be tentatively explained by the influence of estrogen circulating levels on energy balance.[43] Thus, a lack of estrogen in mice was related to obesity, decreasing fasting BGL, activating adenosine monophosphate protein kinase (AMPK), and reducing the expression of gluconeogenic genes, such as *PCK* in the liver.[44,45] However, this hypothesis could not be tested in our samples because estrogen circulating levels were not measured.

To assess the contribution of *PCK1* and *CRTC1* polymorphisms on BMI, analyses combining both SNPs were conducted. An additive association with BMI was observed over treatment duration among carriers of *CRTC1 rs3746266 G-allele* and *PCK1 rs11552145 AA* genotype which had lower BMI when compared to the reference group. As described elsewhere,[46] *PCK* family genes contain in their promoter region a CREB-regulated element binding site where CRTC1 binds, enhancing *PCK* expression. In the present study, the strongest associations

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

were found among psychiatric population under psychotropic treatment which could be explained by the additive effect between *PCK1* and *CRTC1* genes and psychotropic drugs. In particular, *CRTC1* is modulated, among other mechanisms, by AMPK which is increased by antipsychotics.[47] Besides, several polymorphisms on the *AMPK* gene, showed an association with weight gain induced by antipsychotics.[48] *AMPK* has also been related to gluconeogenesis modulation.[49] Another study conducted in rats showed that olanzapine increased the mRNA levels of glucose-6-phosphatase in the liver.[47] Although little is known about *PCK* family genes and psychotropic drugs, *PCK* expression is inhibited by lithium in isolated hepatocytes from fasted rats.[50] In addition, chronic clozapine administration upregulates *PCK* expression in rat liver.[51] Therefore, several genes coding for enzymes implicated in the gluconeogenic pathway have been associated with antipsychotics.

Finally, in our sample, higher associations were found among psychiatric patients rather than in general population possibly explained by the high prevalence of overweight or obesity in psychiatric patients induced by the illness, the lifestyle (diet, physical activity), in addition to the direct effect of drug inducing weight gain.

Some limitations of the present study must be mentioned. First, patients were not drug naive, therefore, we could not assess whether the association between the polymorphisms and BMI or other phenotypes was influenced by the psychiatric illness itself and/or by the psychotropic treatment. Second, although the main inclusion criteria for patients in the present study was that they were receiving psychotropic drugs known to induce weight gain (ie, aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, mirtazapine, lithium, and/or valproate), other drugs possibly inducing weight (psychotropic and/or somatic drugs) were prescribed, the influence of which could not be evaluated. This study was conducted in whites, thus results cannot be extrapolated to other ethnicities. Not all tagging SNPs could be tested due to limited availability of the genotypes. In addition, no significant associations with BMI were found for the 2 other tested SNPs *(rs707555* and *rs8123020*), either because of a lack of effect or a lack of power due to the low MAF. Further replications of this study should increase sample size to test low MAF polymorphisms and to increase the coverage of *PCK1* gene by including other tagging SNPs. Finally, variants obtained through GWAS should be also considered in further analysis, in particular those on gluconeogenic pathway. It has thus been recently shown that *PCK1* expression is regulated by *CAMK1D*,[52] a gene previously related to diabetes in GWAS.[53]

In conclusion, this is the first study investigating the association of *PCK1* polymorphisms with BMI and other metabolic traits in psychiatric populations. Higher associations were found in psychiatric patients treated with psychotropic drugs over short periods, and in women younger than 45 years. In addition, the present study supports research on pathway related genes, such as *CRTC1* and *PCK1*, which may have an additive association with BMI. Further studies on the same and other pathways are therefore warranted, to increase our knowledge on the multiple genetic risk factors influencing obesity, lipid disturbances or metabolic syndrome in psychiatric population. This could ultimately help, by the determination and the combination of multiple genetic and clinical risk factors, to better adapt pharmacological treatments among particular populations at risk.

ACKNOWLEDGMENTS

The authors thank Dr S. Crettol, C. Brogli, V. Hodel (logistical assistance), E. Retamales (bibliographical help), A. C. Aubert, M. Brocard, N. Cochard, M. Delessert, A. Kottelat, M. Brawand, K. Powell Golay, and S. Jaquet (sample analysis). The authors also thank the GIANT consortium for access to their BMI association result in 123,807 individuals and Global Lipids Genetics Consortium.

AUTHOR DISCLOSURE INFORMATION

CBE received research support from Takeda and from the Roche Organ Transplantation Research Foundation in the past 3 years. He received honoraria for conferences or teaching CME courses from Advisis, AstraZeneca, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Otsuka, Sandoz, Servier and Vifor-Pharma in the past 3 years. AVG received honoraria for a conference or a workshop participation from Vifor and Bayer Sheringer in the past 3 years. All authors declare no conflicts of interest.

REFERENCES

1. Nihalani N, Schwartz TL, Siddiqui UA, et al. Obesity and psychotropics. *CNS Neurosci Ther*. 2012;18:57–63.
2. De Hert M, Dekker JM, Wood D, et al. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry*. 2009;24:412–424.
3. Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Curr Opin Psychiatry*. 2012;25:83–88.
4. Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42:937–948.
5. Balt SL, Galloway GP, Baggott MJ, et al. Mechanisms and genetics of antipsychotic-associated weight gain. *Clin Pharmacol Ther*. 2011;90: 179–183.
6. Kao AC, Muller DJ. Genetics of antipsychotic-induced weight gain: update and current perspectives. *Pharmacogenomics*. 2013;14:2067–2083.
7. Beale EG, Harvey BJ, Forest C. PCK1 and PCK2 as candidate diabetes and obesity genes. *Cell Biochem Biophys*. 2007;48:89–95.
8. Yang J, Kalhan SC, Hanson RW. What is the metabolic role of phosphoenolpyruvate carboxykinase? *J Biol Chem*. 2009;284: 27025–27029.
9. Kotelevtsev Y, Holmes MC, Burchell A, et al. 11beta-hydroxysteroid dehydrogenase type 1 knockout mice show attenuated glucocorticoid-inducible responses and resist hyperglycemia on obesity or stress. *Proc Natl Acad Sci U S A*. 1997;94:14924–14929.
10. Oh KJ, Han HS, Kim MJ, et al. CREB and FoxO1: two transcription factors for the regulation of hepatic gluconeogenesis. *BMB Rep*. 2013;46: 567–574.
11. Choong E, Quteineh L, Cardinaux JR, et al. Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and in the general adult population. *JAMA Psychiatry*. 2013;70:1011–1019.
12. Franckhauser S, Munoz S, Elias I, et al. Adipose overexpression of phosphoenolpyruvate carboxykinase leads to high susceptibility to diet-induced insulin resistance and obesity. *Diabetes*. 2006;55:273–280.
13. Valera A, Pujol A, Pelegrin M, et al. Transgenic mice overexpressing phosphoenolpyruvate carboxykinase develop non-insulin-dependent diabetes mellitus. *Proc Natl Acad Sci U S A*. 1994;91:9151–9154.
14. Olswang Y, Cohen H, Papo O, et al. A mutation in the peroxisome proliferator-activated receptor gamma-binding site in the gene for the cytosolic form of phosphoenolpyruvate carboxykinase reduces adipose tissue size and fat content in mice. *Proc Natl Acad Sci U S A*. 2002;99: 625–630.
15. Chang TJ, Lee WJ, Chang HM, et al. Expression of subcutaneous adipose tissue phosphoenolpyruvate carboxykinase correlates with body mass index in nondiabetic women. *Metabolism*. 2008;57:367–372.

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

16. Zhao J, Xiao P, Guo Y, et al. Bivariate genome linkage analysis suggests pleiotropic effects on chromosomes 20p and 3p for body fat mass and lean mass. *Genet Res (Camb)*. 2008;90:259–268.

17. Lee JH, Reed DR, Li WD, et al. Genome scan for human obesity and linkage to markers in 20q13. *Am J Hum Genet*. 1999;64:196–209.

18. Wegner L, Andersen G, Albrechtsen A, et al. Large-scale study of the -232C > G polymorphism of PCK1 in Type 2 diabetes. *Diabet Med*. 2006; 23:1140–1144.

19. Dong Y, Zhang H, Wang X, et al. A Leu184Val polymorphism in PCK1 gene is associated with type 2 diabetes in Eastern Chinese population with BMI < 23 kg/m2. *Diabetes Res Clin Pract*. 2009;83:227–232.

20. Rees SD, Britten AC, Bellary S, et al. The promoter polymorphism -232C/G of the PCK1 gene is associated with type 2 diabetes in a UK-resident South Asian population. *BMC Med Genet*. 2009;10:83.

21. Gouni-Berthold I, Giannakidou E, Faust M, et al. Association of the promoter polymorphism -232C/G of the phosphoenolpyruvate carboxykinase gene (PCK1) with type 2 diabetes mellitus. *Diabet Med*. 2006;23:419–425.

22. Larsen LH, Angquist L, Vimaleswaran KS, et al. Analyses of single nucleotide polymorphisms in selected nutrient-sensitive genes in weight-regain prevention: the DIOGENES study. *Am J Clin Nutr*. 2012;95: 1254–1260.

23. Shin HD, Park BL, Kim LH, et al. Association of a polymorphism in the gene encoding phosphoenolpyruvate carboxykinase 1 with high-density lipoprotein and triglyceride levels. *Diabetologia*. 2005;48:2025–2032.

24. Choong E, Solida A, Lechaire C, et al. Suivi du syndrome métabolique induit par les antipsychotiques atypiques: recomendations et perspectives pharmacogénétiques. *Rev Med Suisse*. 2008;4:1994–1999.

25. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry*. 2011;44:195–235.

26. Choong E, Bondolfi G, Etter M, et al. Psychotropic drug induced weight gain and other metabolic complications in a Swiss Psychiatric population. *J Psychiatr Res*. 2012;46:540–548.

27. Firmann M, Mayor V, Vidal PM, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord*. 2008;8:6.

28. Lango Allen H, Estrada K, Lettre G, et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature*. 2010; 467:832–838.

29. Heid IM, Jackson AU, Randall JC, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet*. 2010;42:949–960.

30. Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature*. 2010;466: 707–713.

31. International HapMap Consortium. The International HapMap Project. *Nature*. 2003;426:789–796.

32. R Core Team. R: A language and environment for statistical computing, R Fondation for Statistical Computing,Vienna, Austria. In: *R Foundation for Statistical Computing*. Vienna, Austria: R Development Core Team; 2013.

33. Lin X, Zhang D. Inference in generalized additive mixed models by using smoothing splines. *J R Statist Soc B*. 1999;61:381–400.

34. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. *Nat Methods*. 2010;7:248–249.

35. Keen JC, Moore HM. The Genotype-Tissue Expression (GTEx) Project: linking clinical data with molecular analysis to advance personalized medicine. *J Pers Med*. 2015;5:22–29.

36. Rosella G, Zajac JD, Baker L, et al. Impaired glucose tolerance and increased weight gain in transgenic rats overexpressing a non-insulin-responsive phosphoenolpyruvate carboxykinase gene. *Mol Endocrinol*. 1995;9:1396–1404.

37. Horikawa Y, Yamasaki T, Nakajima H, et al. Identification of a novel variant in the phosphoenolpyruvate carboxykinase gene promoter in Japanese patients with type 2 diabetes. *Horm Metab Res*. 2003;35: 308–312.

38. Abou-Hussein S, Savona-Ventura C, Grima S, et al. Genetic factors in risk assessment for the development of type 2 diabetes mellitus in a small case series. *Int J Risk Saf Med*. 2011;23:119–123.

39. Vimaleswaran KS, Franks PW, Brage S, et al. Lack of association between PCK1 polymorphisms and obesity, physical activity, and fitness in European Youth Heart Study (EYHS). *Obesity*. 2010;18:1975–1980.

40. De Hert M, Detraux J, van Winkel R, et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2012;8:114–126.

41. Vehof J, Al Hadithy AF, Burger H, et al. Association between the ROBO1 gene and body mass index in patients using antipsychotics. *Psychiatr Genet*. 2011;21:202–207.

42. Gregoor JG, van der Weide J, Loovers HM, et al. Polymorphisms of the LEP, LEPR and HTR2C gene: obesity and BMI change in patients using antipsychotic medication in a naturalistic setting. *Pharmacogenomics*. 2011;12:919–923.

43. Clegg DJ, Brown LM, Woods SC, et al. Gonadal hormones determine sensitivity to central leptin and insulin. *Diabetes*. 2006;55:978–987.

44. Mandour T, Kissebah AH, Wynn V. Mechanism of oestrogen and progesterone effects on lipid and carbohydrate metabolism: alteration in the insulin: glucagon molar ratio and hepatic enzyme activity. *Eur J Clin Invest*. 1977;7:181–187.

45. Kim JY, Jo KJ, Kim OS, et al. Parenteral 17beta-estradiol decreases fasting blood glucose levels in non-obese mice with short-term ovariectomy. *Life Sci*. 2010;87:358–366.

46. Hanson RW, Reshef L. Regulation of phosphoenolpyruvate carboxykinase (GTP) gene expression. *Annu Rev Biochem*. 1997;66:581–611.

47. Ikegami M, Ikeda H, Ohashi T, et al. Olanzapine increases hepatic glucose production through the activation of hypothalamic adenosine 5′-monophosphate-activated protein kinase. *Diabetes Obes Metab*. 2013;15: 1128–1135.

48. Souza RP, Tiwari AK, Chowdhury NI, et al. Association study between variants of AMP-activated protein kinase catalytic and regulatory subunit genes with antipsychotic-induced weight gain. *J Psychiatr Res*. 2012;46: 462–468.

49. Kahn BB, Alquier T, Carling D, et al. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab*. 2005;1:15–25.

50. Bosch F, Rodriguez-Gil JE, Hatzoglou M, et al. Lithium inhibits hepatic gluconeogenesis and phosphoenolpyruvate carboxykinase gene expression. *J Biol Chem*. 1992;267:2888–2893.

51. Tulipano G, Rizzetti C, Bianchi I, et al. Clozapine-induced alteration of glucose homeostasis in the rat: the contribution of hypothalamic-pituitary-adrenal axis activation. *Neuroendocrinology*. 2007; 85:61–70.

52. Haney S, Zhao J, Tiwari S, et al. RNAi screening in primary human hepatocytes of genes implicated in genome-wide association studies for roles in type 2 diabetes identifies roles for CAMK1D and CDKAL1, among others, in hepatic glucose regulation. *PLoS One*. 2013;8:e64946.

53. Zeggini E, Scott LJ, Saxena R, et al. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet*. 2008;40:638–645.

© 2015 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

See commentary by Tohen

It is illegal to post this copyrighted PDF on any website.

Importance of Early Weight Changes to Predict Long-Term Weight Gain During Psychotropic Drug Treatment

Frederik Vandenberghe, PharmD, MSc[a]; Mehdi Gholam-Rezaee, PhD[b]; Núria Saigí-Morgui, PharmD, MPH[a]; Aurélie Delacrétaz, MSc[a]; Eva Choong, PhD[a]; Alessandra Solida-Tozzi, MD[c]; Stéphane Kolly, MD[c]; Jacques Thonney, MD[c]; Sylfa Fassassi Gallo, MD[c]; Ahmed Hedjal, MD[c]; Anne-Emmanuelle Ambresin, MD[e]; Armin von Gunten, MPhil, MD[d]; Philippe Conus, MD[c]; and Chin B. Eap, PhD[a,f,*]

ABSTRACT

Background: Psychotropic drugs can induce substantial weight gain, particularly during the first 6 months of treatment. The authors aimed to determine the potential predictive power of an early weight gain after the introduction of weight gain–inducing psychotropic drugs on long-term weight gain.

Method: Data were obtained from a 1-year longitudinal study ongoing since 2007 including 351 psychiatric (*ICD-10*) patients, with metabolic parameters monitored (baseline and/or 1, 3, 6, 9, 12 months) and with compliance ascertained. International Diabetes Federation and World Health Organization definitions were used to define metabolic syndrome and obesity, respectively.

Results: Prevalences of metabolic syndrome and obesity were 22% and 17%, respectively, at baseline and 32% and 24% after 1 year. Receiver operating characteristic analyses indicated that an early weight gain > 5% after a period of 1 month is the best predictor for important long-term weight gain (≥ 15% after 3 months: sensitivity, 67%; specificity, 88%; ≥ 20% after 12 months: sensitivity, 47%; specificity, 89%). This analysis identified most patients (97% for 3 months, 93% for 12 months) who had weight gain ≤ 5% after 1 month as continuing to have a moderate weight gain after 3 and 12 months. Its predictive power was confirmed by fitting a longitudinal multivariate model (difference between groups in 1 year of 6.4% weight increase as compared to baseline, $P = .0001$).

Conclusion: Following prescription of weight gain–inducing psychotropic drugs, a 5% threshold for weight gain after 1 month should raise clinician concerns about weight-controlling strategies.

J Clin Psychiatry 2015;76(11):e1417–e1423
dx.doi.org/10.4088/JCP.14m09358
© Copyright 2015 Physicians Postgraduate Press, Inc.

[a]Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Hospital of Cery, Prilly, Switzerland
[b]Center for Psychiatric Epidemiology and Psychopathology; [c]Service of General Psychiatry; [d]Service of Old Age Psychiatry, Department of Psychiatry; and [e]Multidisciplinary Team of Adolescent Health, Lausanne University Hospital, Prilly, Switzerland
[f]School of Pharmacy, Department of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland
**Corresponding author:* Chin B. Eap, PhD, Unit of Pharmacogenetics and Clinical Psychopharmacology, Center for Psychiatric Neurosciences, Hospital of Cery, 1008 Prilly—Lausanne, Switzerland (chin.eap@chuv.ch).

A high prevalence of obesity (body mass index [BMI] ≥ 30 kg/m^2, World Health Organization definition) is reported in psychiatric populations, reaching 49% and 55% of bipolar and schizophrenic patients, respectively.[1] Obesity can lead to several metabolic complications, such as hypertension, lipid profile perturbation, or both, contributing to the reported 20-year shorter life expectancy in psychiatric patients as compared to the general population.[2] Several factors contribute to the high prevalence of metabolic disorders in psychiatry, such as the illness itself as well as lifestyle factors. In addition, antipsychotics (most atypicals but also some typicals), mood stabilizers (eg, valproate and lithium), and some antidepressants (eg, mirtazapine) can induce important weight gain.[3,4]

Several factors have been shown to be associated with drug-induced weight gain, including female gender, low baseline BMI, young age, or nonwhite ethnicities.[5] A high interindividual variability of drug-induced weight gain is observed, explained in part by genetic variability (eg, in H_1 receptor, M_3 receptor, or *CRTC1* gene),[6,7] underlining the importance of monitoring metabolic parameters.

The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes guideline[8] considers that a weight gain > 5% during treatment should be a sign to reconsider the treatment. However, no notion of time was defined, so that a weight gain of 5% after 1 month may be inappropriately compared to a comparable weight gain after 1 year of treatment. A joint statement of the European Psychiatric Association, the European Association for the Study of Diabetes, and the European Society of Cardiology defines a weight gain of 7% after 6 weeks of treatment as a clinically significant weight gain.[1] This 7% threshold was chosen for its clinical significance and not for its predictive value for an important weight gain during long-term treatment. To our knowledge, 3 studies have investigated the predictive values of an early weight gain. The first two studies[9,10] found that a 2-kg increase after 1 month was a good predictor for a 10-kg increase after 6 months in patients treated for schizophrenia with olanzapine, ziprasidone, and aripiprazole. The third study[11] in bipolar patients treated with olanzapine found that a 2-kg weight gain after 3 weeks will predict a 7% increase after 30 weeks of treatment. Notably, the above-mentioned studies were post hoc analyses of clinical trials examining the effects of specific drugs, with restrictions on the number of drugs that could be prescribed, conditions that are not comparable to usual clinical practice. In addition, nonobservance of the pharmacologic treatment is poor, particularly during long-term treatment.[12] In the above-mentioned studies, compliance was assessed by patient self-declaration,[13–15] which can be overestimated. Finally, the longest study duration was of 30 weeks, with no long-term data (1 year).

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Clinical Points

- Psychotropic drug–induced weight gain is associated with high morbidity and mortality.
- Rapid detection of high risk patients is of major clinical significance.
- Weight gain of more than 5% after 1 month of treatment was found to be a good predictor for important long-term weight gain.

Because of the high mortality and morbidity associated with obesity, early detection of patients who have a higher risk of developing an important weight gain during psychotropic treatment is of major clinical relevance. In the present study, we sought to determine, in a cohort of psychiatric patients with compliance ascertained by therapeutic drug monitoring, how weight change during short-term treatment (1 month) could predict intermediate (3 months) and long-term (1 year) weight evolution during treatment with psychotropic drugs known to potentially induce important weight gain. Self-reported increase of appetite and modification of physical activity during the first month after drug introduction were also examined as possible weight gain predictors.

METHOD

Study Design

A longitudinal observational study has been ongoing since 2007 in the Department of Psychiatry of the Lausanne University Hospital in which inpatients starting a pharmacologic treatment with clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, lithium, valproate, and/or mirtazapine are included. Baseline clinical data were obtained during hospitalization, and follow-up data (1, 3, 6, 9, and/or 12 months) were obtained in the hospital or in outpatient centers during a medical examination based on the department guideline for metabolic follow-up performed on a routine basis.[16] When a treatment was stopped for more than 2 weeks, or if a drug was replaced by another drug on the list, the follow-up was restarted from baseline. In case of the introduction of a second studied drug, the follow-up was restarted and the last introduced drug considered as the main treatment (for more information, see eMethods 1). If 2 or more follow-ups were available for the same patient, only the longest one was included in the analysis (Supplementary eFigure 1). Diagnoses were based on the *ICD-10* classification (F00–F09, organic disorder; F20.0–F24.9 and F28–F29, psychotic disorders; F25.0–F25.9, schizoaffective disorder; F30.0–F31.9, bipolar disorder; F32.0–F33.9, depression; F10–F19, drug addiction). Anxiety, personality disorder, and mental retardation were classified together as "others." Compliance was evaluated by therapeutic drug monitoring (more information in eMethods 2). The study was approved by the ethics committee of the Lausanne University Hospital. Because of the noninterventional post hoc analysis study design, no informed consent was requested.

Exploratory Statistics

Mean values were presented with their respective standard error (SE), and significance threshold was fixed at $P < .05$.

To assess the predictive value of an early weight gain during the first month of treatment on long-term weight gain (3 and 12 months), sensitivity, specificity, positive predictive value, and negative predictive value were calculated using the *pROC* R package.[17] Sensitivity was defined as the percentage of correctly predicted high-risk patients among all truly long-term high-risk patients. Specificity was defined as the percentage of patients predicted as low-risk patients among all truly low-risk patients. Positive predictive value indicates the percentage of patients with an important long-term weight gain and who were classified as having a high early weight gain. Negative predictive value indicates the percentage of patients who did not have an important long-term weight gain and were classified as having a low early weight gain.

Thresholds for early weight gain were examined in 1% increments (from 2% to 8%) to find the best predictors for long-term weight gain as defined by a minimal weight gain of 10%, 15%, or 20% at 3 and 12 months of treatment (more information in eMethods 3). The same analysis was made to predict the effect of activity and appetite increase on long-term weight gain.

Confirmatory Analysis

A linear mixed-effect model was fitted on the weight gain percentage after separating patients into 2 groups based on their initial weight gain after 1 month of treatment, physical activity, and appetite increase (eMethods 4).

RESULTS

Demographics

Three hundred fifty-one patients were included (selection criteria in Supplementary eFigure 1). Male subjects (47%) were significantly younger (mean [SE] = 39 [1.6] years) than female subjects (51 [1.6] years, $P < .001$), which probably explains the lower prevalence of obesity in men (9%) than in women (23%, $P = .003$) (Supplementary eTable 1). No significant differences in other demographic variables were found between genders. Psychotic disorders (F20.0–F24.9 and F28–F29) were the most frequent diagnosis (41%), and quetiapine was the most frequently prescribed psychotropic drug (32%) (Table 1). Data were available for 313 subjects at 3 months and for 154 subjects at 12 months.

Metabolic Parameters

Twenty-one percent of patients were overweight (BMI = 25–30 kg/m^2) and 17% were obese (BMI ≥ 30 kg/m^2) at baseline (Supplementary eTable 2). In patients with 1-year follow-up, prevalence of patients with normal weight (BMI < 25 kg/m^2) decreased from 61% to 49% ($P = .007$)

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Table 1. Overall Demographic Parameters and Comparisons Between Early and Nonearly Weight Gainers

Demographic	All (N = 351)	First Month Weight Gain ≤ 5% (n = 288)	First Month Weight Gain > 5% (n = 63)	P[a]
Age, mean (SE), y	46 (1.2)	46 (1.3)	43 (2.6)	.4
Men, n/total (%)	164/351 (47)	131/288 (45)	33/63 (52)	.3
Follow-up duration, mean (SE), d	237 (8.18)	240 (8.59)	223 (23.22)	.1
Illness duration, mean (SE), y	8 (0.6)	8 (0.7)	8 (1.2)	.6
Smoking, n/total (%)	76/351 (22)	64/288 (22)	12/63 (19)	.7
Diagnosis, n/total (%)				
Bipolar disorder	59/351 (17)	51/288 (18)	8/63 (13)	.5
Depression	61/351 (17)	49/288 (17)	12/63 (19)	.7
Organic disorders	27/351 (8)	24/288 (8)	3/63 (5)	.4
Psychotic disorders	143/351 (41)	113/288 (39)	30/63 (48)	.3
Schizoaffective disorder	26/351 (7)	22/288 (8)	4/63 (6)	.9
Other	30/351 (9)	26/288 (9)	4/63 (6)	.6
Not available	5/351 (1)	3/288 (1)	2/63 (3)	.2
Medication, n/total (%)				
Amisulpride	36/351 (10)	29/288 (10)	7/63 (11)	.8
Aripiprazole	30/351 (9)	27/288 (9)	3/63 (5)	.3
Clozapine	24/351 (7)	22/288 (8)	2/63 (3)	.3
Lithium	19/351 (5)	15/288 (5)	4/63 (6)	.8
Mirtazapine	11/351 (3)	9/288 (3)	2/63 (3)	.9
Olanzapine	44/351 (13)	29/288 (10)	15/63 (24)	**.006**
Quetiapine	112/351 (32)	95/288 (33)	17/63 (27)	.4
Risperidone	64/351 (18)	53/288 (18)	11/63 (17)	.9
Valproate	10/351 (3)	8/288 (3)	2/63 (3)	.7
Prevalence of metabolic syndrome IDF, n/total (%)[b]				
Baseline	35/161 (22)	34/139 (25)	1/22 (5)	.06
After 1-y treatment	32/100 (32)	21/79 (27)	11/21 (52)	**.04**
Prevalence of overweight status (BMI = 25–30 kg/m^2), n/total (%)				
Baseline	62/294 (21)	21/237 (22)	11/57 (19)	.8
1 Year	36/135 (27)	29/114 (25)	7/21 (33)	.4
Prevalence of obesity (BMI ≥ 30 kg/m^2), n/total (%)				
Baseline	49/294 (17)	46/237 (19)	3/57 (5)	**.009**
1 Year	33/135 (24)	28/114 (25)	5/21 (24)	1

[a]*P* values were calculated using Wilcoxon rank sum tests for continuous variables and Fisher exact tests for categorical variables between both groups. Values in bold are significant.
[b]Metabolic syndrome was present if patients had central obesity (men, ≥ 94 cm; women, ≥ 80 cm) and at least 2 other following factors: triglycerides ≥ 1.7 mmol/L or lipid-lowering treatment; glucose ≥ 5.6 mmol/L or type 2 diabetes treatment; blood pressure ≥ 130/85 mm Hg or treatment for hypertension; and high-density lipoprotein cholesterol (men, ≤ 1.03 mmol/L; women, ≤ 1.29 mmol/L).
Abbreviations: BMI = body mass index, IDF = International Diabetes Foundation, SE = standard error.

(Table 2). Mean BMI increase after 1 year of treatment was dependent on age, being 2.7 kg/m^2 in young patients (aged ≤ 25 years), 2.2 kg/m^2 in young adults (aged 25–45 years), 1.8 kg/m^2 in adult patients (aged 45–65 years), and 1 kg/m^2 in elderly patients (aged > 65 years) (Supplementary eTable 3). Prevalence of metabolic syndrome (MetS [International Diabetes Federation definition]) was 22% at baseline and 32% after 1 year (Supplementary eTable 2). In patients with baseline and 1-year data, a trend for an increased prevalence during treatment was observed (from 9% to 23%, $P = .07$) (Table 2). Other metabolic traits, including their evolutions during treatment, are described in eResults 1.

Short-Term Weight Gain as Predictors of Long-Term Weight Gain

The best early weight gain predictor (highest area under the curve [AUC] values, integrating both sensitivity and specificity of the predictor) was found to be a weight gain of more than 5% (Figure 1) after 1 month of treatment (mean [SE] = 31 [0.4] days) for predicting a weight gain of 15% or more after 3 months of treatment (mean [SE] = 102 [2] days). This threshold had a sensitivity of 67%, specificity of 88%, positive predictive value of 29%, and negative predictive value of 97%. Prevalence of a 15% weight gain after 3 months was 7.5%. The 5% threshold was also found to be the best predictor for a weight gain of 20% or more after 1 year of treatment (mean [SE] = 393 [7] days; sensitivity, 47%; specificity, 89%; positive predictive value, 30%; negative predictive value, 93% [Supplementary eTable 4]). A weight gain > 20% was observed in 10% of patients after 1 year. Patients who had a weight gain > 5% at 1 month and who did not reach a 15% weight gain at 3 months (false positives) had still a higher weight gain than patients with ≤ 5% weight gain (8.1% vs 2.4%, $P = .000005$). However, the difference was not significant anymore after 1 year (6.1% vs 3.9%, $P = .2$). In young adults and adults combined (age, 25–65 years), this threshold was also found to be the best predictor for a 20% weight gain after 3 months (sensitivity, 100%; specificity, 82%; positive predictive value, 7%; negative predictive value, 100%) and after 12 months (sensitivity, 55%; specificity, 83%; positive predictive value, 30%; negative predictive value, 93%) (Supplementary eTable 5). Due to an insufficient number of observations, no specific threshold could be calculated in young (aged ≤ 25 years) and elderly (aged > 65 years) subjects or in different diagnostic and medication groups.

Using the 5% threshold, 18% of patients had a > 5% weight gain after 1 month. By integrating the 5% threshold in a generalized additive mixed model (Figure 2), patients with an early weight gain > 5% had a strong and fast increase of weight gain during the first 3 months of treatment, with a much slower increase thereafter (Supplementary eFigure 2). On the other hand, patients with an early weight gain ≤ 5% had a slower but steady 1-year weight gain. No differences of age, gender, follow-up duration, illness duration, or diagnosis were observed between the 2 groups. Medication was similar between the 2 groups except for olanzapine, which was present in 24% and 10% of the patients gaining more weight versus those gaining less than 5%, respectively ($P = .006$) (Table 1). When considering MetS traits at baseline, only BMI was significantly different between both groups ($P = .001$), being lower in the > 5% group. After 1 year, mean (SE) BMI increases of 1.2 (0.3) kg/m^2 and 3.1 (0.8) kg/m^2 were observed in the low and high weight–gain group, respectively ($P = .01$) (Supplementary eTable 6). A stronger decrease of high-density lipoprotein (HDL) cholesterol ($\beta = -0.3$ mmol/L,

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

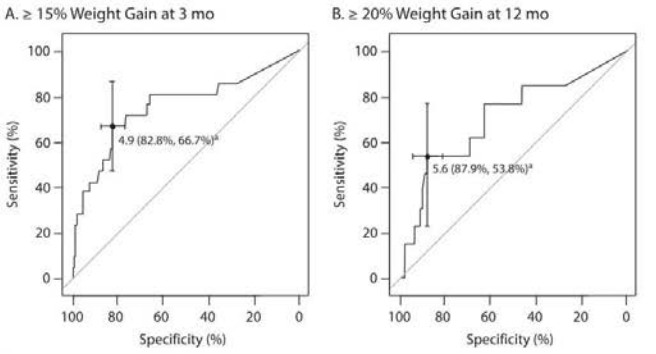
It is illegal to post this copyrighted PDF on any website.

Table 2. Evolution of Metabolic Parameters and Syndrome at Baseline, 3 Months, and 1 Year (only patients with 1-year follow-up included)

Variable	Baseline	3 mo	P^a	1 y	P^a
Prevalence of normal weight, overweight, and obesity, n/total (%)					
Normal weight (BMI < 25 kg/m^2)	71/116 (61)	60/116 (52)	**.01**	57/116 (49)	**.007**
Overweight (BMI = 25–30 kg/m^2)	25/116 (22)	32/116 (28)	.2	33/116 (28)	.2
Obese (BMI ≥ 30 kg/m^2)	20/116 (17)	24/116 (21)	.2	26/116 (22)	.07
Prevalence of abdominal obesity, n/total (%)					
Waist circumference ≥ 94 cm (men), ≥ 80 cm (women)[b]	42/86 (49)	53/86 (62)	**.02**	53/86 (62)	**.02**
Waist circumference ≥ 102 cm (men), ≥ 88 cm (women)[c,d]	25/86 (29)	28/86 (33)	.50	35/86 (41)	**.02**
Prevalence of HDL hypocholesterolemia, n/total (%)					
HDL cholesterol ≤ 1.03 mmol/L (men), ≤ 1.29 mmol/L (women)	18/61 (30)	16/61 (26)	.8	17/61 (28)	1.00
Prevalence of hypertriglyceridemia, n/total (%)					
Triglyceridemia ≥ 1.7 mmol/L or lipid-lowering treatment	13/63 (21)	20/63 (32)	.1	25/63 (40)	**.006**
Prevalence of hyperglycemia, n/total (%)					
Fasting glucose ≥ 5.6 mmol/L or antidiabetic treatment[b,d]	10/61 (16)	16/61 (26)	.1	23/61 (38)	**.002**
Fasting glucose ≥ 6.1 mmol/L or antidiabetic treatment[c]	7/61 (11)	5/61 (8)	.6	9/61 (15)	.7
Prevalence of hypertension, n/total (%)					
Blood pressure ≥ 130/85 mm Hg or antihypertensive treatment	14/80 (18)	15/80 (19)	1	16/80 (20)	.8
Prevalence of metabolic syndrome, n/total (%)					
ATP III[e]	3/35 (9)	1/35 (3)	.6	6/35 (17)	.2
Adapted ATP III[f]	3/35 (9)	2/35 (6)	1	6/35 (17)	.2
IDF[g]	3/35 (9)	6/35 (17)	.5	8/35 (23)	.07

[a]*P* values were calculated using McNemar tests between baseline versus 3 months and baseline versus 12 months. Values in bold are significant.
[b]According to IDF definition.
[c]According to National Cholesterol Education Program's ATP III[18] definition.
[d]According to adapted ATP III definition.
[e]Metabolic syndrome is present if at least 3 of the following criteria are present: central obesity (men, ≥ 102 cm; women, ≥ 88 cm); triglycerides ≥ 1.7 mmol/L or lipid-lowering treatment; glucose ≥ 6.1 mmol/L or type 2 diabetes treatment; blood pressure ≥ 130/85 mm Hg or treatment for hypertension; and HDL cholesterol (men, ≤ 1.03 mmol/L; women, ≤ 1.29 mmol/L).
[f]Same as ATP III definition but the following: glucose ≥ 5.6 mmol/L or type 2 diabetes treatment.
[g]Metabolic syndrome was present if patients had central obesity (men, ≥ 94 cm; women, ≥ 80 cm) and at least 2 other following factors: triglycerides ≥ 1.7 mmol/L or lipid-lowering treatment; glucose ≥ 5.6 mmol/L or type 2 diabetes treatment; blood pressure ≥ 130/85 mm Hg or treatment for hypertension; and HDL cholesterol (men, ≤ 1.03 mmol/L; women, ≤ 1.29 mmol/L).
Abbreviations: ATP III = Adult Treatment Panel III, BMI = body mass index, HDL = high-density lipoprotein, IDF = International Diabetes Foundation.

Figure 1. Receiver Operating Characteristic (ROC) Curves Indicating the Best Early Weight Gain Threshold to Predict a Weight Gain ≥ 15% After 3 Months and ≥ 20% After 1 Year of Treatment



[a]The number on the right side of the cross represents the best weight gain threshold after 1 month of treatment; specificity and sensitivity, respectively, are enclosed within the parentheses.

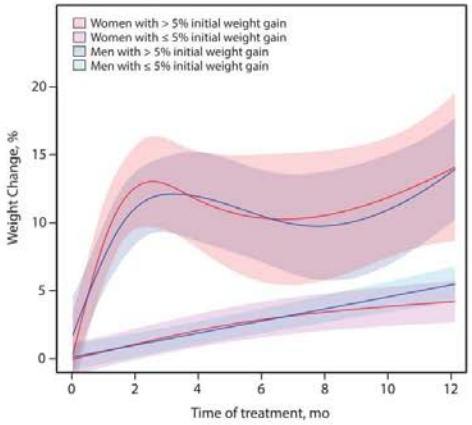
$P_{adjusted} < .0001$) and increase of triglyceride ($\beta = 1.5$ mmol/L, $P_{adjusted} < .0001$) were also observed in the >5% group by using a linear model controlled by several confounders (Table 3). In the final linear mixed model with an early weight gain >5% as predictor, it was confirmed that this threshold was a significant predictor of long-term weight gain over 1 year of treatment (difference between groups in 1 year [β] of 6.4% weight gain as compared to baseline, $P_{adjusted} = .0001$). This predictor was also found significant for a stronger long-term weight gain in young patients (aged ≤25 years) ($\beta = 8.7\%$, $P_{adjusted} < .0001$), young adults (aged 25–45 years) ($\beta = 7.3\%$, $P_{adjusted} = .0001$), adults (aged 45–65 years) ($\beta = 7.4\%$, $P_{adjusted} = .005$), and elderly patients (aged >65 years) ($\beta = 13.6\%$, $P_{adjusted} < .01$). This predictor

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

It is illegal to post this copyrighted PDF on any website.

Figure 2. Generalized Additive Mixed Model Prediction of Weight Over a 1-Year Period in Psychiatric Patients Having a > 5% Weight Increase Versus ≤ 5% After 1 Month Following the Introduction of Weight Gain–Inducing Psychotropic Drugs[a]



[a]Shaded area represents 95% CI. Men and women are represented by blue and red lines, respectively.

Table 3. Linear Model Comparing 1-Year Change of Metabolic Parameters Between Early and Nonearly Weight Gainers[a]

Parameter	Difference Between ≤ 5% and > 5% Weight Gain Group, Adjusted Mean (95% CI)	*P*[b]
Waist circumference, cm	1.7 (−4.8 to 8.2)	.6
Glucose, mmol/L	0.7 (−0.2 to 1.5)	.1
HDL cholesterol, mmol/L	−0.3 (−0.5 to −0.2)	**<.0001**
Triglycerides, mmol/L	1.5 (0.8 to 2.2)	**<.0001**

[a]Results were obtained by fitting a linear model controlling for age, sex, time, baseline body mass index, and current psychotropic drug.
[b]Values in bold are significant.
Abbreviation: HDL = high-density lipoprotein.

was also found significant in patients with psychotic or schizoaffective disorder ($\beta = 7.0\%$, $P_{adjusted} < .0001$), bipolar disorder or depression ($\beta = 9.1\%$, $P_{adjusted} = .0006$), and in the other diagnoses ($\beta = 11.6\%$, $P_{adjusted} < .01$). Significant results were also observed in patients treated with amisulpride or aripiprazole ($\beta = 6.6\%$, $P_{adjusted} = .003$); mirtazapine, lithium, quetiapine, or risperidone ($\beta = 8.4\%$, $P_{adjusted} < .0001$); and finally with clozapine, olanzapine, or valproate ($\beta = 7.4\%$, $P_{adjusted} < 0.0001$) (Supplementary eTable 7).

Effect of Changes in Appetite and Physical Activity During Treatment

Calculations were also made to assess the predictive power value of moderate or high (≥ 30 min/d) physical activity and of an appetite increase during the first month of treatment on long-term weight gain (Supplementary eTables 8 and 9). The AUC value indicated no predictive power for either parameter (AUC ≈ 50).

DISCUSSION

Confirming previous studies in psychiatric patients,[19,20] our study found a high prevalence of overweight status or obesity (39%) in the present cohort at baseline, which even increased after 1 year of treatment (50%). Notably, a higher (68%) prevalence of overweight status or obesity was measured in another Swiss cohort,[20] which is probably explained by the longer treatment duration in the latter cohort (median = 2.3 years vs mean = 0.65 years). The increase of mean BMI after 1 year of treatment was dependent on age (decreasing with increasing age), which is in agreement with previous studies showing that being of young age is a risk factor for a stronger increase in BMI.[21] Although weight gain in elderly patients is subject to controversial results,[22,23] in the present study a moderate mean gain of 1 BMI unit was observed after 1 year in this age group, which is in agreement with the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATI-AD) study[23] conclusion supporting the importance of metabolic monitoring also in elderly patients. Because of the small cohort size after stratification by the type of drugs prescribed, the frequent polymedication, and the previous history of past medications, it was not possible to differentiate the effects of each psychotropic drug separately.

An early weight gain of more than 5% was found to be the best predictor for a weight gain of ≥ 15% after 3 months and of ≥ 20% after 1 year. Of note, AUC values have also been calculated for the previously published threshold of 2 kg after 1 month.[9–11] Similar results to the present analysis in terms of AUC values were found (data not shown). Because an absolute threshold expressed in kilograms does not take into account the large variability of baseline weight, a relative threshold expressed in percentage as presented in this study appears to be more relevant. The high negative predictive value indicates that this measure will correctly predict the future status of most patients (97% for 3 months, 93% for 12 months) who had a weight gain less than or equal to 5% after 1 month as continuing to have a moderate weight gain after 3 and 12 months, respectively. Over 1 year, these patients had a mean BMI increase of 1.2 kg/m^2, which is significantly lower than the 3.1-kg/m^2 increase observed in the high early weight–gain group. The low positive predictive value indicates that 71% and 70% of patients with an early weight gain > 5% will not reach the 15% and 20% threshold at 3 and 12 months. Although weight gain in this false-positive group at 3 months is still significantly higher than in the low weight–gain group, the difference was no longer significant at 12 months, indicating the necessity of long-term weight monitoring also in the group with low initial weight gain. Monitoring of metabolic parameters is performed in our department with advice to take into account significant changes of parameters by different means (discussion with the patients, diet and physical activity counseling, drug evaluation and changes). Because

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

such possible interventions were not collected in this post hoc noninterventional study, it is not known if they could have contributed to part of the false-positive results.

These predictive parameters are in agreement and complete previous results obtained from clinical trials.[9,10,24] Female gender, young age, low baseline BMI, and low triglyceride levels were proposed to predict antipsychotic-induced weight gain.[3,20,25,26] In the present study, only BMI was found to be significantly different between both groups, being lower in the early weight-gain group at baseline. However, triglyceride values increased and HDL cholesterol values decreased with higher amplitude over 1 year, showing that these parameters are worsening faster in the early high weight–gain group, paralleling the faster increase of BMIs.

The threshold of more than 5% in the early phase of the treatment remained significant ($\beta = 6.4\%$, $P_{adjusted} = .0001$), even after adjusting for several confounders. These results indicate the robustness of this predictor and should motivate clinicians to monitor early weight changes more thoroughly for all patients and not only patients with known risk factors (ie, young patients, drug naive, and other factors). Although not formally demonstrated in the present study, the threshold of more than 5% weight gain after 1 month of treatment may also be used to detect some patients who could reach this threshold in a shorter period of time. Thus, very rapid and important weight gain should be evaluated by the treating physician and nurses independently of the usual time schedules for weight monitoring.

No significant influence of prescribed antipsychotics was found in the confirmatory analysis. This is in agreement with a previous study showing that an early weight gain of 2 kg is a good predictor for more weight gain during 24- to 28-week treatment with olanzapine and aripiprazole, 2 drugs with important differences in their potential to induce weight gain.[9] These results suggest that, independently of the prescribed drugs (ie, atypical antipsychotics, mood stabilizers such as lithium or valproate, or sedative antidepressants such as mirtazapine), the 5% threshold should be used when monitoring weight gain during treatment.

To our knowledge, only 1 study[27] previously investigated the role of appetite on long-term weight change, concluding that early weight gain was found to be a better predictor for further weight gain than appetite increase, which is in agreement with the present study. In addition, medium or high physical activity was also a poor predictor. However, the present results do not preclude the use of health promotion intervention, including physical activity or behavioral interventions that have shown some effect in psychiatric populations.[28]

Several limitations of the present study have to be mentioned. First, the majority of patients were not drug naive, and the observed weight gain was probably also the result of past treatments. However, such patients constitute the majority of psychiatric populations, which therefore might even strengthen the clinical validity of the present finding. Second, the follow-up period lasted only 1 year, but previous studies,[29,30] as well as the present study, show that following drug introduction, most of the weight gain occurs during this period. Third, due to an insufficient number of observations, we could not determine an early weight–gain threshold specifically in young and elderly patients. However, the 5% threshold was significantly associated with important weight gain in these 2 age classes. Finally, the results concerning activity and appetite change have to be interpreted with caution because the evaluation was self-reported, used a nonvalidated scale, and may be not sensitive enough.

A strength of the present study is its longitudinal design with weight monitoring at regular time points during 1 year when patients started a weight-inducing psychotropic drug or switched the treatment. In addition, the use of therapeutic drug monitoring allowed us to assess the compliance of the patients, which is an important issue in psychiatric treatment.

In conclusion, this work underlines the importance of weight monitoring at the introduction and after a switch of antipsychotic drugs, mood stabilizers, or sedative antidepressants for all patients, independently of their gender, age, initial body weight, previous treatments, or illness duration. A weight gain of more than 5% during the first month of treatment should be used by the clinician as one of the early warning signs to consider those patients as being at higher risk of important weight gain during long-term treatment. A particular emphasis should be put on such patients by using all available strategies (ie, behavioral interventions or even replacing the causative weight gain–inducing drug if clinically possible, after a careful evaluation of the risk-benefit ratio of a drug switch), considering the major impact weight gain and its consequences have on quality of life and general health of patients.

Submitted: July 3, 2014; accepted November 11, 2014.

Drug names: aripiprazole (Abilify and others), clozapine (Clozaril, FazaClo, and others), lithium (Lithobid and others), mirtazapine (Remeron and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

Author contributions: Drs Vandenberghe and Gholam-Rezaee contributed equally to the work. Dr Eap had full access to all of 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. Acquisition of data was provided by Drs Vandenberghe, Saigí-Morgui, Choong, Solida-Tozzi, Kolly, Gallo, Thonney, Hedjal, Ambresin, von Gunten, and Conus and Ms Delacrétaz. Analysis and interpretation was provided by Drs Vandenberghe and Gholam-Rezaee. Drafting of the manuscript was provided by Drs Vandenberghe and Gholam-Rezaee. Critical revision of the manuscript for important intellectual content was provided by all authors. Statistical analysis was provided by Drs Gholam-Rezaee and Vandenberghe. Drs Eap and Conus obtained funding for the study. Administrative, technical, or material support was provided by Drs von Gunten, Ambresin, and Conus.

Potential conflicts of interest: **Dr Eap** received research support from Takeda and from the Roche Organ Transplantation Research Foundation (#152358701) in the previous 3 years. He received honoraria for conferences or teaching CME courses from Advisis, AstraZeneca, Essex Chemie, Lundbeck, Merck Sharp & Dohme, Sandoz, Servier, and Vifor-Pharma in the previous 3 years. **Dr von Gunten** received honoraria for a conference or a workshop participation from Vifor, Bayer Schering, and Schwabe in the previous 3 years. **Drs Vanderberghe**, **Gholam-Rezaee**, **Saigí-Morgui**, **Choong**, **Solida-Tozzi**, **Kolly**, **Thonney**, **Gallo**, **Hedjal**, **Ambresin**, and **Conus** and **Ms Delacrétaz** declare no conflict of interest in relation to the content of the article.

Funding/support: This work has been funded in part by the Swiss National Research Foundation (CBE and PC: 320030-120686 and 324730-144064).

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Role of the sponsor: The funding sources had no role in the writing of the manuscript or in the decision to submit it for publication.

Previous presentation: Previously presented in part at the 22nd Annual European Congress of Psychiatry; March 1–4, 2014; Munich, Germany • 168th Annual Meeting of the American Psychiatric Association; May 16–20, 2015; Toronto, Canada.

Acknowledgment: The authors are grateful to all participating psychiatrists and medical staff who were involved in the metabolic monitoring program.

Additional information: The original dataset is in possession of Dr Eap.

Supplementary material: See accompanying pages, which includes eTable 10 about comedication possibly inducing weight gain and additional eReferences.

REFERENCES

1. De Hert M, Dekker JM, Wood D, et al. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry*. 2009;24(6):412–424.
2. Newcomer JW. Metabolic syndrome and mental illness. *Am J Manag Care*. 2007;13(suppl):S170–S177.
3. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156(11):1686–1696.
4. Laimer M, Kramer-Reinstadler K, Rauchenzauner M, et al. Effect of mirtazapine treatment on body composition and metabolism. *J Clin Psychiatry*. 2006;67(3):421–424.
5. De Hert M, Detraux J, van Winkel R, et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2012;8(2):114–126.
6. Vehof J, Risselada AJ, Al Hadithy AF, et al. Association of genetic variants of the histamine H1 and muscarinic M3 receptors with BMI and HbA1c values in patients on antipsychotic medication. *Psychopharmacology (Berl)*. 2011;216(2):257–265.
7. 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.
8. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care*. 2004;27(2):596–601.
9. Hoffmann VP, Case M, Stauffer VL, et al. Predictive value of early changes in triglycerides and weight for longer-term changes in metabolic measures during olanzapine, ziprasidone or aripiprazole treatment for schizophrenia and schizoaffective disorder post hoc analyses of 3 randomized, controlled clinical trials. *J Clin Psychopharmacol*. 2010;30(6):656–660.
10. Lipkovich I, Jacobson JG, Hardy TA, et al. Early evaluation of patient risk for substantial weight gain during olanzapine treatment for schizophrenia, schizophreniform, or schizoaffective disorder. *BMC Psychiatry*. 2008;8(1):78.
11. Lipkovich I, Citrome L, Perlis R, et al. Early predictors of substantial weight gain in bipolar patients treated with olanzapine. *J Clin Psychopharmacol*. 2006;26(3):316–320.
12. Ascher-Svanum H, Zhu B, Faries DE, et al. Adherence and persistence to typical and atypical antipsychotics in the naturalistic treatment of patients with schizophrenia. *Patient Prefer Adherence*. 2008;2:67–77.
13. Kane JM, Osuntokun O, Kryzhanovskaya LA, et al. A 28-week, randomized, double-blind study of olanzapine versus aripiprazole in the treatment of schizophrenia. *J Clin Psychiatry*. 2009;70(4):572–581.
14. Breier A, Berg PH, Thakore JH, et al. Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. *Am J Psychiatry*. 2005;162(10):1879–1887.
15. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol*. 1997;17(5):407–418.
16. Choong E, Solida A, Lechaire C, et al. Follow-up of the metabolic syndrome induced by atypical antipsychotics: recommendations and pharmacogenetics perspectives [article in French]. *Rev Med Suisse*. 2008;4(171):1994–1996, 1998–1999.
17. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics*. 2011;12:77.
18. Mitchell AJ, Vancampfort D, De Herdt A, et al. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophr Bull*. 2013;39(2):295–305.
19. Falissard B, Mauri M, Shaw K, et al. The METEOR study: frequency of metabolic disorders in patients with schizophrenia: focus on first and second generation and level of risk of antipsychotic drugs. *Int Clin Psychopharmacol*. 2011;26(6):291–302.
20. Choong E, Bondolfi G, Etter M, et al. Psychotropic drug-induced weight gain and other metabolic complications in a Swiss psychiatric population. *J Psychiatr Res*. 2012;46(4):540–548.
21. Greil W, Häberle A, Schuhmann T, et al. Age and adverse drug reactions from psychopharmacological treatment: data from the AMSP drug surveillance programme in Switzerland. *Swiss Med Wkly*. 2013;143:w13772.
22. Rondanelli M, Sarra S, Antoniello N, et al. No effect of atypical antipsychotic drugs on weight gain and risk of developing type II diabetes or lipid abnormalities among nursing home elderly patients with Alzheimer's disease. *Minerva Med*. 2006;97(2):147–151.
23. Zheng L, Mack WJ, Dagerman KS, et al. Metabolic changes associated with second-generation antipsychotic use in Alzheimer's disease patients: the CATIE-AD study. *Am J Psychiatry*. 2009;166(5):583–590.
24. Kinon BJ, Kaiser CJ, Ahmed S, et al. Association between early and rapid weight gain and change in weight over one year of olanzapine therapy in patients with schizophrenia and related disorders. *J Clin Psychopharmacol*. 2005;25(3):255–258.
25. Verma SK, Subramaniam M, Liew A, et al. Metabolic risk factors in drug-naive patients with first-episode psychosis. *J Clin Psychiatry*. 2009;70(7):997–1000.
26. 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.
27. Case M, Treuer T, Karagianis J, et al. The potential role of appetite in predicting weight changes during treatment with olanzapine. *BMC Psychiatry*. 2010;10(1):72.
28. Daumit GL, Dickerson FB, Wang NY, et al. A behavioral weight-loss intervention in persons with serious mental illness. *N Engl J Med*. 2013;368(17):1594–1602.
29. Pérez-Iglesias R, Martínez-García O, Pardo-Garcia G, et al. Course of weight gain and metabolic abnormalities in first treated episode of psychosis: the first year is a critical period for development of cardiovascular risk factors. *Int J Neuropsychopharmacol*. 2014;17(1):41–51.
30. Novick D, Haro JM, Perrin E, et al. Tolerability of outpatient antipsychotic treatment: 36-month results from the European Schizophrenia Outpatient Health Outcomes (SOHO) study. *Eur Neuropsychopharmacol*. 2009;19(8):542–550.

Supplementary material follows this article.

It is illegal to post this copyrighted PDF on any website.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Importance of Early Weight Changes to Predict Long-Term Weight Gain During Psychotropic Drug Treatment

Authors: Frederik Vandenberghe, PharmD, MSc; Mehdi Gholamrezaee, PhD; Nuria Saigi Morgui, PharmD, MPH; Aurélie Delacrétaz, MSc; Eva Choong, PhD; Alessandra Solida-Tozzi, MD; Stéphane Kolly, MD; Jacques Thonney, MD; Sylfa Fassassi Gallo, MD; Ahmed Hedjal, MD; Anne-Emmanuelle Ambresin, MD; Armin von Gunten, MPhil, MD; Philippe Conus, MD; and Chin B. Eap, PhD

DOI Number: 10.4088/JCP.14m09358

List of Supplementary Material for the article

© Copyright 2015 Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

9.	eTable 4	Receiver operating parameters for a one month weight change predicting a weight gain after 3 months of treatment (upper panel) and 12 months (lower panel) in all ages
10.	eTable 5	Receiver operating parameters for a one month weight change predicting a weight gain after 3 months of treatment (upper panel) and 12 months (lower panel) for adults (]25-65])
11.	eTable 6	Overall metabolic parameters (left column) and comparison between early and nonearly weight gainers
12.	eTable 7	Linear mixed effect model fitted on weight gain (%) over time
13.	eTable 8	Receiver operating parameters for an activity > 30 minutes/day at month 1 predicting a weight gain at 3 and 12 months
14.	eTable 9	Receiver operating parameters for an appetite increase between baseline and one month predicting a weight gain at 3 and 12 months
15.	eTable 10	Co-medication possibly inducing weight gain
16.	eFigure 1	Flow chart for selection of patients
17.	eFigure 2	Weight changes at 1 month, 2 months, 3 months, 6 months, 9 months and one year
18.	eReferences	References

Disclaimer
This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

© Copyright 2015 Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

Supplementary data

eMethods 1: Study design and subject selection.

eMethods 2: Determinations of clinical chemistry parameters and drug plasma concentrations.

eMethods 3: Exploratory analysis.

eMethods 4: Confirmatory Analysis.

eResults 1: Metabolic parameters.

eTable 1: Baseline demographics stratified by gender.

eTable 2: Metabolic parameters and syndrome at baseline, 3 months and one year.

eTable 3: Demographic and clinical parameters stratified for age and gender at baseline and 12 months of treatment.

eTable 4: Receiver operating parameters for a one month weight change predicting a weight gain after 3 months of treatment (upper panel) and 12 months (lower panel) in all ages.

eTable 5: Receiver operating parameters for a one month weight change predicting a weight gain after 3 months of treatment (upper panel) and 12 months (lower panel) for adults (]25-65]).

eTable 6: Overall metabolic parameters (left column) and comparison between early and non early weight gainers.

eTable 7: Linear mixed effect model fitted on weight gain (%) over time.

eTable 8: Receiver operating parameters for an activity > 30 minutes/day at month 1 predicting a weight gain at 3 and 12 months.

eTable 9: Receiver operating parameters for an appetite increase between baseline and one month predicting a weight gain at 3 and 12 months.

eTable 10: Co-medication possibly inducing weight gain[1, 2].

eFigure 1: Flow chart for selection of patients.

eFigure 2: Weight changes at 1 month (mean(se) 31(0.4) days), 2 months (mean(se) 64(1.8) days), 3 months (mean(se) 102(2) days), 6 months (mean(se) 189(2.3) days), 9 months (mean(se) 278(3.7) days) and one year (mean(se) 393(7.1) days). Red and blue box plots represent the patient's observation with a first month weight gain of more than 5% and less or equal to 5%, respectively. Dotted black line represents no weight change; red dotted line represents 5% weight increase.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eMethods 1: Study design and subject selection.

Patients with missing weight at baseline or at one month were excluded from analysis (eFigure 1). If two or more studied drugs (clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, lithium, valproate and/or mirtazapine) were prescribed concomitantly, the latest introduced compound was considered as the main treatment and the other drugs were pooled with co-medication possibly inducing weight gain (eTable 10). Medications could be changed by the treating physician according to the response to treatment and side-effects with no influence of the inclusion of patients in the study (non-interventional study).Weight was measured in the morning in fasting conditions by using professional medical scales. No retrospective or self-estimated patient data was used. Appetite assessment was based on a five item scale (self evaluation): low, moderate, medium, high and very high appetite. Physical activity, which was defined as walking, climbing stairs or specific sport activity, was based on daily physical activity duration (self evaluation): <30 min, 30-60 min, >60 min. For statistical tests on long term weight gain, appetite increase was defined as an elevation of appetite between baseline and the first month of treatment (eg. low to moderate, moderate to high). In addition, physical activity was defined by the daily activity duration at one month treatment (less vs equal or more than 30 minutes).

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eMethods 2: Determinations of clinical chemistry parameters and drug plasma concentrations.

Metabolic syndrome (MetS) prevalence was assessed according to the Adult Treatment Panel III (ATP III) [3], the adapted definition (ATP III-A) [4] and the International Diabetes Federation (IDF) [5] which has different cut-offs for waist circumference (WC) depending on the ethnicities (e.g. for the 95% of our patients who are Caucasian, Sub-Saharan Africans, Eastern Mediterranean and Middle East populations, WC of 90 cm for men and 80 cm for women are used for the definition of metabolic syndrome. This same cut-off was used for the 5% other patients who were Asians (n=2) or of unknown ethnic group (n=17)). Blood samples were drawn in the morning in fasting conditions (blood samples drawn after 10H00 AM were excluded from analysis) to measure clinical chemistry parameters and drug plasma concentrations. Plasma drug concentrations were quantified at one, three and 12 months in trough conditions (in the morning before the next drug intake). Liquid chromatography/mass spectrometry methods were used for measuring aripiprazole, clozapine, or olanzapine plasma levels as previously described[6], and also for risperidone, OH-risperidone, quetiapine or amisulpride (Eap et al., unpublished data, available on request). Mirtazapine was measured by gas-chromatography-nitrogen detector (Eap et al., unpublished data, available on request), valproate 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 in our accredited laboratory (ISO 15189 and 17025), with external quality controls (LGC Standards Proficiency Testing (Teddington, United Kingdom); Arvecon (Walldorf, Germany; Quality Control Centre Switzerland (Chêne-Bourg, Switzerland)). Patients were considered compliant when drug plasma concentrations were higher than 10 % of the lower value of the recommended therapeutic range [7]. For this purpose, for all substances except risperidone, the concentration of the prescribed drug was used, while for risperidone, the sum of risperidone and of its metabolite 9-OH risperidone was used. Drug plasma concentration at month one and three, and at month one and 12 were evaluated for follow ups shorter or equal to 12 months, respectively. Reports of non-compliance as observed by the medical or nursing staff were also taken into account. Patients who were considered non-compliant at any of the time periods of observations were excluded from analysis.

Patients' blood pressures were measured once after five minutes rest in a sitting position.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eMethods 3: Exploratory analysis.

Marginal analyses were done using Wilcoxon rank-sum (*W+*) and Kruskal-Wallis tests (*KW*) for comparing continuous traits. Fisher's exact tests (*FET*) were used to compare categorical variables and McNemar tests (*MN*) were used to compare the prevalence of outrange metabolic parameters between baseline, three and 12 months. Thresholds for early WG were examined by 1% increments (ranging from 2% to 8%) to find the best predictors for long term WG as defined by a minimal WG of 10%, 15% or 20% at 3 and 12 months of treatment. These analyses allowed to assess the best relation between SN and SP to find an acceptable threshold for short and long term WG. To explore the adequacy of linear evolution of BMI along time, a Generalized Additive Mixed Model (GAMM) was also fitted to the same data. The response variable in this model corresponded to the ratio of the weight at each time point divided by the weight at baseline, which represents the weight gain at that time point. Observations made at two, three, six, nine and 12 months (analyzed as a continuous variable) were used to fit the model, while observations made at baseline and/or at the first month were used to construct the grouping variable. The effect of time on weight gain was not considered as linear but was better represented by a smooth semi-parametric curve (with cubic regression spline basis). GAMMs were fitted separately for each sub-group to give the possibility of capturing the weight-gain trend without restraint at each sub-group (otherwise, a parallel trend in time would have been imposed on all sub-groups). These models were not adjusted for multiple comparisons, covariates or cofactors as they were used only to explore the data and the adequacy of the final model.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eMethods 4: Confirmatory Analysis.

The "nlme" package of R[8] was used to fit a linear mixed effect model adjusted for age (at baseline), gender, BMI (at baseline), psychotropic drugs, presence of co-medication possibly inducing weight gain, triglycerides, glucose and HDL concentrations. The fitted linear mixed effect model[9] had a random effect at the subject level. To be more robust in inferences, a bootstrap analysis[10] 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 for 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.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eResults 1: Metabolic parameters.

Abdominal obesity (M≥94cm, F≥80cm) was observed in 54% of patients at baseline, and increased from 49% to 62% after one year (p=0.02, table 2) in patients with one year follow-up. This prevalence increased significantly with age (from 30% to 66% at baseline, p=0.001 and from 45% to 76% at one year, p=0.004) (eTable 3).Hypo HDL-cholesterolemia (M≤1.03mmol/l; F≤1.29mmol/l)) was observed in 31% of patients at baseline with no evolution during treatment. Prevalence at baseline was higher in women except in elderly patients (young, p=0.02; young adults, p=0.03: adults, p=0.01). Baseline hypertriglyceridemia (≥1.7mmol/l or presence of lipid lowering drug) was observed in 28% of the patients at baseline. In patients with baseline and one year data, hypertriglyceridemia increased from 21% to 40% after one year (p=0.006). Hypertriglyceridemia increased along the four age categories from 8% to 36% at baseline (p=0.01) (eTable 3). Hyperglycemia or diabetes (≥5.6mmol/l or antidiabetic medication) was observed in 25% of patients at baseline. In patients with baseline and one year data, hyperglycemia increased from 16% to 38% (p=0.002). No gender differences were observed at baseline and after one year, however hyperglycemia was significantly increased with increasing age (p=0.003). No gender differences in the prevalence of hypertension (130/85mmHg or antihypertensive medication) were observed, with an unchanged prevalence during treatment. However, as expected, hypertension was found to increase significantly with increasing age both at baseline and after one year (p=0.001). Prevalence of metabolic syndrome (MetS, IDF definition) was 22% at baseline. In patients with baseline and one year data, a trend for an increased prevalence during treatment was observed (from 9% to 23%, p=0.07). In agreement with other parameters, MetS increases with increasing age (6% to 44%, p=0.001) at baseline, however no significant age related increase was observed after one year.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

175 **eTable 1: Baseline demographics stratified by gender.**

Characteristics	Total (351)	Men (164)	Women (187)	P [a]
Age, mean (se), years	46 (1.2)	39 (1.6)	51 (1.6)	**<0.001**
BMI				
Mean (se), kg/m^2	24.4 (0.3)	24.1 (0.3)	24.7 (0.5)	0.7
Overweight [25-30[kg/m^2, n/total n (%)	62/294 (21%)	35/130 (27%)	27/164 (16%)	**0.03**
Obese ≥ 30 kg/m^2, n/total n (%)	49/294 (17%)	12/130 (9%)	37/164 (23%)	**0.003**
Smoking, n/total n (%)	76/137 (55%)	42/67 (63%)	34/70 (49%)	0.9
Illness duration, mean (se), years	8.0 (0.6)	6.7 (0.8)	9 (1)	0.4
Follow up duration, mean (se), days	237.2 (8.2)	253.8 (12.9)	222.7 (10.3)	0.1
Month 1, mean (se), days	31 (0.4)	31 (0.6)	32 (0.5)	0.3
Month 3, mean (se), days	102 (2)	100 (1.8)	103 (3.6)	0.9
Month 12, mean (se), days	393 (7.1)	404 (12.8)	381 (5.8)	0.2
Medication, n/total n (%)				
Amisulpride	36/351 (10%)	20/164 (12%)	16/187 (9%)	0.3
Aripiprazole	30/351 (9%)	14/164 (9%)	16/187 (9%)	0.9
Clozapine	24/351 (7%)	12/164 (7%)	12/187 (6%)	0.8
Lithium	19/351 (5%)	10/164 (6%)	9/187 (5%)	0.6
Mirtazapine	11/351 (3%)	5/164 (3%)	6/187 (3%)	0.9
Olanzapine	44/351 (13%)	19/164 (12%)	25/187 (13%)	0.6
Quetiapine	112/351 (32%)	48/164 (29%)	64/187 (34%)	0.4
Risperidone	64/351 (18%)	32/164 (20%)	32/187 (17%)	0.6
Valproate	10/351 (3%)	3/164 (2%)	7/187 (4%)	0.3
More than one AP, n/total n (%)	110/351 (31%)	50/164 (30%)	60/187 (32%)	0.8
AP and mirtazapine, n/total n (%)	16/351 (5%)	8/164 (5%)	8/187 (4%)	0.8
AP and MS, n/total n (%)	47/351 (13%)	19/164 (12%)	28/187 (15%)	0.4
Co-mediation possibly causing weight gain, n/total n (%)	46/255 (18%)	19/106 (18%)	27/149 (18%)	0.9

[a] p-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between genders.

Abbreviations :AP = Atypical antipsychotics; MS = lithium, valproic acid.

176

177

178

179

180

181

182

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eTable 2: Metabolic parameters and syndrome at baseline, 3 months and one year.

	Baseline	3 Months	P[a]	One year	P[b]
Prevalence of normal weight, overweight and obesity, n/total n (%)					
Normal weight: BMI < 25 kg/m2	183 /294 (62%)	132 /241 (55%)	**0.0005**	66 /135 (49%)	**0.01**
Overweight: BMI [25-30[kg/m^2	62/294 (21%)	63/241 (26%)	0.05	36/135 (27%)	0.32
Obese: BMI ≥ 30 kg/m^2	49/294 (17%)	46/241 (19%)	0.4	33/135 (24%)	**0.03**
Prevalence of abdominal obesity, n/total n (%)					
Waist circumference Men ≥ 94 cm , Women ≥ 80 cm[c]	162/300 (54%)	142/231 (61%)	**0.0004**	89/135 (66%)	**0.01**
Waist circumference Men ≥ 102 cm, Women ≥ 88 cm[d,e]	99/300 (33%)	87/231 (38%)	**0.01**	58/135 (43%)	**0.03**
Prevalence of hypocholesterolemia, n/total n (%)					
HDL-chol. Men ≤ 1.03 mmol/l, Women ≤ 1.29 mmol/l	61/194 (31%)	56/198 (28%)	0.8	35/122 (29%)	1.00
Prevalence of hypertriglyceridemia, n/total n (%)					
Triglyceridemia ≥ 1.7 mmol/l or lipid lowering treatment	56/201 (28%)	70/207 (34%)	**0.03**	42/123 (34%)	**0.01**
Prevalence of hyperglycemia, n/total n (%)					
Fasting glucose ≥ 5.6 mmol/l or antidiabetic treatment[e,c]	50/204 (25%)	55/202 (27%)	0.7	53/122 (43%)	**0.0001**
Fasting glucose ≥ 6.1 mmol/l or antidiabetic treatment[d]	25/204 (12%)	22/202 (11%)	1	22/122 (18%)	0.15
Prevalence of hypertension, n/total n (%)					
Blood pressure ≥ 130 / 85 mmHg or antihypertensive treatment	58/305 (19%)	41/229 (18%)	1	27/134 (20%)	0.50
Prevalence of metabolic syndrome, n/total n (%)					
ATP-III[f]	24/161 (15%)	23/154 (15%)	1	23/100 (23%)	0.22
ATP-III-A[g]	30/161 (19%)	27/154 (18%)	1	28/100 (28%)	0.22
IDF[h]	35/161 (22%)	33/154 (21%)	0.5	32/100 (32%)	**0.04**

[a] p-value were calculated using McNemar tests between baseline and 3 months.
[b] p-value were calculated using McNemar tests between baseline and 12 months.
[c] According to IDF definition.
[d] According to ATP-III definition.
[e] According to ATP-III-A definition.
[f] Metabolic syndrome is present if at least 3 criterias are present: central obesity (M ≥ 102 cm , F ≥ 88 cm); triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 6.1 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85mmHg or treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.
[g] Same as [e] but: glucose ≥ 5.6 mmol/l or type 2 diabetes treatment.
[h] Metabolic syndrome is present if: presence of central obesity (M ≥ 94 cm, F ≥ 80 cm) and at least two other following factors: triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 5.6 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85 mmHg of treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eTable 3: Demographic and clinical parameters stratified for age and gender at baseline and 12 months of treatment.

Baseline, (age range)	Young (age ≤ 25)				Young adult (age :]25-45])				Adult (age :]45-65])				Elderly (age : > 65)				Overal p[a]
Gender, (total n)	All (72)	Men (47)	Women (25)	P[b]	All (114)	Men (62)	Women (52)	P[b]	All (78)	Men (30)	Women (48)	P[b]	All (87)	Men (25)	Women (62)	P[b]	
BMI																	
Mean (se), kg/m^2	22.9 (0.5)	23.7 (0.6)	21.3 (1.0)	**0.002**	25.3 (0.6)	24.4 (0.5)	26.3 (1.0)	0.4	25.6 (0.8)	24.4 (0.9)	26.3 (1.1)	0.6	23.8 (0.6)	24 (1.0)	23.7 (0.7)	0.8	**0.01**
Overweight [25-30[kg/m^2, n/total n (%)	9/67 (13%)	8/45 (18%)	1/22 (5%)	0.3	21/89 (24%)	13/44 (30%)	8/45 (18%)	0.2	15/61 (25%)	7/21 (33%)	8/40 (20%)	0.3	17/77 (22%)	7/20 (35%)	10/57 (18%)	0.1	0.4
Obese ≥ 30 kg/m^2, n/total n (%)	7/67 (10%)	5/45 (11%)	2/22 (9%)	0.9	17/89 (19%)	3/44 (7%)	14/45 (31%)	**0.006**	13/61 (21%)	2/21 (10%)	11/40 (28%)	0.2	12/77 (16%)	2/20 (10%)	10/57 (18%)	0.7	0.4
Waist circumference																	
Mean (se), cm	83 (1)	87 (2)	78 (2)	**0.01**	91 (1)	90 (1)	92 (2)	0.8	91 (2)	96 (2)	89 (3)	**0.02**	90 (2)	93 (2)	89 (2)	0.1	**0.0004**
M ≥ 94cm , F ≥ 80cm[c], n/total n (%)	19/64 (30%)	10/41 (24%)	9/23 (39%)	0.3	49/91 (54%)	17/49 (35%)	32/42 (76%)	**0.0001**	43/68 (63%)	16/27 (59%)	27/41 (66%)	0.6	51/77 (66%)	13/22 (59%)	38/55 (69%)	0.4	**0.001**
M ≥ 102cm , F ≥ 88cm[d,e], n/total n (%)	9/64 (14%)	6/41 (15%)	3/23 (13%)	0.9	31/91 (34%)	7/49 (14%)	24/42 (57%)	**0.0001**	26/68 (38%)	8/27 (30%)	18/41 (44%)	0.3	33/77 (43%)	5/22 (23%)	28/55 (51%)	**0.04**	**0.002**
HDL-Cholesterol																	
Mean (se), mmol/l	1.32 (0.07)	1.3 (0.07)	1.37 (0.14)	0.9	1.3 (0.05)	1.26 (0.06)	1.35 (0.09)	0.6	1.51 (0.07)	1.42 (0.09)	1.58 (0.1)	0.3	1.45 (0.06)	1.35 (0.09)	1.49 (0.07)	0.3	0.05
M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l, n/total n (%)	12/38 (32%)	5/27 (19%)	7/11 (64%)	**0.02**	21/61 (34%)	7/33 (21%)	14/28 (50%)	**0.03**	11/43 (26%)	1/18 (6%)	10/25 (40%)	**0.01**	17/52 (33%)	2/14 (14%)	15/38 (39%)	0.1	0.8
Triglyceride																	
Mean (se), mmol/l	1.09 (0.12)	1.19 (0.18)	0.91 (0.09)	0.7	1.58 (0.17)	1.7 (0.3)	1.45 (0.16)	0.9	1.58 (0.19)	2 (0.42)	1.28 (0.11)	0.08	1.27 (0.08)	1.25 (0.16)	1.27 (0.1)	0.8	**0.004**
≥ 1.7mmol/l or lipid lowering treatment, n/total n (%)	3/38 (8%)	3/25 (12%)	0/13 (0%)		19/63 (30%)	11/35 (31%)	8/28 (29%)	0.9	14/44 (32%)	8/18 (44%)	6/26 (23%)	0.2	20/56 (36%)	6/15 (40%)	14/41 (34%)	0.8	**0.01**
Glucose																	
Mean (se), mmol/l	4.89 (0.07)	4.94 (0.09)	4.79 (0.08)	0.4	5.02 (0.08)	4.94 (0.12)	5.11 (0.1)	0.7	5.47 (0.25)	5.7 (0.47)	5.29 (0.26)	0.2	5.45 (0.13)	5.5 (0.17)	5.43 (0.16)	0.4	**0.01**
≥ 5.6mmol/l or antidiabetic treatment[e,c], n/total n (%)	4/43 (9%)	4/29 (14%)	0/14 (0%)		15/65 (23%)	7/34 (21%)	8/31 (26%)	0.8	10/45 (22%)	4/20 (20%)	6/25 (24%)	0.9	21/51 (41%)	7/14 (50%)	14/37 (38%)	0.5	**0.003**
≥ 6.1mmol/l or antidiabetic treatment[d], n/total n (%)	1/43 (2%)	1/29 (3%)	0/14 (0%)		7/65 (11%)	4/34 (12%)	3/31 (10%)	0.9	5/45 (11%)	3/20 (15%)	2/25 (8%)	0.6	12/51 (24%)	3/14 (21%)	9/37 (24%)	0.9	**0.02**
Blood pressure																	
Systolic, mean (se), mmHg	119 (2)	125 (2)	108 (3)	0.10	122 (1)	126 (2)	118 (2)	**0.003**	119 (2)	124 (4)	116 (3)	0.1	135 (2)	140 (4)	133 (3)	0.09	**0.00001**
Diastolic, mean (se), mmHg	72 (2)	75 (2)	66 (2)	**0.01**	79 (1)	79 (2)	78 (2)	0.5	80 (2)	84 (4)	77 (2)	0.09	75 (1)	78 (3)	74 (2)	0.3	**0.0002**
≥ 130/85mmHg or antihypertensive treatment, n/total n (%)	4/65 (6%)	3/43 (7%)	1/22 (5%)	0.9	12/96 (13%)	10/52 (19%)	2/44 (5%)	**0.03**	11/66 (17%)	7/25 (28%)	4/41 (10%)	0.09	31/78 (40%)	9/23 (39%)	22/55 (40%)	0.9	**0.001**
Prevalence of metabolic syndrome																	
ATP-III[f], n/total n (%)	1/32 (3%)	1/22 (5%)	0/10 (0%)		3/48 (6%)	0/25 (0%)	3/23 (13%)	0.1	6/38 (16%)	3/17 (18%)	3/21 (14%)	0.9	14/43 (33%)	2/12 (17%)	12/31 (39%)	0.3	**0.002**
ATP-III-A[g], n/total n (%)	1/32 (3%)	1/22 (5%)	0/10 (0%)		4/48 (8%)	1/25 (4%)	3/23 (13%)	0.3	7/38 (18%)	3/17 (18%)	4/21 (19%)	0.9	18/43 (42%)	4/12 (33%)	14/31 (45%)	0.7	**0.001**
IDF[h], n/total n (%)	2/32 (6%)	2/22 (9%)	0/10 (0%)		6/48 (13%)	2/25 (8%)	4/23 (17%)	0.4	8/38 (21%)	4/17 (24%)	4/21 (19%)	0.9	19/43 (44%)	3/12 (25%)	16/31 (52%)	0.2	**0.001**

[a] p-value were calculated using Kruskal-Wallis tests for continuous variables and Fisher's exact tests for categorical variables between age groups.
[b] p-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between genders.
[c] According to IDF definition for Caucasian.
[d] According to ATP-III definition.
[e] According to ATP-III-A definition.
[f] Metabolic syndrome is present if at least 3 criterias are present: central obesity (M ≥ 102 cm , F ≥ 88 cm); triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 6.1 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85mmHg or treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.
[g] Same as [f] but: glucose ≥ 5.6 mmol/l or type 2 diabetes treatment.
[h] Metabolic syndrome is present if: presence of central obesity (M ≥ 94 cm , F ≥ 80 cm) and at least two other following factors: triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 5.6 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85 mmHg of treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

One year, (age range)	Young (age ≤ 25)				Young adult (age :]25-45])				Adult (age :]45-65])				Elderly (age : > 65)				Overal p[a]
Gender, (total n)	All (32)	Men (22)	Women (10)	P[b]	All (55)	Men (30)	Women (25)	P[b]	All (38)	Men (16)	Women (22)	P[b]	All (23)	Men (7)	Women (16)	P[b]	
BMI																	
Mean (se), kg/m^2	25.6 (0.9)	26.4 (1.1)	24 (1.9)	**0.03**	27.5 (0.8)	26.3 (0.8)	28.7 (1.3)	0.3	27.4 (1.1)	26.2 (1.0)	28.1 (1.6)	0.9	24.8 (1.3)	26.5 (2.7)	24.1 (1.5)	0.4	0.08
Overweight [25-30[kg/m^2, n/total n (%)	8/32 (25%)	7/22 (32%)	1/10 (10%)	0.4	11/48 (23%)	9/24 (38%)	2/24 (8%)	0.04	13/34 (38%)	9/13 (69%)	4/21 (19%)	**0.009**	4/21 (19%)	2/6 (33%)	2/15 (13%)	0.5	0.4
Obese ≥ 30 kg/m^2, n/total n (%)	5/32 (16%)	4/22 (18%)	1/10 (10%)	0.9	17/48 (35%)	4/24 (17%)	13/24 (54%)	**0.01**	7/34 (21%)	1/13 (8%)	6/21 (29%)	0.2	4/21 (19%)	1/6 (17%)	3/15 (20%)	0.9	0.2
Waist circumference																	
Mean (se), cm	91 (3)	94 (4)	83 (6)	0.05	94 (2)	94 (2)	95 (4)	1.0	98 (3)	101 (2)	96 (4)	0.1	97 (4)	102 (6)	95 (6)	0.6	0.2
M ≥ 94cm , F ≥ 80cm[c], n/total n (%)	14/31 (45%)	10/21 (48%)	4/10 (40%)	0.9	31/51 (61%)	16/30 (53%)	15/21 (71%)	0.2	31/36 (86%)	13/15 (87%)	18/21 (86%)	0.9	13/17 (76%)	4/5 (80%)	9/12 (75%)	0.9	**0.004**
M ≥ 102cm , F ≥ 88cm[d,e], n/total n (%)	9/31 (29%)	7/21 (33%)	2/10 (20%)	0.7	20/51 (39%)	8/30 (27%)	12/21 (57%)	**0.04**	18/36 (50%)	7/15 (47%)	11/21 (52%)	0.9	11/17 (65%)	3/5 (60%)	8/12 (67%)	0.9	0.07
HDL-Cholesterol																	
Mean (se), mmol/l	1.28 (0.08)	1.17 (0.09)	1.59 (0.11)	**0.01**	1.25 (0.06)	1.2 (0.08)	1.32 (0.08)	0.3	1.44 (0.12)	1.27 (0.11)	1.56 (0.18)	0.4	1.47 (0.08)	1.33 (0.09)	1.55 (0.11)	0.2	0.2
M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l, n/total n (%)	6/27 (22%)	6/20 (30%)	0/7 (0%)		14/43 (33%)	5/25 (20%)	9/18 (50%)	0.05	11/32 (34%)	2/13 (15%)	9/19 (47%)	0.1	4/20 (20%)	0/7 (0%)	4/13 (31%)	0.2	0.6
Triglyceride																	
Mean (se), mmol/l	1.27 (0.14)	1.41 (0.17)	0.86 (0.15)	0.07	1.7 (0.21)	2.09 (0.33)	1.19 (0.14)	0.2	1.66 (0.17)	1.72 (0.32)	1.63 (0.2)	0.9	1.53 (0.2)	1.33 (0.27)	1.65 (0.28)	0.4	0.2
≥ 1.7mmol/l or lipid lowering treatment, n/total n (%)	6/27 (22%)	6/20 (30%)	0/7 (0%)		13/44 (30%)	10/25 (40%)	3/19 (16%)	0.1	12/31 (39%)	5/13 (38%)	7/18 (39%)	0.9	11/21 (52%)	3/7 (43%)	8/14 (57%)	0.7	0.2
Glucose																	
Mean (se), mmol/l	5.19 (0.23)	5.33 (0.3)	4.83 (0.22)	0.3	5.43 (0.21)	5.55 (0.36)	5.27 (0.13)	0.9	5.63 (0.18)	5.81 (0.17)	5.51 (0.28)	0.08	5.63 (0.33)	6.09 (0.71)	5.34 (0.3)	0.6	0.05
≥ 5.6mmol/l or antidiabetic treatment[e,c], n/total n (%)	4/26 (15%)	3/19 (16%)	1/7 (14%)	0.9	19/45 (42%)	10/25 (40%)	9/20 (45%)	0.8	19/32 (59%)	10/13 (77%)	9/19 (47%)	0.1	11/19 (58%)	4/7 (57%)	7/12 (58%)	0.9	**0.003**
≥ 6.1mmol/l or antidiabetic treatment[d], n/total n (%)	2/26 (8%)	2/19 (11%)	0/7 (0%)	0.9	6/45 (13%)	4/25 (16%)	2/20 (10%)	0.7	7/32 (22%)	4/13 (31%)	3/19 (16%)	0.4	7/19 (37%)	2/7 (29%)	5/12 (42%)	0.7	0.07
Blood pressure																	
Systolic, mean (se), mmHg	122 (3)	130 (3)	107 (4)	**0.0002**	121 (3)	128 (4)	113 (3)	**0.007**	121 (2)	123 (3)	119 (3)	0.4	139 (4)	146 (5)	135 (5)	0.2	**0.001**
Diastolic, mean (se), mmHg	74 (2)	78 (3)	66 (2)	**0.005**	80 (2)	82 (3)	77 (2)	0.2	80 (2)	81 (2)	78 (2)	0.4	76 (2)	78 (3)	75 (2)	0.4	0.1
≥ 130/85mmHg or antihypertensive treatment, n/total n (%)	2/28 (7%)	2/18 (11%)	0/10 (0%)	0.5	8/47 (17%)	6/24 (25%)	2/23 (9%)	0.2	4/36 (11%)	3/16 (19%)	1/20 (5%)	0.3	13/23 (57%)	5/7 (71%)	8/16 (50%)	0.4	**0.001**
Prevalence of metabolic syndrome																	
ATP-III[f], n/total n (%)	2/22 (9%)	2/15 (13%)	0/7 (0%)		6/36 (17%)	4/21 (19%)	2/15 (13%)	0.9	9/29 (31%)	4/12 (33%)	5/17 (29%)	0.9	6/13 (46%)	2/5 (40%)	4/8 (50%)	0.9	**0.04**
ATP-III-A[g], n/total n (%)	3/22 (14%)	3/15 (20%)	0/7 (0%)		10/36 (28%)	6/21 (29%)	4/15 (27%)	0.9	9/29 (31%)	4/12 (33%)	5/17 (29%)	0.9	6/13 (46%)	2/5 (40%)	4/8 (50%)	0.9	0.21
IDF[h], n/total n (%)	3/22 (14%)	3/15 (20%)	0/7 (0%)		12/36 (33%)	7/21 (33%)	5/15 (33%)	0.9	11/29 (38%)	5/12 (42%)	6/17 (35%)	0.9	6/13 (46%)	2/5 (40%)	4/8 (50%)	0.9	0.14

[a] p-value were calculated using Kruskal-Wallis tests for continuous variables and Fisher's exact tests for categorical variables between age groups.
[b] p-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between genders.
[c] According to IDF definition for Caucasian.
[d] According to ATP-III definition.
[e] According to ATP-III-A definition.
[f] Metabolic syndrome is present if at least 3 criterias are present: central obesity (M ≥ 102 cm , F ≥ 88 cm); triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 6.1 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85mmHg or treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.
[g] Same as [f] but: glucose ≥ 5.6 mmol/l or type 2 diabetes treatment.
[h] Metabolic syndrome is present if: presence of central obesity (M ≥ 94 cm, F ≥ 80 cm) and at least two other following factors: triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 5.6 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85 mmHg of treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eTable 4: Receiver operating parameters for a one month weight change predicting a weight gain after 3 months of treatment (upper panel) and 12 months (lower panel) in all ages.

Weight change (%) at		PPV	NPV	Sensitivity	Specificity	AUC
1 Month	3 Months					
2	10	35	93	72	72	72
2	15	14	98	76	67	72
2	20	5	99	71	65	68
5	10	54	89	48	92	70
5	**15**	**29**	**97**	**67**	**88**	**79**
5	20	10	99	71	86	78
8	10	68	86	24	98	61
8	15	47	96	43	97	70
8	20	16	99	43	95	69
1 Month	12 Months					
2	10	52	78	55	76	66
2	15	35	89	62	73	66
2	20	21	94	65	70	66
5	10	61	73	29	91	60
5	15	39	85	31	89	60
5	**20**	**30**	**93**	**47**	**89**	**68**
8	10	56	70	10	96	53
8	15	33	82	10	95	53
8	20	33	90	18	96	57

The left column indicates the weight change after one month and the second left column indicates the weight change after 3 months (upper panel) and 12 months (lower panel).
In Bold, the retained prediction based on the highest AUC for 3 and 12 months.
Abbreviations: PPV = positive predictive values, NPV = negative predictive values, AUC = area under the curve.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eTable 5: Receiver operating parameters for a one month weight change predicting a weight gain after 3 months of treatment (upper panel) and 12 months (lower panel) for adults (]25-65] years old).

Weight change (%) at		PPV	NPV	Sensitivity	Specificity	AUC
1 Month	3 Months					
2	10	36	93	74	71	73
2	15	16	98	82	67	74
2	20	4	100	100	64	82
5	10	48	89	52	88	70
5	15	24	97	64	84	74
5	**20**	**7**	**100**	**100**	**82**	**91**
8	10	64	86	26	97	61
8	15	36	95	36	95	66
8	20	0	99	0	93	46
1 Month	12 Months					
2	10	27	88	59	64	62
2	15	46	77	57	68	62
2	20	19	93	64	63	64
5	10	55	74	37	86	61
5	15	35	86	41	83	62
5	**20**	**30**	**93**	**55**	**83**	**69**
8	10	25	82	12	92	52
8	15	50	69	13	94	53
8	20	25	89	18	93	55

The left column indicates the weight change after one month and the second left column indicates the weight change after 3 months (upper panel) and 12 months (lower panel).
In Bold, the retained prediction based on the highest AUC for 3 and 12 months.
Abbreviations: PPV = positive predictive values, NPV = negative predictive values, AUC = area under the curve.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eTable 6: Overall metabolic parameters (left column) and comparison between early and non early weight gainers.

	All	First month weight gain ≤ 5% (n=288)	First month weight gain > 5% (n=63)	P[a]
Weight, kg				
Baseline, mean (se)	69.24 (0.93)	70.1 (1)	65.47 (2.34)	**0.03**
Δ 3 months, mean (se)	2.81 (0.31)	2.05 (0.32)	6.95 (0.62)	**< 0.0001**
Δ 12 months, mean (se)[b]	4.37 (0.77)	3.73 (0.8)	7.71 (2.27)	**0.03**
Weight, %				
Δ 3 months (%), mean (se)	4.34 (0.44)	3.12 (0.45)	11.07 (0.97)	**< 0.0001**
Δ 12 months (%), mean (se)[b]	6.72 (0.94)	5.44 (0.91)	13.69 (3.12)	**0.0045**
BMI, kg/m2				
Baseline, mean (se)	24.4 (0.31)	25 (0.35)	22.2 (0.59)	**0.001**
Δ 12 months, mean (se)[b]	1.5 (0.26)	1.2 (0.26)	3.1 (0.8)	**0.01**
Waist circumference, cm				
Baseline, mean (se)	89 (0.83)	90 (0.91)	86 (1.97)	0.06
Δ 12 months, mean (se)[b]	4 (0.96)	4 (1.02)	5 (2.91)	0.7
HDL-Cholesterol, mmol/l				
Baseline, mean (se)	1.39 (0.03)	1.38 (0.04)	1.44 (0.06)	0.2
Δ 12 months, mean (se)[b]	-0.08 (0.03)	-0.02 (0.03)	-0.36 (0.07)	**0.0001**
Triglyceride, mmol/l				
Baseline, mean (se)	1.4 (0.08)	1.42 (0.09)	1.33 (0.11)	0.9
Δ 12 months, mean (se)[b]	0.3 (0.13)	0.06 (0.1)	1.46 (0.53)	**0.004**
Glucose, mmol/l				
Baseline, mean (se)	5.2 (0.07)	5.22 (0.08)	5.13 (0.19)	0.2
Δ 12 months, mean (se)[b]	0.2 (0.15)	0.1 (0.16)	0.73 (0.25)	**0.02**
Blood pressure, mmHg				
Baseline systolic (se)	124 (1.05)	124 (1.11)	122 (2.86)	0.5
Δ 12 months, mean (se)[b]	-0.71 (1.61)	-0.22 (1.7)	-3.11 (4.72)	0.8
Baseline diastolic (se)	77 (0.75)	77 (0.8)	76 (1.96)	0.6
Δ 12 months, mean (se)[b]	-0.09 (1.4)	-0.73 (1.5)	3. (3.84)	0.6

[a] p-value were calculated using Wilcoxon rank-sum between both groups.

[b] Difference between baseline and 12 months values.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eTable 7: Linear mixed effect model fitted on weight gain (%) over time.

	Difference of weight change (%) between ≤ 5% and >5% weight gain group (95%IC).	P
All sample[a]	6.4 % (3.6% to 9.0%)	0.0001
Gender stratification[b]:		
Men	6.6% (3.4% to 9.8%)	0.0002
Women	9.7% (6.9% to 12.5%)	<0.0001
Age stratification[b]:		
Young (≤ 25)	8.7 % (5.2% to 12.5%)	<0.0001
Young adult (]25-45])	7.3% (3.8% to 10.7%)	0.0001
Adult (]45-65])	7.4% (2.0% to 13.1%)	0.0051
Elderly (> 65)	13.6% (5.6% to 18.8%)	<0.01[c]
Diagnostic stratification[b] :		
Psychotic & schizoaffective disorder	7.0% (4.5% to 9.6%)	<0.0001
Bipolar disorder & depression	9.1% (4.2% to 14.1%)	0.0006
Others[d]	11.6% (3.9% to 19%)	<0.01[c]
Medication stratification[b] :		
Monotherapy	7.0 % (4.5% to 9.4%)	<0.0001
Polytherapy	7.7% (4.2% to 11.3%)	<0.0001
Amisulpride & aripiprazole	6.6% (2.2% to 11.2%)	0.003
Mirtazapine & lithium & quetiapine & risperidone	8.4% (4.8% to 12.1%)	<0.0001
Clozapine & olanzapine & valproate	7.4% (4.1% to 10.7%)	<0.0001

[a]Results were obtained by fitting a linear mixed model controlling for age, sex, time, baseline BMI, current psychotropic drug, co-medication possibly inducing weight gain, glucose levels, triglyceride levels, HDL levels .
[b]Results were obtained by fitting a linear mixed model controlling for age, sex, time, and baseline BMI if applicable.
[c]Due to low number of observations, one hundred boostraps were used for the analysis.
[d]Others include the following diagnostics :anxiety, drug addiction, mental retardation, personality disorder, organic disorders.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eTable 8: Receiver operating parameters for an activity > 30 minutes/day at month 1 predicting a weight gain at 3 and 12 months.

Weight change (%) at:	PPV	NPV	Sensitivity	Specificity	AUC
3 Months					
5	36	58	54	53	54
10	15	83	53	51	52
15	5	94	55	51	53
12 Months					
5	52	44	53	51	52
10	21	67	62	53	57
15	12	78	67	52	59

Upper panel indicates the weight increase at 3 months and the lower panel a weight increase at 12 months.
Abbreviations: PPV = positive predictive values, NPV = negative predictive values, AUC = area under the curve.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eTable 9: Receiver operating parameters for an appetite increase between baseline and one month predicting a weight gain at 3 and 12 months.

Weight change (%) at:	PPV	NPV	Sensitivity	Specificity	AUC
3 Months					
5	36	59	28	67	47
10	19	84	35	69	52
15	5	93	25	68	47
12 Months					
5	59	46	27	77	52
10	29	72	26	75	51
15	12	80	17	73	45

Upper panel indicates the weight increase at 3 months and the lower panel a weight increase at 12 months.
Abbreviations: PPV = positive predictive values, NPV = negative predictive values, AUC = area under the curve.

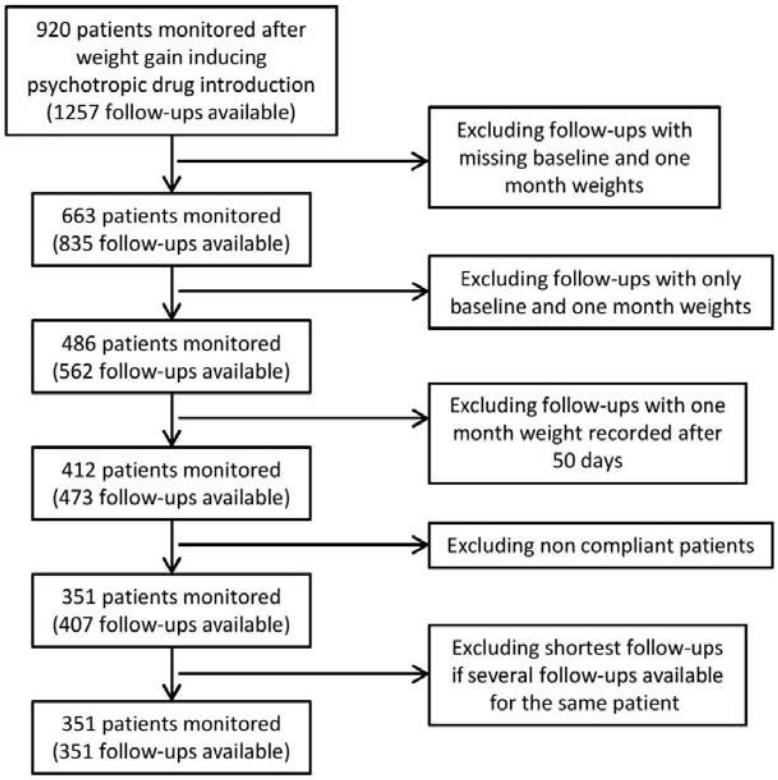
It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

eTable 10: Co-medication possibly inducing weight gain[1, 2].

Anti-diabetic drug :		
pioglitazone	rosiglitazone	
Anti-histaminergic drug :		
cinnarizine	levocetirizine	
Contraceptive drugs :		
chlormadinone	desogestrel	ethinylestradiol
estradiol	gestodene	levonorgestrel
medroxyprogesterone	norelgestromin	
Psychotropic drugs (‡):		
carbamazepine	chlorprothixene	clomipramine
flupentixol	mianserine	pregabalin
zuclopenthixol		

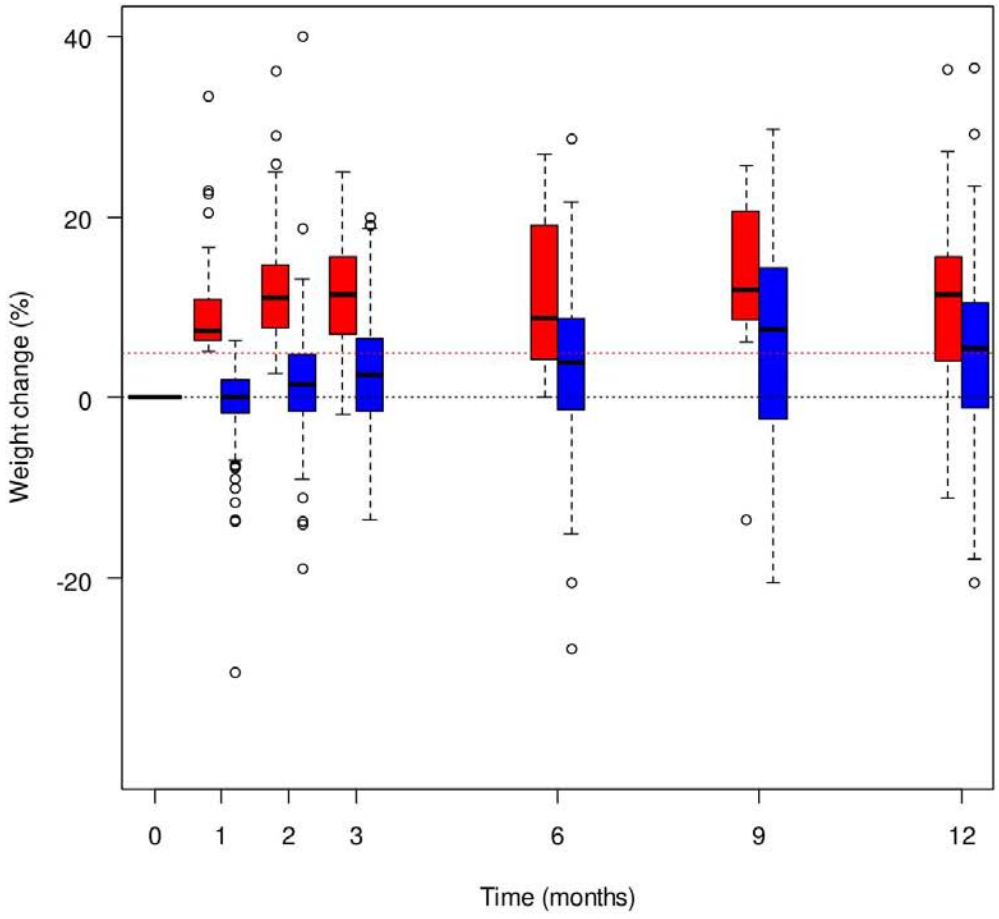
‡ Investigated drugs (clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, lithium, valproate and mirtazapine) are not mentioned as co-medication if they are prescribed as monotherapy.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.



eFigure 1: Flow chart for selection of patients.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.



eFigure 2: Weight changes at 1 month (mean(se) 31(0.4) days), 2 months (mean(se) 64(1.8) days), 3 months (mean(se) 102(2) days), 6 months (mean(se) 189(2.3) days), 9 months (mean(se) 278(3.7) days) and one year (mean(se) 393(7.1) days). Red and blue box plots represent the patient's observation with a first month weight gain of more than 5% and less or equal to 5%, respectively. Dotted black line represents no weight change; red dotted line represents 5% weight increase.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

REFERENCES:

1. Compendium Suisse des Medicaments. 2014 [cited 2014 24 février, 2014]; Available from: http://www.swissmedicinfo.ch
2. MICROMEDEX ® 1.0 (Healthcare series). 2011 [cited 2011 November 15, 2011]; Available from: http://www.micromedex.com/
3. 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.
4. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005 Oct 25;112(17):2735-2752.
5. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006 May;23(5):469-480.
6. Choong E, Rudaz S, Kottelat A, Guillarme D, Veuthey JL, Eap CB. Therapeutic drug monitoring of seven psychotropic drugs and four metabolites in human plasma by HPLC-MS. J Pharm Biomed Anal 2009;50:1000-1008.
7. Hiemke C, Baumann P, Bergemann N, et al. AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011. Pharmacopsychiatry 2011;44(6):195-235.
8. Pinheiro J, Bates D, DebRoy S, Sarkar D, Team RC. nlme: linear and nonlinear mixed effects models. 2013.
9. Pinheiro JC, Bates DM. Mixed-Effects Models in S and S-PLUS: Springer; 2000.
10. Davison AC, Hinkley DV. Bootstrap Methods and their Application. Cambridge, New York: Cambridge University Press; 1997.

It is illegal to post this copyrighted PDF on any website. ♦ © 2015 Copyright Physicians Postgraduate Press, Inc.

Association of genetic risk scores with body mass index in Swiss psychiatric cohorts

Núria Saigi-Morgui[a], Frederik Vandenberghe[a], Aurélie Delacrétaz[a], Lina Quteineh[a], Mehdi Gholamrezaee[b], Jean-Michel Aubry[e], Armin von Gunten[c], Zoltán Kutalik[g,h], Philippe Conus[d] and Chin B. Eap[a,f]

Objective **Weight gain is associated with psychiatric disorders and/or with psychotropic drug treatments. We analyzed in three psychiatric cohorts under psychotropic treatment the association of weighted genetic risk scores (w-GRSs) with BMI by integrating BMI-related polymorphisms from the candidate-gene approach and Genome-Wide Association Studies (GWAS).**

Materials and methods **w-GRS of 32 polymorphisms associated previously with BMI in general population GWAS and 20 polymorphisms associated with antipsychotics-induced weight gain were investigated in three independent psychiatric samples.**

Results **w-GRS of 32 polymorphisms were significantly associated with BMI in the psychiatric sample 1 ($n = 425$) and were replicated in another sample ($n = 177$). Those at the percentile 95 (p95) of the score had 2.26 and 2.99 kg/m^2 higher predicted BMI compared with individuals at the percentile 5 (p5) in sample 1 and in sample 3 ($P = 0.009$ and 0.04, respectively). When combining all samples together ($n = 750$), a significant difference of 1.89 kg/m^2 predicted BMI was found between p95 and p5 individuals at 12 months of treatment. Stronger associations were found among men (difference: 2.91 kg/m^2 of predicted BMI between p95 and p5, $P = 0.0002$), whereas no association was found among women. w-GRS of 20 polymorphisms was not associated with BMI. The w-GRS of 52 polymorphisms and the clinical variables (age, sex, treatment) explained 1.99 and 3.15%, respectively, of BMI variability.**

Conclusion **The present study replicated in psychiatric cohorts previously identified BMI risk variants obtained in GWAS analyses from population-based samples. Sex-specific analysis should be considered in further analysis. *Pharmacogenetics and Genomics* 26:208–217**
Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Pharmacogenetics and Genomics 2016, **26**:208–217

Keywords: body mass index, genetic risk score, psychiatry, psychotropic drugs

[a]Unit of Pharmacogenetics and Clinical Psychopharmacology, Department of Psychiatry, Centre for Psychiatric Neuroscience, [b]Department of Psychiatry, Centre of Psychiatric Epidemiology and Psychopathology, [c]Service of Old Age Psychiatry, Department of Psychiatry, [d]Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly, [e]Department of Mental Health and Psychiatry, University Hospital of Geneva, [f]School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, [g]Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital and [h]Swiss Institute of Bioinformatics, Lausanne, Switzerland

Correspondence to Chin B. Eap, PhD, Unit of Pharmacogenetics and Clinical Psychopharmacology, Department of Psychiatry, Centre for Psychiatric Neuroscience, Lausanne University Hospital, Prilly 1008, Switzerland
Tel: +41 21 314 2604; fax: +41 21 314 2444; e-mail: chin.eap@chuv.ch

Received 3 August 2015 **Accepted** 1 February 2016

Introduction

Obesity has become a major public health concern, its prevalence increasing considerably over the last decades. Obesity is a complex disease that results from imbalance of energy intake and energy expenditure, being highly influenced by an individual's lifestyle or environment (i.e. diet, physical activity) and also by genetic predisposition [1]. Twin and family studies reported 40–80% of heritability in obesity [2,3]. Several forms of monogenic obesity have been described, especially those related to leptin–melanocortin pathways [4,5]. The most prevalent form of obesity, however, is the polygenic or common obesity, which results from the combined effect of common genetic variants as well as additional rare variants, copy number variants, and epigenetic changes [6]. Among psychiatric populations, the risk of developing obesity and related problems is increased compared with the general population [7]. Several factors have been attributed to this increased risk of obesity, such as the illness, the lifestyle, and/or the medication [8,9].

Since their introduction onto the market, second-generation antipsychotics have been used widely over first-generation antipsychotics as they clearly show an advantage in terms of reduced risks of extrapyramidal side-effects as well as some advantages for the treatment of negative symptoms. However, most second-generation antipsychotics can induce strong metabolic disturbances in particular as a consequence of the dual antagonism on serotonin and dopamine receptors and its effect on food

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (*www.pharmacogeneticsandgenomics.com*).

1744-6872 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/FPC.0000000000000210

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

intake regulation [10]. Over the last decade, pharmacogenetics of psychotropic-induced weight gain has been studied widely through hypothesis-driven candidate-gene (CG) approaches. The most studied and best-replicated polymorphisms focused on dopamine and serotonin receptors [11,12]. In addition, other genes implicated in leptin–melanocortin pathways (e.g. *LEP*, *LEPR*, *MC4R*, *NPY*), endocannabinoids (*CNR1*), or genes involved in fatty acids and cholesterol production (*SCARB1*, *INSIG2*) showed an association with weight gain among psychiatric cohorts treated with antipsychotics (see review in Lett *et al.* [13]). Recently, research carried out in our laboratory showed other CGs that could potentially induce weight gain among psychiatric populations under psychotropic treatment. These genes code for enzymes involved in metabolic pathways (PCK1, 11βHSD1) [14–16] for receptors (MCHR2, IRS2, and PPARGC1A) and for transcriptional coactivators (CRTC1, CRTC2) involved in energy balance, appetite regulation, and glucose homeostasis [17–21].

With the emergence of Genome-Wide Association Studies (GWAS), thousands of new polymorphisms associated with obesity and metabolic phenotypes have been elucidated. In particular, the associations with BMI and/or obesity in the *FTO* [22–25], *MC4R* [26–28], and *TMEM18* [23,24,28,29] genes have been replicated widely in general populations. The largest BMI meta-analysis of GWAS carried out to date in general populations reported 97 polymorphisms [30]. These variants also included 32 previously reported loci [31] that have been replicated in other cohorts and different ethnicities [32–34]. Individually, these variants have shown little effect on the BMI [31]. As an alternative way of testing individual single-nucleotide polymorphism (SNP) effects, genetic risk scores (GRSs) summarize risk-associated variations across the genome by aggregating information from multiple-risk SNPs [35], with small effects increasing the consistency and power to determine genetic risk in polygenic diseases (i.e. obesity) [36]. To date, GRS methods have been used in diabetes [37], schizophrenia [38], and obesity [31], among other diseases. Studies on obesity have been carried out in adults [36,39] or children from the general population [40,41], and recently, two studies were carried out among depressed patients [42,43]. The aim of the present study was to determine whether GRS constructed from previous BMI and/or weight gain-related variants from GWAS and CGs were associated with BMI in three independent psychiatric samples. In addition, we aimed to analyze whether previous variants related to diabetes (21 SNPs) and psychiatric disorders (nine SNPs) also showed an association with BMI as these diseases seem to share some genetic components with obesity [8,44,45].

Materials and methods

Samples description

Psychiatric samples

Sample 1 ($n = 425$) consisted of an on-going follow-up study that started in 2007 in the psychiatric ward from the Lausanne University Hospital already described elsewhere [46]. Briefly, 425 White patients starting psychotropic treatment including atypical antipsychotics, mood stabilizers, and/or mirtazapine were recruited. Anthropometric parameters such as weight, height, and waist circumference were measured. Other demographic covariates (i.e. sex, age, and ethnicity) as well as history of treatment (treatment duration, psychotropic treatment) were obtained from medical files or during the interview. Medical questionnaires were filled in and blood samples were collected at baseline and at 1, 2, 3, 6, and 12 months after initiating psychotropic treatment according to guidelines [47,48]. Patients switching to one of the studied treatments were also included. BMI (kg/m^2), the outcome in the present study, was used as a continuous variable and whenever required, stratified into three categories as normal (BMI < 25 kg/m^2), overweight ($25 \geq$ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Twenty-one percent of patients had the first psychotic episode and/or were diagnosed within the first year of study inclusion [first episode and newly diagnosed (FEND) patients].

Two other psychiatric samples were used as replication. They consisted of two retrospective studies from outpatient settings in Geneva and in Lausanne (sample $2 = 148$, sample $3 = 177$, respectively). Both samples included patients receiving atypical antipsychotics and/or mood stabilizers (i.e. aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, lithium, and/or valproate). The Geneva study was conducted in 2007 in an outpatient Geneva setting and patients recruited had been under psychotropic treatment for at least 3 months. In the Lausanne study (sample 3 started in 2010, inclusions ongoing), most of the patients had been treated for more than 1 year in a Lausanne outpatient setting. For both studies, blood samples were collected and questionnaires were filled out during one of the routine checkups. Weight, height, waist circumference, serum lipids, and/or glucose were measured and several clinical variables (e.g. treatment, treatment duration) were recorded. Baseline weight (before the current psychotropic treatment) was extracted from medical files or self-reported. Further description of these samples has been published elsewhere [46].

Psychiatric diagnoses for the three samples were made according to ICD-10 classification criteria. The main diagnostic groups were F20.0–F24.9 and F28–F29: psychotic disorders; F25.0–F25.9: schizoaffective disorders; F30.0–F31.9: bipolar disorders; F32.00–F33.9: depression. The latest introduced psychotropic medication was considered the main psychotropic treatment. Written

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

informed consent was provided by all individuals or by their legal representatives and the studies were approved by the ethics committee of the corresponding centers.

General population-based sample

The Genetic Investigation of Anthropometric Traits Consortium (GIANT) carried out a meta-analysis of GWAS data with a discovery set of 123 865 individuals of European ancestry from 46 studies for height [49], BMI [31], and waist-to-hip ratio [50]. This general population-based sample was used to obtain β-coefficients (allele effect) that assigned weights to each variant when constructing the GRSs.

Single-nucleotide polymorphism selection, genotyping, and construction of genetic risk scores

The initial 32 polymorphisms selected for the present study had been associated with BMI in a GWAS meta-analysis carried out in an adult general population [31]. All selected variants reached GWAS significance ($P < 5 \times 10^{-8}$) (Supplementary Table S1, Supplemental digital content 1, *http://links.lww.com/FPC/A990*). Another 20 SNPs that had been previously related to antipsychotic-induced weight gain through the CG approach were also selected [13]. From the reviewed variants, only SNPs or proxies of SNPs genotyped in our sample and in GIANT, and only those in the literature yielding significant results in both sexes were retained for the analysis. A detailed description of the SNPs considered can be found in Supplementary Table S2 (Supplemental digital content 1, *http://links.lww.com/FPC/A990*).

Finally, we considered two meta-analyses of GWAS on the basis of 21 SNPs associated with type 2 diabetes (8130 cases and 38 987 controls; Supplementary Table S3, Supplemental digital content 1, *http://links.lww.com/FPC/A990*) and another one on the basis of nine SNPs associated with five major psychiatric disorders (final dataset: 33 332 cases and 27 888 controls; Supplementary Table S4, Supplemental digital content 1, *http://links.lww.com/FPC/A990*) including schizophrenia, bipolar disorder, major depressive disorder, autism, and attention deficit-hyperactivity disorder [51,52]. To avoid an indirect correlation between variants [i.e. in high linkage disequilibrium (LD) correlation], which is one of the problems when constructing GRS [53], and to avoid overrepresentation of a particular gene, only one SNP per gene was considered. Selection was made by selecting the SNP with the lowest *P*-value. We verified that the resulting SNPs were not in LD. Note that this approach is analogous to an LD-based pruning, but we typically select less SNPs by ignoring secondary (independent) SNP contributions from the same gene (allelic heterogeneity). The study protocol was approved by the ethics committees of the recruiting centers and all patients provided written informed consent for the genetic analysis. DNA was extracted from blood samples as described by the manufacturer's protocols using the Flexigene DNA Kit (Qiagen AG, Hombrechtikon, Switzerland) and the QIAamp DNA Blood Mini QIAcube Kit (Qiagen AG).

Genotyping of 895 White patients was performed using the Illumina 200K CardiometaboChip (Illumina, San Diego, California, USA). Briefly, the CardiometaboChip is a custom Illumina iSelect genotyping array designed to test DNA variation of 200 000 SNPs from regions identified by large-scale meta-analyses of GWAS for metabolic and cardiovascular traits [54]. A quality control was performed for the genotyped SNPs. Polymorphisms or proxies were chosen on the basis of genotype availability in the CardiometaboChip and GIANT cohort. In addition, samples were excluded from the analysis if sex was inconsistent with genetic data from X-linked markers and when genotype call rate was less than 0.96, gene call score less than 0.15, and minor allele frequency less than 0.05. GenomeStudio Data Analysis Software (San Diego, California, USA) was used to export results generated by Illumina CardiometaboChip. In addition, the rs7799039 from the *LEP* gene largely associated with antipsychotic-induced weight gain [55] and that was not available in CardiometaboChip was genotyped by the KBioscience Institute in UK using the novel fluorescence-based competitive allele-specific PCR technology (KASP; details of this technology are available at: *http://www.lgcgenomics.com/genotyping/kasp-genotyping-chemistry/*). Out of the 895 White genotyped individuals, 750 were finally analyzed (145 patients excluded because of missing data).

Among the several existing methods to build a GRS, it has been shown in disease risk modeling that weighted genetic risk score (w-GRS) methods are preferred to the simple count method when relative risks vary among SNPs [56]. Supplementary Fig. 1 (Supplemental digital content 2, *http://links.lww.com/FPC/A991*) represents the distribution of the weighted genetic score by the number of risk alleles (unweighted score) calculated for each individual in the entire cohort showing that weighted and unweighted scores are not perfectly correlated, thus highlighting the importance of weighting each risk allele using w-GRS methods. The w-GRS for selected SNPs was calculated as described previously [31]. In summary, genotypes from each SNP were coded as 0, 1, or 2 according to the number of BMI risk alleles. Then, each polymorphism was weighted by its β-coefficient (allele effect) on the basis of the assumption that all SNP of interest have independent effects and contribute in an additive manner toward BMI. Allele effect on BMI was assessed by performing lookups from the summary statistics of an independent population sample (GIANT, $n = 123\,865$), thus preserving the homogeneity of β-coefficient calculations (Supplementary Table S5, Supplemental digital content 1, *http://links.lww.com/FPC/A990*) for all SNPs included in the genetic score.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Statistical analyses

Principal components of ancestry was used to assess ethnicity and only Whites were considered in the analysis. Hardy–Weinberg equilibrium (HWE) was determined for each polymorphism using a χ^2-test. HWE and genotype frequencies are shown in Supplementary Tables S1 and S2 (Supplemental digital content 1, *http://links.lww.com/FPC/A990*). *P*-values equal to or less than 0.05 were considered statistically significant and Bonferroni's correction for multiple tests was applied when necessary. Initially, individual SNP effects on BMI were calculated for sample 1. Genotypes were analyzed in an additive model of inheritance, except for one SNP (*HSD11β1* rs3753519C > T), which had too few homozygous for the variant allele ($n = 7$) and a dominant model was used. Second, a GRS was built and tested in sample 1 and it was further tested for replication in two other psychiatric samples (samples 2 and 3). Finally, to determine the general effect of the GRS on BMI, we combined all samples as they were similar overall in terms of the individual's origin (Lausanne and Geneva regions), type of treatment, age, and diagnostic. Because of interdependence between observations (i.e. BMI) made on the same individual over time, a generalized linear mixed model (GLMM) was fitted using the MASS library of R language [57,58] to assess the influence of genetic parameters on BMI in a model adjusted by age, sex, main psychotropic treatment, and treatment duration. The appropriate link function that we chose for the BMI variable is the inverse function, which is the canonical link function for the gamma family. GLMMs combine both linear mixed models (which incorporate random effects) and generalized linear models (which deal with non-normal data using link functions and exponential family) [59]. The glmmPQL function of the MASS library uses the penalized quasi-likelihood to estimate model parameters [60]. Finally, predicted BMI differences were calculated at baseline, 12, and 24 months of treatment between the percentile 95 (p95) (the upper extreme of an unfavorable genetic background) and percentile 5 (p5) (the lower extreme of an unfavorable genetic background) of the GRS. To preserve homogeneity within samples and to deal with treatment durations when combining all samples together (i.e. shorter treatment duration up to 12 months in sample 1), predicted BMI was obtained at baseline and at 12 months of treatment. The corresponding 95% confidence intervals (95% CIs) were calculated. Some exploratory analyses were also carried out to obtain the explained variance of BMI by genetic and nongenetic covariates in the psychiatric sample 1 for a subgroup of individuals aged between 18 and 65 years. A generalized additive mixed model was used to deal with complex and nonlinear BMI evolution in time and the presence of multiple observations per individual introducing interdependence among observations. A random effect at the patient level was also introduced to take the dependence structure of observed data into account. The generalized additive mixed models were fitted using the mgcv package of R (settings were fixed at package defaults). To be more conservative, the uncertainty of estimated parameters was assessed by 10 000 bootstraps on individuals [57,61,62]. Individuals with missing data or genotypes were excluded from the analysis (see Supplementary Methods for further details, Supplemental digital content 3, *http://links.lww.com/FPC/A992*).

Results

Population description

Table 1 presents the characteristics of sample 1 ($n = 425$) and replication samples 2 and 3 ($n_1 = 148$, $n_2 = 177$). All samples together included 750 White individuals, with 50% men and a median age of 45 years (range: 13–97 years). Sample 2 had the highest prevalence of obesity (BMI ≥ 30 kg/m^2) (35% compared with 18% in samples 1 and 3, $P = 0.006$). Sample 1 had the lowest olanzapine and clozapine prescription (11 and 8%, respectively, compared with 16 and 14% in sample 2, respectively, and 12 and 9% in sample 3, respectively, $P = 0.001$) as well as the shortest treatment duration (6 months) compared with samples 2 and 3 (27 and 36 months, respectively). Supplementary Tables S6 (Supplemental digital content 1, *http://links.lww.com/FPC/A990*) and S7 (Supplemental digital content 1, *http://links.lww.com/FPC/A990*) show the characteristics of the combined cohort stratified by sex and by FEND patients, respectively. Men were younger than women (median: 40 vs. 49 years, respectively, $P = 0.0001$) and had higher BMI at baseline (24.6 vs. 24.1 kg/m^2 in men and women, respectively, $P = 0.004$). Besides, treatment duration was longer for men than women (9 months compared with 6 months, respectively, $P = 0.05$) (Supplementary Table S6, Supplemental digital content 1, *http://links.lww.com/FPC/A990*).

Genetic analysis

Genotype analysis

Supplementary Tables S1 and S2 (Supplemental digital content 1, *http://links.lww.com/FPC/A990*) list the 32 and 20 SNPs from GWAS and CG studies, respectively, analyzed in the psychiatric samples. All of them were in HWE after multiple test correction ($P_{\text{corrected}} < 0.001$). Thirty-two previously reported SNPs associated with BMI in the general population [31] were analyzed in sample 1. One SNP located in *CADM2* gene showed a nominal association with BMI over time ($P = 0.01$) (Table 2). At 12 months of treatment, the rs13078807 polymorphism showed a 1.04 BMI units increase per additional risk allele. Twenty other SNPs were selected from CG studies associated with psychotropic-induced weight gain and two of them (i.e. *HSD11β1* rs3753519 and *CRTC2* rs8450) showed an association with BMI (difference of predicted BMI of −2.35 units for

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Table 1 Description of demographic and clinical psychiatric White samples

Characteristics	Sample 1 ($n=425$)	Sample 2 ($n=148$)	Sample 3 ($n=177$)	Combined sample ($n=750$)
Male (%)	43	55	62	50
Age [median (range)] (years)	51 (13–97)	42 (19–64)	42 (18–69)	45 (13–97)
Diagnosis (%)				
Psychotic disorders	28.6	24.5	9.0	31.4
Schizoaffective disorders	7.3	17.0	12.1	10.3
Bipolar disorders	18.8	34.7	16.8	21.5
Depression disorders	16.4	17.0	12.7	15.7
Other diagnosis	28.9	6.8	14.5	21.2
Initial BMI status (kg/m^2)[a]				
BMI [median (range)]	23 (13–44)	25 (15–46)	24 (16–46)	24 (13–46)
25 ≥ initial BMI < 30 (%)	22	37	31	28
Initial BMI ≥ 30 (%)	13	16	15	14
Current BMI status (kg/m^2)[b]				
BMI [median (range)]	25 (15–50)	28 (16–40)	25 (17–43)	26 (15–50)
25 ≥ current BMI < 30 (%)	25	38	29	27
Current BMI ≥ 30 (%)	18	35	18	21
Initial WC (cm)[a]				
WC [median (range)]	87 (54–138)	–	–	87 (54–138)
High WC ≥ 94 (male), ≥ 88 (female) (%)	41	–	–	41
Current WC (cm)[b]				
WC [median (range)]	93 (57–162)	–	92 (73–136)	90 (57–162)
High WC ≥ 94 (male), ≥ 88 (female) (%)	51	–	53	51
Initial lipid status (%)[a]				
High LDL cholesterol[c]	9	–	–	9
High triglycerides[d]	18	–	–	18
Low HDL cholesterol[e]	23	–	–	23
Current lipid status (%)[b]				
High LDL cholesterol[c]	15	–	–	15
High triglycerides[d]	28	–	–	28
Low HDL cholesterol[e]	26	26	17	26
Smoker (%)	46	59	76	56
Prescribed psychotropic drug (%)[f]				
Amisulpride	8	–	11	7
Aripiprazole	8	–	7	6
Clozapine	8	14	9	9
Olanzapine	11	16	12	12
Quetiapine	35	20	24	29
Risperidone	15	17	17	16
Lithium	8	20	12	11
Valproate	5	14	8	8
Treatment duration [median (range)] (months)	6 (1–12)	27 (3–333)	36 (1–390)	12 (1–390)

WC, waist circumference; –, missing clinical values or obtained in nonfasting conditions.
[a]Before the current psychotropic treatment.
[b]For samples 2 and 3: current observation; for sample 1: last observed data.
[c]High LDL cholesterol: ≥ 4.1 mmol/l.
[d]High triglycerides: ≥ 2.2 mmol/l.
[e]Low HDL cholesterol: < 1 mmol/l.
[f]2% of the sample 1 was under paliperidone treatment.

rs3753519 at 12 months of treatment between patients homozygous for the variant allele and wild types and 0.69 units of BMI increase per additional risk allele for rs8450 ($P=0.00001$, 0.04, respectively; Table 2).

Genetic risk score analysis

On combining all 32 GWAS SNPs in a w-GRS (w-GRS 32), the score was significantly associated with BMI in sample 1 ($P=0.009$), in sample 3 ($P=0.04$), and also in the three combined samples ($P=0.002$) (see Table 3). In sample 1, those at the p95 of the GRS (i.e. a high GRS) had 2.26 units more of predicted BMI when compared with those individuals at the p5 of the GRS (low GRS) at 12 months of treatment. Results were similar in sample 3 and when all samples were combined together at 24 and 12 months of treatment (difference of predicted BMI between p95 and p5 of the GRS: 2.99 and 1.89 units, respectively). A higher effect on BMI was found among men when analyses were stratified by sex in the combined sample (interaction sex × GRS, $P<0.10$): individuals at the p95 score had 2.91 units more of predicted BMI compared with individuals at the p5 score at 24 months of treatment ($P=0.0002$). For the subgroup of FEND patients, a difference of predicted BMI of 3.79 units was observed between individuals at the p95 and p5 of the GRS ($P=0.008$) (Table 3). Figure 1 shows the evolution of BMI (nonadjusted) over time between extreme percentiles [low genetic risk (p5) vs. high genetic risk (p95)]. In addition, predicted BMI differences between p10 and p90 extremes are presented in Supplementary Table S8 (Supplemental digital content 1, *http://links.lww.com/FPC/A990*) and Supplementary Fig. S2 (Supplemental digital content 2, *http://links.lww.com/FPC/A991*).

When pooling all samples together, 1 unit increase of the risk allele at 24 months of treatment in the GRS was associated with an increase in BMI of 0.19 units ($P=0.011$). Among men, this increase in BMI was of 0.30 units ($P=0.0001$), whereas in women it was of 0.08 ($P=0.38$).

In contrast to what we found with GWAS SNPs, when the 20 CG SNPs were combined in a w-GRS (w-GRS 20), no association with BMI was observed in the entire sample ($P=0.46$) (Supplementary Table S9, Supplemental digital content 1, *http://links.lww.com/FPC/A990*).

Finally, the 20 CG SNPs were combined with the 32 GWAS SNPs in another w-GRS (w-GRS 52) (Supplementary Table S10, Supplemental digital content 1, *http://links.lww.com/FPC/A990*). w-GRS 52 was significantly associated with BMI in sample 1 ($P=0.01$), sample 3 ($P=0.04$), and when combining all samples ($P=0.001$). Only a trend was observed in samples 2 and 3 when pooled together ($P=0.06$). Thus, an individual in the p95 score had 2.08, 2.79, and 1.94 more predicted units of BMI in sample 1 (12 months of treatment), in sample 3 (24 months of treatment), and in all samples combined together (12 months of treatment) compared with individuals at the p5 of the score, respectively. When analyses were stratified by sex, a significant effect

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Table 2 Significant results obtained from individual single-nucleotide polymorphism association with body mass index in the psychiatric sample 1 at baseline and at 12 months of follow-up treatment

			Difference of predicted BMI per risk allele increase (95% CI)		
Nearest genes	SNP	Major/minor allele	At baseline	At 12 months of treatment	*P*-value
CADM2	rs13078807	A>G	0.93 (0.89–1.97)	1.04 (−0.14–2.22)	**0.01***
HSD11β1	rs3753519[a]	C>T	−2.11 (−3.22 to −1.00)	−2.35 (−3.60 to −1.10)	**0.00001**
CRTC2	rs8450	G>A	0.62 (0.28–1.62)	0.69 (−0.44–1.83)	**0.04***

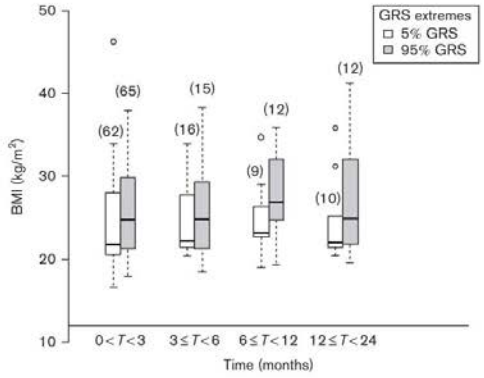
Bold values: significant at $P \leq 0.05$.
Predicted differences of BMI were calculated for polymorphisms that showed significant results ($P < 0.05$).
CI, confidence interval; SNP, single-nucleotide polymorphism.
[a]A dominant model was used for this SNP (carriers of the variant allele were compared with the wild type).
*Not significant after Bonferroni's correction.

Table 3 Weighted genetic risk score association with body mass index obtained from 32 Genome-Wide Association Studies single-nucleotide polymorphisms

		BMI difference between GRS p95 and GRS p5 (95% CI)			
	n	At baseline	At 12 months	At 24 months	*P*-value
Sample 1[a]	425	2.01 (0.52–3.51)	2.26 (0.48–4.04)	–	**0.009**
Sample 2[b]	148	−0.51 (−3.02–2.00)	−0.61 (−3.61–2.40)	−0.73 (−4.67–3.22)	0.7
Sample 3[b]	177	2.54 (0.26–4.81)	2.75 (0.23–5.27)	2.99 (−0.01–6.00)	**0.04**
Samples 2 and 3[b]	325	1.43 (−0.27–3.13)	1.61 (−0.33–3.56)	1.82 (−0.59–4.24)	0.1
All samples combined	750	1.68 (0.65–2.72)	1.89 (0.71–3.06)	–	**0.002**
FEND patients[a]	116	3.29 (0.79–5.78)	3.79 (0.88–6.71)	–	**0.008**
Men	375	2.59 (1.45–3.74)	2.91 (1.06–4.22)	–	**0.0002**
Women	375	0.76 (−0.55–2.06)	0.84 (−0.63–2.32)	–	0.3

Bold values: significant at $P \leq 0.05$.
CI, confidence interval; FEND, first episode and newly diagnosed; GRS, genetic risk score; p5, percentile 5 of GRS; p95, percentile 95 of GRS.
[a]Follow-up to 12 months of treatment.
[b]Follow-up to 24 months of treatment.

Fig. 1



Evolution of BMI over time between genetic risk score (GRS) extreme percentiles. Boxplots show the median values of BMI for each time of the treatment duration (solid horizontal line), 25th and 75th percentile values (box outline), the lowest and upper value within 1.5 interquartile range (whiskers), and outlier values (open circles). Values given in parentheses correspond to number of individuals.

was found among men at the p95 of the score, who showed 3.09 more units of predicted BMI compared with men at the p5 ($P = 0.0001$). FEND patients who were at the top percentile (p95) also had 3.66 more units of predicted BMI compared with patients at the p5 of the GRS ($P = 0.01$).

GLMM according to different quartiles showed significant differences between individuals within the third and fourth quartile of the GRS compared with the first quartile. At 24 months of treatment, those at the third and fourth quartiles had 1.84 (0.40–3.29) and 1.91 (0.51–3.32) more units of predicted BMI compared with the first quartile, respectively (results not shown). Table 4 shows the characteristics for the four groups stratified by GRS quartiles. Those at the fourth quartile had higher BMI before starting and during the current psychotropic treatment (baseline and current median BMI: 25.1 and 25.9 kg/m^2, respectively) compared with the first quartile (baseline and current median BMI: 23.2 and 24.3 kg/m^2, respectively), which could possibly be explained by the interaction between genetics, previous psychiatric episodes, and/or psychotropic treatments. The prevalence of baseline overweight and obesity increased in higher quartiles (i.e. 48% in the fourth quartile vs. 30% in the first quartile, $P = 0.007$). No differences in age, treatment, treatment duration, high waist circumference prevalence, diagnostic, and FEND individuals distribution were observed between the different quartile groups (Table 4).

Finally, on comparing the distribution of genetic scores without adjusting by other covariates, no differences

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Table 4 Description of four quartiles of genetic risk score for 32 single-nucleotide polymorphism in the combined sample

GRS (*n*)	1st quartile (192)	2nd quartile (170)	3rd quartile (186)	4th quartile (202)	*P*-value
Score [mean (SD)]	0.87 (0.06)	0.97 (0.02)	1.05 (0.02)	1.16 (0.07)	**0.0001**
Men (%)	47	55	44	53	0.1
Age [median (range)] (years)	47 (17–96)	47 (13–90)	48 (14–97)	48 (15–93)	0.9
Initial BMI [median (range)] (kg/m^2)[a]	23.2 (13–46)	24.6 (15–39)	25.1 (16–46)	25.1 (14–39)	**0.0005**
Current BMI [median (range)] (kg/m^2)[b]	24.3 (16–40)	25.2 (15–40)	25.9 (16–50)	25.9 (17–41)	**0.04**
First episode and newly diagnosed patients (%)	13	15	16	17	0.6
Treatment prescription					
Ami, Ari, Li, Quet, Risp	74	70	71	67	0.5
Clo, Olan, Valp	26	30	29	33	
Treatment duration [median (range)] (months)	6 (1–23)	3 (1–21)	3 (1–24)	3 (1–24)	0.9
High WC (≥94 cm men, 88 cm women) (%)	40	47	49	53	0.2
Diagnostic (%)					
Psychotic disorders	42	42	38	46	0.6
Bipolar disorders	21	22	21	21	
Depression disorders	17	15	17	14	

Bold values: significant at $P \leq 0.05$.
Ami, amisulpride; Ari, aripiprazole; Clo, clozapine; GRS, genetic risk score; Li, lithium; Olan, olanzapine; Quet, quetiapine; Risp, risperidone; Valp, valproate; WC, waist circumference.
[a]Before the current psychotropic treatment.
[b]Last observed data.

were found between men and women (Supplementary Table S6, Supplemental digital content 1, *http://links.lww.com/FPC/A990*) or FEND patients (Supplementary Table S7, Supplemental digital content 1, *http://links.lww.com/FPC/A990*).

Genetic risk scores and Genome-Wide Association Studies genes for psychiatric diseases and diabetes

The SNPs selected from GWAS associated with psychiatric diseases (i.e. schizophrenia, bipolar disorder, major depressive disorder, autism, and hyperattention deficit) and diabetes were combined in two different w-GRS and tested for association with BMI. No significant results were found (results not shown).

Explained variability

We calculated the BMI variability explained by the clinical and genetic covariates in sample 1 for individuals ranging in age from 18 to 65 years ($n = 263$). Thus, in our model, the genetic component considering the w-GRS 32 explained 1.97% of BMI variability, whereas nongenetic components such as age, sex, and treatment explained 2.23, 0.42, and 0.6%, respectively, out of the total 7.01% BMI variability explained by the model. Finally, the BMI-explained variance of the 52 SNPs (32 SNPs added to the 20 SNPs) was 1.99%, whereas the important clinical variables known to influence weight (age, sex, treatment) represented altogether 3.15% of the BMI variability.

Discussion

In the present study, we found that w-GRS built from 32 polymorphisms previously associated with BMI in the general population GWAS were also significantly associated with BMI in our sample 1, being replicated in another sample. The stronger effects were found among men and FEND patients. Some studies have replicated the association of the 32-SNPs GRS with BMI and obesity-related genotypes in different cohorts and ethnicities [32–34]. Two cross-sectional studies using a Mendelian randomization approach [42] and a case–control design [43] replicated the association of w-GRS in depressed patients. However, type of treatment, treatment duration, or BMI variation over time were not taken into account, whereas BMI at baseline and treatment duration are known moderators of weight gain in populations under psychotropic treatment [9]. Moreover, the number of patients treated was not described in the previous studies. The present study, in contrast, includes longitudinal data considering long treatment duration (i.e. analysis has been carried out up to 24 months), type of treatment, and other diagnostics in addition to depression. Explained BMI variability by GRS when including 32-SNPs GWAS GRS in our model was slightly higher than that reported initially in general population cohorts in the literature (1.45%) [31] or that found in French and Chinese general populations (1 and 0.90%, respectively). It is noteworthy that addition of the 20 CG in the model did not improve the explained BMI variability (1.97 vs. 1.99%). The effect on BMI per risk allele increase of the 32-SNPs GWAS GRS was similar to those reported previously (0.11 [32] and 0.13 [34]) when considering both sexes together. However, higher BMI increase per risk allele was found among men.

Individual SNP analyses showed few significant effects in sample 1. Only one GWAS SNP (rs13078807) located in the *CADM2* gene region was nominally associated with BMI. *CADM2* has been associated previously with obesity in Whites and other ethnicities [31,63,64]. Among the CG polymorphisms, two SNPs (*HSD11β1* rs3753519 and *CRTC2* rs8450) were associated with BMI in sample 1; however, rs8450 did not survive Bonferroni's correction. In addition to weight gain association in psychiatric samples [16], *HSD11β1* has been associated with metabolic syndrome in a general population [14] and *CRTC2*

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

has been associated with type 2 diabetes in Asian populations [65]. CRTC2 is a coactivator that binds to CREB and stimulates the expression of PEPCK and G6Pase and this increases hepatic gluconeogenesis through dephosphorylation [17,66]. In addition, a deletion of CRTC2 impairs the expression of the gluconeogenic genes and the ability of glucagon to stimulate glucose production in hepatocytes [67]. The *HSD11β1* gene codes for a microsomal enzyme-catalyzing tissue regeneration of active cortisol from the inactive form cortisone [68]. It is highly expressed in metabolic tissues such as the liver and adipose tissue. Increased plasma cortisol levels have been associated with visceral obesity and metabolic syndrome. An overexpression of this gene has been associated with hyperphagia and obesity in mice [69,70].

The stronger effects observed when combining all SNPs in a w-GRS could be explained by the fact that common variants individually have little effect on BMI and very large sample sizes are needed to detect small effects. Thus, when integrating many small variant effects in a w-GRS, the consistency and the power to detect these effects increase, even in smaller sample sizes [35]. In addition, the BMI explained variability in the entire model was 7.01%, with 1.97% of it corresponding to the w-GRS. It is noteworthy that although this is not a high percentage, it represents 28% of the total BMI variability explained by the model. The present study is in the same line as a very recently published study on GWAS meta-analysis of large population data-sets (>300 000 individuals) where the genetic component (i.e. w-GRS) explained up to 2.7% of BMI variability [30].

The w-GRS 32 SNPs could not be replicated in sample 2. This might be tentatively explained by the fact that BMI and overweight prevalence at baseline were the highest among the three samples. Low BMI at baseline has been described as a risk factor for gaining weight [71]. In the same line, when analyzing the 20 CG variants previously associated with antipsychotic-induced weight gain in a w-GRS, no significant association was observed between the w-GRS and BMI. SNPs from CG studies that were selected included very heterogeneous studies, with small sample sizes and with different ethnicities, treatment, and treatment durations (see Supplementary Table S2, Supplemental digital content 1, *http://links.lww.com/FPC/A990*), which could explain the nonsignificant results in our psychiatric samples. In addition, some very promising variants (i.e. *5HT$_{2C}$ receptor*) could not be included in our w-GRS model as the allele effect (β-coefficient) calculation was not available, but on calculating unweighted GRS (in which this variant was included), the results did not change significantly ($P=0.22$). Finally, an a-priori use of an additive model for the effect of all variants could have contributed toward the negative findings.

We also found significant effects for the w-GRS 32 among FEND patients who had lower BMI and obesity prevalence at baseline and shorter treatment duration compared with others. This is in agreement with previous studies showing that low baseline BMI and first-episode patients are known risk factors for important weight gain during psychotropic drug treatment [9]. To our knowledge, this is the first study reporting a stronger effect in men when analyzing the influence of genetic scores on BMI despite the fact that sex differences in fat storage and metabolism have already been described [72]. This emphasizes the need to consider sex when studying obesity-related phenotypes such as BMI. In the present study, men were, on average, younger and had longer treatment duration compared with women, which could contribute toward the observed sex effect as both young age and treatment duration are known risk factors for important weight gain [9]. It is noteworthy that when calculating GRS and sex interaction, a trend was observed when all three samples were combined ($P=0.09$, $n=750$). Because of the exploratory nature of these findings, further analysis including sex stratification should be carried out in larger psychiatric cohorts.

Finally, no association was found with BMI of GRS built from SNPs obtained from psychiatric disorders and diabetes GWAS. Although obesity, type 2 diabetes, and psychiatric disorders are known to share common etiological pathways [8], these results could be considered as negative controls as we only obtained significant BMI–GRS association results when we combined previously BMI-related SNPs.

This study has some limitations that should be mentioned: weighted scores were calculated from β-coefficients obtained from general population samples and the relative influence of these genes might differ in psychiatric patients. Other factors influencing weight gain, such as previous treatment history, were not reported. This study has been carried out in Whites; therefore, these results cannot be extrapolated to other ethnicities. Variants included in the genetic score model should be consistent with their effects (i.e. tested in large sample sizes and replicated effects). Finally, the 95% CI suggests that the genetic effect is variable within the groups and sample size should increase to narrow 95% CI and improve outcome precision.

In conclusion, the present study replicated in psychiatric cohorts previously identified BMI risk variants obtained in GWAS analyses from population-based samples. GRS can be a useful tool to integrate multiple variants with low impact, which, when tested individually, do not show any significant effect. This approach can contribute toward a better understanding of the genetic variability of polygenic obesity in psychiatric patients and our results suggest that particular care should be taken in sex-specific analyses when working with GRS. Thus, the

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

clinical utility of the w-GRS in obesity-related traits needs to be explored further in prospective studies, especially among populations at high risk of developing metabolic disorders.

Acknowledgements

The authors thank Dr S. Crettol, C. Brogli, V. Hodel (logistical assistance), E. Retamales (bibliographical help), A.C. Aubert, M. Brocard, N. Cochard, M. Delessert, A. Kottelat, M. Brawand, K. Powell Golay, and S. Jaquet (sample analysis). They also thank the GIANT for access to their BMI association result in 123 807 individuals and Global Lipids Genetics Consortium. They also thank the iGE3 genomics platform of the University of Geneva (*http://www.ige3.unige.ch/genomics-platform.php*) for the CardiometaboChip genotyping analysis.

This work has been funded in part by the Swiss National Research Foundation (C.B.E. and P.C.: 320030-120686 and 324730-144064). Z.K. received support from the Leenaards Foundation and the Swiss National Science Foundation (31003A-143914). The funding sources played no role in the writing of the manuscript or in the decision to submit it for publication.

Conflicts of interest

C.B.E. has received research support from Takeda and from the Roche Organ Transplantation Research Foundation in the past 3 years. He has received honoraria for conferences or teaching CME courses from Advisis, Astra Zeneca, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Otsuka, Sandoz, Servier, and Vifor-Pharma in the past 3 years. A.v.G. has received honoraria for a conference and a workshop participation unrelated to the topic of this study from Vifor and Bayer Sheringer in the past 3 years. For the remaining authors there are no conflicts of interest.

References

1 Yang W, Kelly T, He J. Genetic epidemiology of obesity. *Epidemiol Rev* 2007; **29**:49–61.
2 Stunkard AJ, Sørensen TI, Hanis C, Teasdale TW, Chakraborty R, Schull WJ, Schulsinger F. An adoption study of human obesity. *N Engl J Med* 1986; **314**:193–198.
3 Katzmarzyk PT, Malina RM, Pérusse L, Rice T, Province MA, Rao DC, Bouchard C. Familial resemblance in fatness and fat distribution. *Am J Hum Biol* 2000; **12**:395–404.
4 Farooqi IS, O'Rahilly S. Monogenic obesity in humans. *Annu Rev Med* 2005; **56**:443–458.
5 Strobel A, Issad T, Camoin L, Ozata M, Strosberg AD. A leptin missense mutation associated with hypogonadism and morbid obesity. *Nat Genet* 1998; **18**:213–215.
6 Waalen J. The genetics of human obesity. *Transl Res* 2014; **164**:293–301.
7 De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry* 2009; **24**:412–424.
8 Lopresti AL, Drummond PD. Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment. *Prog Neuropsychopharmacol Biol Psychiatry* 2013; **45**:92–99.
9 De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* 2011; **8**:114–126.
10 Stahl S. *Stahl's essential psychopharmacology neuroscientific basis and practical applications*, 3rd ed. New York: Cambridge University Press; 2008.
11 Ryu S, Cho EY, Park T, Oh S, Jang WS, Kim SK, *et al.* −759 C/T polymorphism of 5-HT2C receptor gene and early phase weight gain associated with antipsychotic drug treatment. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31**:673–677.
12 Balt SL, Galloway GP, Baggott MJ, Schwartz Z, Mendelson J. Mechanisms and genetics of antipsychotic-associated weight gain. *Clin Pharmacol Ther* 2011; **90**:179–183.
13 Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Müller DJ. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Mol Psychiatry* 2012; **17**:242–266.
14 Wamil M, Seckl JR. Inhibition of 11beta-hydroxysteroid dehydrogenase type 1 as a promising therapeutic target. *Drug Discov Today* 2007; **12**:504–520.
15 Beale EG, Harvey BJ, Forest C. PCK1 and PCK2 as candidate diabetes and obesity genes. *Cell Biochem Biophys* 2007; **48**:89–95.
16 Quteineh L, Vandenberghe F, Saigi Morgui N, Delacrétaz A, Choong E, Gholam-Rezaee M, *et al.* Impact of HSD11B1 polymorphisms on BMI and components of the metabolic syndrome in patients receiving psychotropic treatments. *Pharmacogenet Genomics* 2015; **25**:246–258.
17 Koo SH, Flechner L, Qi L, Zhang X, Screaton RA, Jeffries S, *et al.* The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism. *Nature* 2005; **437**:1109–1111.
18 Gibson WT, Pissios P, Trombly DJ, Luan J, Keogh J, Wareham NJ, *et al.* Melanin-concentrating hormone receptor mutations and human obesity: functional analysis. *Obes Res* 2004; **12**:743–749.
19 Sadagurski M, Leshan RL, Patterson C, Rozzo A, Kuznetsova A, Skorupski J, *et al.* IRS2 signaling in LepR-b neurons suppresses FoxO1 to control energy balance independently of leptin action. *Cell Metab* 2012; **15**:703–712.
20 Esterbauer H, Oberkofler H, Krempler F, Patsch W. Human peroxisome proliferator activated receptor gamma coactivator 1 (PPARGC1) gene: cDNA sequence, genomic organization, chromosomal localization, and tissue expression. *Genomics* 1999; **62**:98–102.
21 Choong E, Quteineh L, Cardinaux JR, Gholam-Rezaee M, Vandenberghe F, Dobrinas M, *et al.* Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and the general adult population. *JAMA Psychiatry* 2013; **70**:1011–1019.
22 Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, *et al.* A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007; **316**:889–894.
23 Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, *et al.* Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet* 2009; **41**:25–34.
24 Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, Helgadottir A, *et al.* Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet* 2009; **41**:18–24.
25 Okada Y, Kubo M, Ohmiya H, Takahashi A, Kumasaka N, Hosono N, *et al.* Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. *Nat Genet* 2012; **44**:302–306.
26 Loos RJ, Lindgren CM, Li S, Wheeler E, Zhao JH, Prokopenko I, *et al.* Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nat Genet* 2008; **40**:768–775.
27 Pei YF, Zhang L, Liu Y, Li J, Shen H, Liu YZ, *et al.* Meta-analysis of genome-wide association data identifies novel susceptibility loci for obesity. *Hum Mol Genet* 2014; **23**:820–830.
28 Berndt SI, Gustafsson S, Mägi R, Ganna A, Wheeler E, Feitosa MF, *et al.* Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. *Nat Genet* 2013; **45**:501–512.
29 Wheeler E, Huang N, Bochukova EG, Keogh JM, Lindsay S, Garg S, *et al.* Genome-wide SNP and CNV analysis identifies common and low-frequency variants associated with severe early-onset obesity. *Nat Genet* 2013; **45**:513–517.
30 Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, *et al.* Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015; **518**:197–206.
31 Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, *et al.* Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010; **42**:937–948.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

32 Zhu J, Loos RJ, Lu L, Zong G, Gan W, Ye X, *et al.* Associations of genetic risk score with obesity and related traits and the modifying effect of physical activity in a Chinese Han population. *PLoS One* 2014; **9**:e91442.

33 Peterson RE, Maes HH, Lin P, Kramer JR, Hesselbrock VM, Bauer LO, *et al.* On the association of common and rare genetic variation influencing body mass index: a combined SNP and CNV analysis. *BMC Genomics* 2014; **15**:368.

34 Goumidi L, Cottel D, Dallongeville J, Amouyel P, Meirhaeghe A. Effects of established BMI-associated loci on obesity-related traits in a French representative population sample. *BMC Genet* 2014; **15**:62.

35 Horne BD, Anderson JL, Carlquist JF, Muhlestein JB, Renlund DG, Bair TL, *et al.* Generating genetic risk scores from intermediate phenotypes for use in association studies of clinically significant endpoints. *Ann Hum Genet* 2005; **69** (Pt 2):176–186.

36 Belsky DW, Moffitt TE, Sugden K, Williams B, Houts R, McCarthy J, Caspi A. Development and evaluation of a genetic risk score for obesity. *Biodemography Soc Biol* 2013; **59**:85–100.

37 Lin X, Song K, Lim N, Yuan X, Johnson T, Abderrahmani A, *et al.* Risk prediction of prevalent diabetes in a Swiss population using a weighted genetic score – the CoLaus Study. *Diabetologia* 2009; **52**:600–608.

38 Derks EM, Vorstman JA, Ripke S, Kahn RS, Ophoff RA. Schizophrenia Psychiatric Genomic Consortium. Investigation of the genetic association between quantitative measures of psychosis and schizophrenia: a polygenic risk score analysis. *PLoS One* 2012; **7**:e37852.

39 Rouskas K, Kouvatsi A, Paletas K, Papazoglou D, Tsapas A, Lobbens S, *et al.* Common variants in FTO, MC4R, TMEM18, PRL, AIF1, and PCSK1 show evidence of association with adult obesity in the Greek population. *Obesity (Silver Spring)* 2012; **20**:389–395.

40 Ntalla I, Panoutsopoulou K, Vlachou P, Southam L, William Rayner N, Zeggini E, Dedoussis GV. Replication of established common genetic variants for adult BMI and childhood obesity in Greek adolescents: the TEENAGE study. *Ann Hum Genet* 2013; **77**:268–274.

41 Warrington NM, Howe LD, Wu YY, Timpson NJ, Tilling K, Pennell CE, *et al.* Association of a body mass index genetic risk score with growth throughout childhood and adolescence. *PLoS One* 2013; **8**:e79547.

42 Hung CF, Rivera M, Craddock N, Owen MJ, Gill M, Korszun A, *et al.* Relationship between obesity and the risk of clinically significant depression: Mendelian randomisation study. *Br J Psychiatry* 2014; **205**:24–28.

43 Hung CF, Breen G, Czamara D, Corre T, Wolf C, Kloiber S, *et al.* A genetic risk score combining 32 SNPs is associated with body mass index and improves obesity prediction in people with major depressive disorder. *BMC Med* 2015; **13**:86.

44 Wali JA, Thomas HE, Sutherland AP. Linking obesity with type 2 diabetes: the role of T-bet. *Diabetes Metab Syndr Obes* 2014; **7**:331–340.

45 Rui L. SH2B1 regulation of energy balance, body weight, and glucose metabolism. *World J Diabetes* 2014; **5**:511–526.

46 Choong E, Quteineh L, Cardinaux JR, Gholam-Rezaee M, Vandenberghe F, Dobrinas M, *et al.* Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and the general adult population. *JAMA Psychiatry* 2013; **70**:1011–1019.

47 [No authors listed]. Comparative study of the efficacy of dipyrone, diclofenac sodium and pethidine in acute renal colic. Collaborative Group of the Spanish Society of Clinical Pharmacology. *Eur J Clin Pharmacol* 1991; **40**:543–546.

48 American Diabetes A, American Psychiatric A, American Association of Clinical E, North American Association for the Study of O. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; **27**:596–601.

49 Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, *et al.* Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* 2010; **467**:832–838.

50 Heid IM, Jackson AU, Randall JC, Winkler TW, Qi L, Steinthorsdottir V, *et al.* Meta-analysis identifies 13 new loci associated with waist–hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet* 2010; **42**:949–960.

51 Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, *et al.* Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet* 2010; **42**:579–589.

52 Cross-Disorder Group of the Psychiatric Genomics Consortium, Smoller JW, Craddock N, Kendler K, Lee PH, Neale BM, *et al.* Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 2013; **381**:1371–1379.

53 Winham SJ, Colby CL, Freimuth RR, Wang X, de Andrade M, Huebner M, Biernacka JM. SNP interaction detection with Random Forests in high-dimensional genetic data. *BMC Bioinformatics* 2012; **13**:164.

54 Voight BF, Kang HM, Ding J, Palmer CD, Sidore C, Chines PS, *et al.* The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. *PLoS Genet* 2012; **8**:e1002793.

55 Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Müller DJ. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Mol Psychiatry* 2012; **17**:242–266.

56 Che R, Motsinger-Reif AA. A new explained-variance based genetic risk score for predictive modeling of disease risk. *Stat Appl Genet Mol Biol* 2012; **11**:Article 15.

57 R Core Team. *R: A language and environment for statistical computing, R Fondation for Statistical Computing*. Vienna, Austria: R Development Core Team; 2013. Available at: *http://www.R-project.org*. [Accessed 11 June 2014].

58 Venables WN, Ripley BD. *Modern applied statistics with S*. New York: Springer; 2002.

59 Bolker BM, Brooks ME, Clark CJ, Geange SW, Poulsen JR, Stevens MH, White JS. Generalized linear mixed models: a practical guide for ecology and evolution. *Trends Ecol Evol* 2009; **24**:127–135.

60 Wolfinger R, O'connell M. Generalized linear mixed models: a pseudo-likelihood approach. *J Statist Comput Simulation* 1993; **48**:233–243.

61 Lin X, Zhang D. Inference in generalized additive mixed models by using smoothing splines. *J R Statist Soc B* 1999; **61**:381–400.

62 Wood SN. GAMMs with R. In: Carlin BP, Chatfield C, Tanner M, Zidek J, editors. *Generalized additive models – an introduction with R*. Broken: Chapman & Hall/CRC; 2006. pp. 319–324.

63 Dorajoo R, Blakemore AI, Sim X, Ong RT, Ng DP, Seielstad M, *et al.* Replication of 13 obesity loci among Singaporean Chinese, Malay and Asian-Indian populations. *Int J Obes (Lond)* 2012; **36**:159–163.

64 Wen W, Cho YS, Zheng W, Dorajoo R, Kato N, Qi L, *et al.* Meta-analysis identifies common variants associated with body mass index in east Asians. *Nat Genet* 2012; **44**:307–311.

65 Keshavarz P, Inoue H, Nakamura N, Yoshikawa T, Tanahashi T, Itakura M. Single nucleotide polymorphisms in genes encoding LKB1 (STK11), TORC2 (CRTC2) and AMPK alpha2-subunit (PRKAA2) and risk of type 2 diabetes. *Mol Genet Metab* 2008; **93**:200–209.

66 Zhou XY, Shibusawa N, Naik K, Porras D, Temple K, Ou H, *et al.* Insulin regulation of hepatic gluconeogenesis through phosphorylation of CREB-binding protein. *Nat Med* 2004; **10**:633–637.

67 Wang Y, Inoue H, Ravnskjaer K, Viste K, Miller N, Liu Y, *et al.* Targeted disruption of the CREB coactivator Crtc2 increases insulin sensitivity. *Proc Natl Acad Sci USA* 2010; **107**:3087–3092.

68 Tomlinson JW, Walker EA, Bujalska IJ, Draper N, Lavery GG, Cooper MS, *et al.* 11Beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. *Endocr Rev* 2004; **25**:831–866.

69 Masuzaki H, Paterson J, Shinyama H, Morton NM, Mullins JJ, Seckl JR, Flier JS. A transgenic model of visceral obesity and the metabolic syndrome. *Science* 2001; **294**:2166–2170.

70 Paterson JM, Morton NM, Fievet C, Kenyon CJ, Holmes MC, Staels B, *et al.* Metabolic syndrome without obesity: hepatic overexpression of 11beta-hydroxysteroid dehydrogenase type 1 in transgenic mice. *Proc Natl Acad Sci USA* 2004; **101**:7088–7093.

71 De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry* 2009; **24**:412–424.

72 Power ML, Schulkin J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *Br J Nutr* 2008; **99**:931–940.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Journal of Affective Disorders 198 (2016) 43–49

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Association of *CRTC1* polymorphisms with obesity markers in subjects from the general population with lifetime depression

Lina Quteineh [a], Martin Preisig [b], Margarita Rivera [c,d,e], Yuri Milaneschi [f], Enrique Castelao [b], Mehdi Gholam-Rezaee [b], Frederik Vandenberghe [a], Nuria Saigi-Morgui [a], Aurélie Delacrétaz [a], Jean-René Cardinaux [g,h], Gonneke Willemsen [i], Dorret I. Boomsma [i], Brenda W.J.H. Penninx [f], Ana Ching-López [d], Philippe Conus [j], Chin B. Eap [a,k,*]

[a] Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland
[b] Centre of Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland
[c] Instituto de Investigación Biosanitaria ibs.GRANADA, Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain
[d] CIBERSAM-University of Granada and Institute of Neurosciences Federico Olóriz, Centro de Investigación Biomédica, University of Granada, Spain
[e] MRC Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
[f] Department of Psychiatry, EMGO Institute for Health and Care Research and Neuroscience Campus Amsterdam, VU University Medical Center/GGZ inGeest, Amsterdam, The Netherlands
[g] Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland
[h] Child and Adolescent Psychiatric Clinic, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland
[i] Department of Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands
[j] Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland
[k] School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 23 November 2015
Received in revised form
10 February 2016
Accepted 9 March 2016
Available online 10 March 2016

Keywords:
Obesity
Major depressive disorder
Psychiatric disorders
Psychotropic drugs
Pharmacogenetics
Genetic polymorphisms

ABSTRACT

Background: Psychiatric disorders have been hypothesized to share common etiological pathways with obesity, suggesting related neurobiological bases. We aimed to examine whether *CRTC1* polymorphisms were associated with major depressive disorder (MDD) and to test the association of these polymorphisms with obesity markers in several large case-control samples with MDD.

Methods: The association between *CRTC1* polymorphisms and MDD was investigated in three case-control samples with MDD (PsyCoLaus $n_1=3,362$, Radiant $n_2=3,148$ and NESDA/NTR $n_3=4,663$). The effect of *CRTC1* polymorphisms on obesity markers was then explored.

Results: *CRTC1* polymorphisms were not associated with MDD in the three samples. *CRTC1 rs6510997C > T* was significantly associated with fat mass in the PsyCoLaus study. In fact, a protective effect of this polymorphism was found in MDD cases ($n=1,434$, $\beta=-1.32\%$, 95% CI -2.07 to -0.57, $p<0.001$), but not in controls. In the Radiant study, *CRTC1* polymorphisms were associated with BMI, exclusively in individuals with MDD ($n=2,138$, $\beta=-0.75$ kg/m^2, 95% CI -1.30 to -0.21, $p=0.007$), while no association with BMI was found in the NESDA/NTR study.

Limitations: Estimated fat mass using bioimpedance that capture more accurately adiposity was only present in the PsyCoLaus sample.

Conclusions: *CRTC1* polymorphisms seem to play a role with obesity markers in individuals with MDD rather than non-depressive individuals. Therefore, the weak association previously reported in the population-based samples was driven by cases diagnosed with lifetime MDD. However, CRTC1 seems not to be implicated directly in the development of psychiatric diseases.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

Based on a growing body of evidence, it has been hypothesized that psychiatric disorders, such as schizophrenia and mood disorders, are causally related to or share common etiological pathways with obesity, suggesting that comorbid obesity and psychiatric disorders

* Correspondence to: Hôpital de Cery, 1008 Prilly, Lausanne, Switzerland.
E-mail address: chin.eap@chuv.ch (C.B. Eap).

http://dx.doi.org/10.1016/j.jad.2016.03.031
0165-0327/© 2016 Elsevier B.V. All rights reserved.

have related neurobiological bases (Farmer et al., 2008; Forty et al., 2014). Increased appetite, weight gain and obesity are common symptoms of depression (Blaine, 2008; Luppino et al., 2010). On the other hand, obese individuals were also found to have higher prevalence of depression (Luppino et al., 2010). Shared genetic factors were previously suggested (Afari et al., 2010; Comings et al., 1996; Rivera et al., 2012; Samaan et al., 2013), however, due to the pathological complexity of both conditions and the polygenic factors affecting them, many genetic factors are still to unravel. Additionally, due to heterogeneity of depression, genetic association studies could give conflicting results. One example is the fat mass and obesity-associated gene (*FTO*) for which the common *rs9939609-A* variant previously associated with increased body mass index (BMI) and obesity in several studies (Frayling et al., 2007; Qi et al., 2008; Scuteri et al., 2007) was shown to be negatively associated with depression in a meta-analysis of four large studies (Samaan et al., 2013). On the other hand, the same variant was found to be positively associated with depression in a recent large case-control study (Milaneschi et al., 2014), but this association was entirely driven by the atypical depression subtype (subtype characterized typically by increased appetite, weight gain and hypersomnia).

We previously showed an association between a coding single nucleotide polymorphism (SNP) within the *CREB-regulated transcription coactivator 1 (CRTC1)* gene (*rs3746266A > G*) and BMI in 3 independent psychiatric samples (brief description of these samples is given in the Supplementary data and is described in details in ref (Choong et al., 2013)). Carriers of the *rs3746266-G* variant showed significantly protective effect against obesity compared to non-carriers. The sex-stratified analysis in the 3 combined psychiatric samples showed a protective effect for the *G* allele both in men and women. However, the strongest and most clinically relevant association was observed in women younger than 45 years old. Although the effect was weaker, we also found a protective effect of the *T* allele of the *CRTC1 rs6510997C > T* (a proxy of *rs3746266A > G*, $r^2=0.7$) on fat accumulation in a large population-based sample (CoLaus), with the strongest association again in premenopausal women (Choong et al., 2013).

In animal models, we previously showed that mice lacking CRTC1 exhibit neurobehavioral endophenotypes related to mood disorders, depression-related behavior and a blunted behavioral response to antidepressants (Breuillaud et al., 2012). *Crtc1* knockout mice also developed obese features, including obesity-related metabolic complications, under normal diets (Altarejos et al., 2008; Breuillaud et al., 2009). Altogether, these findings suggest that the *Crtc1* gene might play a common role in obesity and depression-related behavior.

In the present study, we aimed to examine whether *CRTC1* SNPs are associated with major depressive disorder (MDD), and to test the association of *CRTC1* SNPs with obesity markers in several large case-control samples with MDD. The same *CRTC1* SNPs (*rs3746266A > G* and *rs6510997C > T*) investigated previously (Choong et al., 2013) were used in the current study.

2. Patients and methods

The associations between *CRTC1* polymorphisms and obesity markers were first tested in the PsyCoLaus sample and tested for replication in the Radiant and NESDA/NTR study. Supplementary Table S1 presents the main similarities and differences between these samples.

3. Discovery cohort: CoLaus|PsyCoLaus

Participants aged 35–75 years in this population-based cohort study (CoLaus; n=6,734) were recruited between June 2003 and May 2006 in Lausanne, Switzerland as previously described (Firmann et al., 2008). The assessments at baseline and at the first follow-up included cardiovascular risk factors such as BMI, fat mass, blood pressure, glucose and lipid profiles. In addition, a genome-wide association study was performed in all Caucasians (91% of the sample). All participants of CoLaus were asked to also participate in the psychiatric evaluations (PsyCoLaus (Preisig et al., 2009)), which included the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994; Preisig et al., 1999). The assignment of the lifetime diagnosis of MDD and the subtyping into atypical and non-atypical MDD was performed according to DSM-IV criteria. Complete physical and psychiatric data were available for 3354 participants aged 35–65 year-old who completed the psychiatric evaluation either at the baseline or the first follow-up ($n_{total}=3362$). 1434 cases of lifetime depression were compared with 1920 controls with no previous history of depression. Genotyping for the CoLaus/PsyCoLaus subjects was performed using the Affymetrix GeneChipR Human Mapping 500 K array set. The *CRTC1 rs6510997C > T* SNP was directly genotyped (Choong et al., 2013). The *CRTC1 rs7257846T > C*, which is in linkage disequilibrium (LD) with *rs3746266A > G* ($r^2=0.93$), was imputed and analyzed (r^2hat value was 0.70).

The Institutional Ethics Committee of the University of Lausanne approved the CoLaus and subsequently the PsyCoLaus study. All participants signed a written informed consent to participate in the study.

3.1. The radiant study

The Radiant study was founded from three studies: the Depression Case–Control (DeCC) study, Depression Network (DeNT) study and the Genome-Based Therapeutic Drugs for Depression (GENDEP) study. The DeCC study is a multicentre case-control study conducted over three investigative sites in UK (London, Cardiff and Birmingham) (Cohen-Woods et al., 2009). The DeNT study is a family-based study that recruited sibling pairs affected with unipolar depression from eight European clinical sites and one in the USA (Farmer et al., 2004; McGuffin et al., 2005). Participants in the DeCC and DeNT studies were included if they had lifetime diagnosis of two or more episodes of MDD of at least moderate severity. Subjects in the GENDEP study were recruited from nine European centers if they experienced at least one depressive episode of at least moderate severity (Uher et al., 2009). Diagnosis of MDD was defined as of illness fulfilling ICD–10 and/or DSM–IV criteria and was ascertained using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview in all three studies (Wing et al., 1990). Control subjects were recruited via the Medical Research Council general practice research framework (Sham et al., 2000). They were screened for lifetime absence of any psychiatric disorder using a modified version of the Past History Schedule (McGuffin et al., 1986). Self-reported height and weight were obtained from participants in the MDD group via the SCAN interview and from the controls via telephone interview. The reliability of self-report of height and weight was assessed in the GENDEP dataset (n=811) where also height and weight were measured. The correlations for measured versus self-reported height, weight and BMI were 0.97, 0.95 and 0.95, respectively (Hung et al., 2014, 2015). All cases and controls were of white European ancestry. Genotyping for the Radiant subjects was performed using the Illumina HumanHap610-Quad BeadChips by the Centre National de Génotypage (CNG), Evry, France, as previously described (Lewis et al., 2010). *CRTC1 rs3746266A > G* was successfully imputed using *the Beagle Program* (BEAGLE Version 3.0 Copyright (c) 2007–2010 Brian L Browning), with imputation quality > 0.8. The *CRTC1 rs2075017T > C*, which is in complete linkage disequilibrium (LD) with *the rs6510997C > T*, was also

selected for the association analyses.

Approval was obtained from the local research ethics committees/institutional research boards of all of the participating sites. All participants provided written informed consent.

3.2. NESDA/NTR study

This sample consisted of 4663 unrelated participants of European ancestry from the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008) (1636 cases and 425 controls) and from the Netherlands Twin Registry (NTR) (Boomsma et al., 2006) (132 cases and 2470 controls). The diagnosis of lifetime and/or current MDD according to DSM-IV was ascertained using the Composite Interview Diagnostic Instrument (WHO WMH-CIDI, 2015). Weight and height were measured at the study clinic during the visit for NESDA (Penninx et al., 2008), and during the home visit for NTR-Biobank (Willemsen et al., 2010). Genotyping was performed on multiple chip platforms in (partially overlapping) different subsets of the total sample (Affymetrix-Perlegen 5.0, Illumina 370 K, Illumina 660 K, Illumina Omni 1 M and Affymetrix 6.0) and data were imputed using the 1000 Genomes phase 1 INTEGRATED RELEASE version 3 ALL panel (r^2hat value was 0.99 for *rs6510997C > T* and 0.77 for *rs3746266A > G*).

The NESDA/NTR study was approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam, and all subjects provided written informed consent.

4. Statistical analysis

For association studies, chi-square (Chi^2) or Fisher exact tests for binomial variables were used. Differences in genotype frequencies as well as deviation from Hardy-Weinberg equilibrium were assessed using Chi^2 test. All genetic analyses for *CRTC1* SNPs were performed using a dominant model (wild type vs. variant allele carriers), the same model used for the previously mentioned psychiatric samples (Choong et al., 2013).

Multivariable regression analyses were used to test the association between the *CRTC1* SNPs and MDD adjusting for age, sex and BMI. For PsyCoLaus data, a Generalized Linear Model (GLM) adjusted for age and sex was used to test the association between *CRTC1 rs6510997C > T* polymorphism and obesity markers (BMI, fat mass and waist circumference) using SAS 9.3 version (SAS Institute Inc., Cary, NC, USA). In a first step, we tested for the interaction between *CRTC1* SNPs and MDD status for an effect on obesity markers. For the Radiant and NESDA/NTR studies BMI was the only available obesity marker. For the data of these studies, linear regression models adjusted for age, sex and principal components were used to test the association between *CRTC1* polymorphisms and BMI.

5. Results

5.1. Demographic characteristics of the study samples

General characteristics of the PsyCoLaus sample are presented in Supplementary Table S2. The Radiant study included 3148 subjects (2338 cases and 810 controls), mean age ± standard deviation (s.d.) was 43.9 ± 12.8 years. Females represent nearly 68% of the study sample. Mean BMI in the total study sample was 25.9 kg/m^2 (s.d. 5.4). The NESDA/NTR study included 4663 subjects, mean age ± s.d. was 42.7 ± 14.0 years. Females represent nearly 64% of the study sample. Mean BMI in the total study sample was 25.0 kg/m^2 (s.d. 4.5).

Table 1
Genotype distribution in the total study samples, among MDD subjects and controls.

Patients	Total	N (%)			HWE
PsyCoLaus					
rs6510997 C > T [a]		***CC***	***CT***	***TT***	
Total	3347	2128 (63.6)	1092 (32.6)	127 (3.8)	0.37
MDD cases	1431	912 (63.7)	468 (32.7)	51 (3.6)	
Controls	1916	1216 (63.5)	624 (32.6)	76 (3.9)	
The radiant study					
rs3746266A > G		***AA***	***AG***	***GG***	
Total	2842	2173 (76.5)	626 (22.0)	43 (1.5)	0.78
MDD cases	2142	1637 (76.4)	468 (21.9)	37 (1.7)	
Controls	700	536 (76.5)	158 (22.6)	6 (0.9)	
rs2075017T > C [a]		***TT***	***TC***	***CC***	
Total	2160	1357 (62.8)	720 (33.3)	83 (3.9)	0.30
MDD cases	1352	849 (62.8)	450 (33.3)	53 (3.9)	
Controls	808	508 (62.9)	270 (33.4)	30 (3.7)	
NESDA/NTR study					
rs3746266A > G		***AA***	***AG***	***GG***	
Total	4663	3235 (69.4)	1306 (28.0)	122 (2.6)	0.47
MDD cases	1768	1234 (69.8)	485 (27.4)	49 (2.8)	
Controls	2895	2001 (69.1)	821 (28.5)	73 (2.5)	
rs6510997 C > T		***CC***	***CT***	***TT***	
Total	4663	2952 (63.3)	1522 (32.6)	189 (4.1)	0.68
MDD cases	1768	1124 (63.6)	567 (32.1)	77 (4.4)	
Controls	2895	1828 (63.1)	955 (33.0)	112 (3.9)	

MDD: Major depressive disorder, N: number, HWE: Hardy-Weinberg Equilibrium.
[a] Both SNPs are in complete linkage disequilibrium ($r^2 = 1$).

5.2. *CRTC1* polymorphisms and MDD

Genotype distribution in the overall study samples and among MDD cases and controls are presented in Table 1. Genotype distribution did not differ between MDD cases and controls in any of the three studies (Table 1). Multivariate analyses adjusted for age and sex confirmed the absence of an association between *CRTC1* polymorphisms and MDD in the three studies (data not shown).

5.3. *CRTC1* polymorphisms and obesity markers

5.3.1. PsyCoLaus

CRTC1 rs6510997C > T was significantly associated with fat mass in the global PsyCoLaus sample (Table 2). We observed interactions between *CRTC1 rs6510997 C > T* and sex ($p = 0.03$) as well as between this SNP and MDD status ($p = 0.01$) regarding the fat mass, indicating a significantly stronger effect of this genetic variant in females and in subjects with MDD. Indeed, this SNP was significantly associated with lower fat mass in females but not in males. Similarly, this SNP was significantly associated with lower fat mass in subjects with MDD but not in controls (Table 2). Additionally, the 3-way interaction between CRTC1 *rs6510997C > T*, sex and MDD regarding the fat mass was not significant ($p = 0.54$). In females, we did not find an interaction between the *CRTC1 rs6510997C > T SNP* and menopausal status and among depressed subjects there was no interaction between this SNP and the atypical depression subtype to affect the fat mass. Regarding the BMI and waist circumference there was no evidence of an interaction between *CRTC1 rs6510997C > T* and sex or MDD status and the SNP was not associated with these obesity markers (Table 2).

No difference on the associations between *CRTC1 rs6510997C > T* and fat mass was noticed by adjusting the GLM model for other available co-variables that could affect the gene association with obesity markers, like socioeconomic status, drug dependence, alcohol

Table 2
Association between *CRTC1 rs6510997C > T* polymorphism and fat mass, BMI and waist circumference in the PsyCoLaus sample, among sex-stratified and MDD subjects and controls.

		Fat mass[a,b]		BMI[c]		Waist circumference[c]	
	n	Estimates (95% C.I.)	p-Value	Estimates (95% C.I.)	p-Value	Estimates (95% C.I.)	p-Value
All subjects	3362	−0.66 (−1.28 to −0.04)	**0.04**	−0.28 (−0.60 to 0.04)	0.09	−0.70 (−1.64 to 0.24)	0.14
Males	1576	−0.03 (−0.56 to 0.51)	0.92				
Females	1786	−1.08 (−1.81 to −0.34)	**0.004**				
Subjects with MDD	1434	−1.32 (−2.07 to −0.57)	**< 0.001**				
Controls	1920	−0.01 (−0.60 to 0.57)	0.97				

Models were adjusted for age and sex (when appropriate).
BMI: body mass index, C.I.: confidence interval, MDD: Major depressive disorder.
[a] *CRTC1 rs6510997C > T* and MDD status interaction regarding fat mass: p = 0.014.
[b] *CRTC1 rs6510997C > T* and sex interaction regarding fat mass: estimate: p = 0.026.
[c] *CRTC1 rs6510997C > T* and MDD status and/or sex interactions regarding BMI and waist circumference: p > 0.05.

consumption, former and current tobacco consumer (Supplementary Table S3). Nearly the same associations with obesity markers were observed in PsyCoLaus for *CRTC1 rs7257846T > C* (in strong LD with *rs3746266A > G*, $r^2 = 0.93$)(Supplementary Table S4).

5.3.2. The radiant and NESDA/NTR studies

The *CRTC1 rs3746266A > G* SNP was associated with BMI in the total Radiant sample and exclusively in females (Table 3). By stratifying MDD cases and controls, the protective effect of the *rs3746266G-allele* was only observed in MDD cases, while no association was observed in controls. A weak association was observed between *CRTC1 rs2075017T > C* (in complete LD with the *rs6510997C > T*) and BMI in the Radiant sample (Table 3). Regarding the NESDA/NTR study, *CRTC1* SNPs were not associated with BMI (Table 4).

6. Discussion

We previously showed a protective effect of the variant *CRTC1 rs3746266G-allele* on increased BMI in three independent psychiatric samples (Choong et al., 2013). The same protective effect was also observed in a population-based sample (CoLaus) between the *rs6510997T-allele* (in a strong LD with the *rs3746266G-allele*) and fat mass. However, the effect of the SNP was weaker compared to the psychiatric samples (Choong et al., 2013). In the present study, we were able to show in the psychiatrically evaluated sub-sample of CoLaus (PsyCoLaus) that the effect of *CRTC1 rs6510997C > T* on fat mass was restricted to subjects with a lifetime history of MDD. In these subjects, the *CRTC1 rs6510997T-allele* showed a significant protective effect for the fat mass. Although there was no significant interaction between the *CRTC1* SNPs and MDD, similar trend regarding the BMI was observed in the Radiant sample (no fat mass data available in this sample), which included more severe treated cases with lifetime recurrent depression. The *CRTC1 rs3746266A > G* SNP only reached the level of statistical significance in MDD cases. However, these results could not be replicated in a third case-control sample with lifetime depression, the NESDA/NTR study.

CRTC1 rs6510997C > T was associated with fat mass exclusively among depressive cases but not unaffected individuals in the PsyCoLaus sample. This association in depressed subjects did not differ in function of the depression subtypes (atypical versus others). Such an association with the BMI was not observed in the whole PsyCoLaus sample, but *CRTC1 SNPs* were associated with BMI in the Radiant study. BMI may less accurately capture adiposity than estimated fat mass using bioimpedance (Marques-Vidal et al., 2009; Prentice and Jebb, 2001). Using the whole CoLaus sample, previous work established that fat mass enables capture of 3 times more subjects with high cardiovascular risk than BMI (Marques-Vidal et al., 2009) and we also showed that this sample is better powered to detect an association of the *rs6510997C > T* SNP with fat mass than with BMI (Choong et al., 2013). In the psychiatric samples, based on subjects at high risk of metabolic abnormalities because of the disorder and of the psychotropic medications, an association between *CRTC1* SNPs and BMI could be observed (Choong et al., 2013). Accordingly, the association

Table 3
Association between *CRTC1* polymorphisms and BMI in the total, sex-stratified sample and in depressive cases and controls of the Radiant study sample.

	rs3746266A > G[a]			***rs2075017T > C***[b]		
	n	**Estimates (95% C.I.)**	***p***	***n***	**Estimates (95% C.I.)**	***p***
All subjects[c]	2822	−0.67 (−1.13 to −0.21)	***0.004***	2136	−0.50 (−0.95 to −0.05)	***0.03***
Male	909	−0.38 (−1.05 to 0.30)	*0.28*	713	−0.25 (−0.93 to 0.42)	*0.46*
Female	1916	−0.79 (−1.38 to −0.21)	***0.008***	1424	−0.62 (−1.20 to −0.04)	***0.04***
Subjects with MDD	2138	−0.75 (−1.30 to −0.21)	**0.007**	1346	−0.59 (−1.20 to 0.02)	0.06
Controls	684	−0.41 (−1.20 to 0.39)	*0.32*	790	−0.32 (−0.95 to 0.31)	*0.32*

Model were adjusted for age and sex (when appropriate) and principal components
C.I.: confidence interval, MDD: Major depressive disorder
[a] *CRTC1 rs3746266A > G* and MDD status and/or sex interactions regarding BMI: p > 0.05.
[b] *CRTC1 rs2075017T > C* and MDD status and/or sex interactions regarding BMI: p > 0.05.
[c] Available subjects with clinical and genetic data.

Table 4
Association between *CRTC1* polymorphisms and BMI in the total, sex-stratified sample and in depressive cases and controls of the NESDA/NTR study sample.

		rs3746266A > G		***rs6510997C > T***	
	n	**Estimates (SE)**	***p***	**Estimates (SE)**	***p***
All subjects	4663	−0.047 (0.130)	0.73	0.014 (0.130)	0.91
Male	1676	0.072 (0.202)	0.72	−0.053 (0.193)	0.78
Female	2987	−0.121 (0.179)	0.50	0.046 (0.172)	0.79
Subjects with MDD	1768	0.038 (0.256)	0.88	0.166 (0.245)	0.50
Controls	2895	−0.076 (0.150)	0.61	−0.054 (0.144)	0.71

Model were adjusted for age and sex (when appropriate) and principal components.
SE: standard error, MDD: Major depressive disorder.

between *CRTC1* SNPs and BMI observed in the Radiant study could be explained by the higher degree of severity of the disorder in this sample compared to that in the PsyCoLaus. Interestingly, post hoc analysis also revealed a significant protective effect of the *CRTC1 rs6510997C > T* SNP on BMI and waist circumference in PsyCoLaus subjects with MDD (but not in the overall sample) which would be in line with our hypothesis that the impact of *CRTC1* variants on adiposity markers is restricted to affected subjects.

CRTC1 SNPs were associated with obesity markers in both PsyCoLaus and Radiant studies, but the association was attributable to MDD cases. On the other hand, *CRTC1* SNPs were not associated with BMI in the NESDA/NTR study, neither in the whole sample, nor in the stratified MDD case-control analyses. Previously, PsyCoLaus and DeCC (from the Radiant study) samples detected a protective effect of the *FTO rs9939609-A* variant on MDD (Samaan et al., 2013), while in the NESDA/NTR study the SNP was positively associated with MDD, especially in the atypical depression subtype (Milaneschi et al., 2014). Therefore, an inconsistency was already observed before for these studies which could be partly explained by the heterogeneity of depression in genetic association studies.

Obesity results from an imbalance between energy intake and energy expenditure. Recent studies have shown that mice lacking the *Crtc1* gene eat more and have less energy expenditure than wild-type mice, thus developing an obese feature, including obesity-related metabolic complications, under normal diets (Altarejos et al., 2008; Breuillaud et al., 2009). These results suggest that CRTC1 is playing a major role in the hypothalamic control of food intake. CRTC1 is mainly expressed in the brain (Altarejos et al., 2008; Breuillaud et al., 2009; Conkright et al., 2003; Kovacs et al., 2007; Wu et al., 2006) where it may modulate leptin anorexic effect in the hypothalamus. In the cell, the inactive phosphorylated form of CRTC1 is sequestered in the cytoplasm, and its migration to the nucleus requires the concomitant activation of the phosphatase calcineurin and the inactivation of kinases of the 5′ adenosine monophosphate-activated protein kinase (AMPK) family (Altarejos and Montminy, 2011). Interestingly, psychotropic drugs may increase weight by selective and potent stimulation of hypothalamic AMPK (Minokoshi et al., 2004) which has been shown to regulate food intake and reverse the actions of the anorexigenic hormone leptin (Kim et al., 2007).

In the PsyCoLaus sample, an interaction between *CRTC1* SNP and sex was observed regarding the fat mass and the protective effect of the SNP was mainly observed in females from the global sample. The same protective effect of *CRTC1* SNP on BMI was also observed in females from the global Radiant sample. This is in line with our previous results in the psychiatric and CoLaus samples (Choong et al., 2013). This stronger association found in females compared to males could be caused by a differential role of the leptin mediating satiety pathway in the enhancement of CRTC1 activity. Women have much higher leptin levels than men (Rosenbaum et al., 1996) and female sex was found to predict stronger weight gain during psychotropic treatment (Gebhardt et al., 2009). A hypothetical mechanism of the effect of CRTC1 and its interaction with sex hormones was published previously (Choong et al., 2013). Additionally, a meta-analysis of GWAS reported an association of an intronic SNP of *CRTC1* (*rs10423674A > C*) with the age of menarche (Elks et al., 2010), supporting a potential interaction between sex hormones and CRTC1.

The *CRTC1* SNPs were not associated with depression in our three MDD case-control studies. Animal models lacking the *Crtc1* gene showed behavioral abnormalities and depression-related behavior (Breuillaud et al., 2012), but this finding could not be translated in our study. However, the functional activities of these SNPs in humans are still unknown and possibly the complete absence of the *CRTC1* gene could lead to the observed behavioral disturbances in animal models, which is probably not the case for effect of the tested SNPs on *CRTC1* expression. On the other hand, the observed effect of the *CRTC1* SNPs on obesity markers was uniquely detected in subjects with MDD. The lack of association between *CRTC1* SNPs and obesity markers in controls from the PsyCoLaus and the Radiant samples explains the weak association previously found in the population-based sample (Choong et al., 2013). It also confirms our hypothesis in which psychiatric illness and/or treatment with potentially weight gain-inducing psychotropic drugs could play a role in genetically mediated energy homeostasis and that the effect of *CRTC1* variations on obesity markers was unmasked in this group of subjects. Interestingly, a study in animal models (Mastronardi et al., 2011) showed that rats exposed to a high-fat diet after stress and treatment for a short period with antidepressants, to have more body weight and size from 17 to 22 weeks following antidepressant discontinuation compared to rats with the same conditions but treated with saline (Mastronardi et al., 2011). These findings support our concept of persistent, long-term effects of pharmacological–environment interactions on body weight regulation, even if the exposure to these medications was in any period in their lifetime.

This study has several limitations. Estimated fat mass using bioimpedance was only measured in the PsyCoLaus sample while only BMI was the only adiposity marker measured in the replication samples. Additionally, height and weight were self-reported in the Radiant study, which might influence the accuracy of BMI measurements in this sample, although the reliability of self-report of height and weight was assessed in the GENDEP dataset. Psychotropic medications were not available in the Radiant sample, therefore, associations between *CRTC1* SNPs and BMI in treated vs. untreated cases could not be calculated. Both *CRTC1* SNPs (*rs6510997C > T and rs3746266A > G*) were not always available in our three case-control samples; however, SNPs with nearly complete LD ($r^2 > 0.9$) were selected and used as proxies, and results from these proxies could be generalized to our 2 *CRTC1* SNPs (meaning that the genotype present at one locus of the SNPs in LD is independent of the genotype at the second locus, both SNPs having the same allele frequency and could represent each other). On the other hand, SNPs were not always directly genotyped and different imputation methods with different imputation qualities were used which can potentially influence the results on the associations between different imputated *CRTC1* SNPs and obesity markers in our studies.

In conclusion, we showed in this study that *CRTC1* polymorphisms play no role in obesity markers in the general population and that the weak effect previously reported was driven by cases diagnosed with lifetime MDD. *CRTC1* seems to play an important role in the high prevalence of overweight and obesity specifically in psychiatric samples, a population at risk of developing obesity because of the disease itself and/or the medications. However, *CRTC1* seems not to be implicated directly in the development of psychiatric diseases.

Conflict of interest

CBE received honoraria for conferences or teaching CME courses from Astra Zeneca, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Mepha, Otsuka, Servier and Vifor-Pharma in the past 3 years. MP was part of an advisory board of Lundbeck in the past 3 years.

All authors declare no conflict of interest in relation to the content of the paper.

Author disclosure:

CBE received research support the Swiss National Research Foundation (320030-120686 and 324730-144064), from Takeda and from the Roche Organ Transplantation Research Foundation in the past 3 years. The CoLaus/PsyCoLaus study received financial contributions from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, the Swiss National Science Foundation (105993, 118308, 122661, 139468, 148401).

The Radiant study was funded by the Medical Research Council, UK. GlaxoSmithKline (G0701420) funded the DeNT study and they were co-funder with the Medical Research Centre for the GWAS of the whole sample. The GENDEP study was funded by a European Commission Framework 6 grant, EC Contract Ref.: LSHB-CT-2003-503428. This study presents independent research [part-] funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Netherlands Study of Depression and Anxiety and Netherland Twin Register: funding was obtained from the Netherlands Organization for Scientific Research (NWO) and MagW/ZonMW grants Middelgroot-911-09-032, Spinozapremie 56-464-14192, Geestkracht program of the Netherlands Organization for Health Research and Development (ZonMW 10-000-1002), Center for Medical Systems Biology (CSMB, NOW Genomics), Genetic influences on stability and change in psychopathology from childhood to young adulthood (ZonMW 912-10-020), NBIC/BioAssist/RK (2008.024), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI–NL, 184.021.007), VU University's Institute for Health and Care Research (EMGO+) and Neuroscience Campus Amsterdam (NCA); the European Science Council (ERC Advanced, 230374). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health, Rutgers University Cell and DNA Repository (NIMH U24 MH068457-06), the Avera Institute, Sioux Falls, South Dakota (USA) and the National Institutes of Health (NIH R01 HD042157-01A1, MH081802, Grand Opportunity grants 1RC2 MH089951 and 1RC2 MH089995). Computing was supported by BiG Grid, the Dutch e-Science Grid, which is financially supported by NWO.

Author Contributions:

Drs Preisig (PsyCoLaus), Rivera (Radiant) and Milaneschi (NESDA/NTR) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Preisig and Eap.

Acquisition of data: Preisig, Rivera, Milaneschi, Willemsen

Analysis and interpretation of data: Quteineh, Eap, Preisig, Castelao, Gholam-Rezaee, Rivera, Milaneschi

Drafting of the manuscript: Quteineh

Critical revision of the manuscript for important intellectual content: Quteineh, Preisig, Rivera, Milaneschi, Castelao, Gholam-Rezaee, Vandenberghe, Saigi-Morgui, Delacrétaz, Cardinaux, Willemsen, Boomsma, Penninx, Ching-López, Conus, Eap

Statistical analysis: Castelao, Gholam-Rezaee, Rivera, Ching-López, Milaneschi

Obtained funding: Preisig, Eap

Administrative, technical, and material support: Preisig, Rivera, Milaneschi

Study supervision: Preisig and Eap.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.03.031.

References

WHO WMH-CIDI, 2015. The World Health Organization World Mental Health Composite International Diagnostic Interview.

Afari, N., Noonan, C., Goldberg, J., Roy-Byrne, P., Schur, E., Golnari, G., Buchwald, D., 2010. Depression and obesity: do shared genes explain the relationship? Depress Anxiety 27, 799–806.

Altarejos, J.Y., Goebel, N., Conkright, M.D., Inoue, H., Xie, J., Arias, C.M., Sawchenko, P.E., Montminy, M., 2008. The Creb1 coactivator Crtc1 is required for energy balance and fertility. Nat. Med. 14, 1112–1117.

Altarejos, J.Y., Montminy, M., 2011. CREB and the CRTC co-activators: sensors for hormonal and metabolic signals. Nat. Rev. Mol. Cell Biol. 12, 141–151.

Blaine, B., 2008. Does depression cause obesity?: A meta-analysis of longitudinal studies of depression and weight control. J. Health Psychol. 13, 1190–1197.

Boomsma, D.I., de Geus, E.J., Vink, J.M., Stubbe, J.H., Distel, M.A., Hottenga, J.J., Posthuma, D., van Beijsterveldt, T.C., Hudziak, J.J., Bartels, M., Willemsen, G., 2006. Netherlands Twin Register: from twins to twin families. Twin Res. Hum. Genet. 9, 849–857.

Breuillaud, L., Halfon, O., Magistretti, P.J., Pralong, F.P., Cardinaux, J.R., 2009. Mouse fertility is not dependent on the CREB coactivator Crtc1. Nat. Med. 15, 989–990.

Breuillaud, L., Rossetti, C., Meylan, E.M., Merinat, C., Halfon, O., Magistretti, P.J., Cardinaux, J.R., 2012. Deletion of CREB-regulated transcription coactivator 1 induces pathological aggression, depression-related behaviors, and neuroplasticity genes dysregulation in mice. Biol. Psychiatry 72, 528–536.

Choong, E., Quteineh, L., Cardinaux, J.R., Gholam-Rezaee, M., Vandenberghe, F., Dobrinas, M., Bondolfi, G., Etter, M., Holzer, L., Magistretti, P., Von Gunten, A., Preisig, M., Vollenweider, P., Consortium, T.G., team, T.O., Beckmann, J.S., Pralong, F.P., Waeber, G., Kutalik, Z., Conus, P., Bochud, M., Eap, C.B., 2013. Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and in the general adult population. Jama Psychiatry 70, 1011–1019.

Cohen-Woods, S., Gaysina, D., Craddock, N., Farmer, A., Gray, J., Gunasinghe, C., Hoda, F., Jones, L., Knight, J., Korszun, A., Owen, M.J., Sterne, A., Craig, I.W., McGuffin, P., 2009. Depression Case Control (DeCC) Study fails to support involvement of the muscarinic acetylcholine receptor M2 (CHRM2) gene in recurrent major depressive disorder. Hum. Mol. Genet 18, 1504–1509.

Comings, D.E., Gade, R., MacMurray, J.P., Muhleman, D., Peters, W.R., 1996. Genetic variants of the human obesity (OB) gene: association with body mass index in young women, psychiatric symptoms, and interaction with the dopamine D2 receptor (DRD2) gene. Mol. Psychiatry 1, 325–335.

Conkright, M.D., Canettieri, G., Screaton, R., Guzman, E., Miraglia, L., Hogenesch, J.B., Montminy, M., 2003. TORCs: transducers of regulated CREB activity. Mol. Cell 12, 413–423.

Elks, C.E., Perry, J.R., Sulem, P., Chasman, D.I., Franceschini, N., He, C., Lunetta, K.L., Visser, J.A., Byrne, E.M., Cousminer, D.L., Gudbjartsson, D.F., Esko, T., Feenstra, B., Hottenga, J.J., Koller, D.L., Kutalik, Z., Lin, P., Mangino, M., Marongiu, M., McArdle, P.F., Smith, A.V., Stolk, L., van Wingerden, S.H., Zhao, J.H., Albrecht, E., Corre, T., Ingelsson, E., Hayward, C., Magnusson, P.K., Smith, E.N., Ulivi, S., Warrington, N.M., Zgaga, L., Alavere, H., Amin, N., Aspelund, T., Bandinelli, S., Barroso, I., Berenson, G.S., Bergmann, S., Blackburn, H., Boerwinkle, E., Buring, J. E., Busonero, F., Campbell, H., Chanock, S.J., Chen, W., Cornelis, M.C., Couper, D., Coviello, A.D., d'Adamo, P., De Faire, U., De Geus, E.J., Deloukas, P., Doring, A., Smith, G.D., Easton, D.F., Eiriksdottir, G., Emilsson, V., Eriksson, J., Ferrucci, L., Folsom, A.R., Foroud, T., Garcia, M., Gasparini, P., Geller, F., Gieger, C., Gudnason, V., Hall, P., Hankinson, S.E., Ferreli, L., Heath, A.C., Hernandez, D.G., Hofman, A., Hu, F.B., Illig, T., Jarvelin, M.R., Johnson, A.D., Karasik, D., Khaw, K.T., Kiel, D.P., Kilpelainen, T.O., Kolcic, I., Kraft, P., Launer, L.J., Laven, J.S., Li, S., Liu, J., Levy, D., Martin, N.G., McArdle, W.L., Melbye, M., Mooser, V., Murray, J.C., Murray, S.S., Nalls, M.A., Navarro, P., Nelis, M., Ness, A.R., Northstone, K., Oostra, B.A., Peacock, M., Palmer, L.J., Palotie, A., Pare, G., Parker, A.N., Pedersen, N.L., Peltonen, L., Pennell, C.E., Pharoah, P., Polasek, O., Plump, A.S., Pouta, A., Porcu, E., Rafnar, T., Rice, J.P., Ring, S.M., Rivadeneira, F., Rudan, I., Sala, C., Salomaa, V., Sanna, S., Schlessinger, D., Schork, N.J., Scuteri, A., Segre, A.V., Shuldiner, A.R., Soranzo, N., Sovio, U., Srinivasan, S.R., Strachan, D.P., Tammesoo, M.L., Tikkanen, E., Toniolo, D., Tsui, K., Tryggvadottir, L., Tyrer, J., Uda, M., van Dam, R.M., van Meurs, J.B., Vollenweider, P., Waeber, G., Wareham, N.J., Waterworth, D.M., Weedon, M.N., Wichmann, H.E., Willemsen, G., Wilson, J.F., Wright, A.F., Young, L., Zhai, G., Zhuang, W.V., Bierut, L.J., Boomsma, D.I., Boyd, H.A., Crisponi, L., Demerath, E. W., van Duijn, C.M., Econs, M.J., Harris, T.B., Hunter, D.J., Loos, R.J., Metspalu, A., Montgomery, G.W., Ridker, P.M., Spector, T.D., Streeten, E.A., Stefansson, K., Thorsteinsdottir, U., Uitterlinden, A.G., Widen, E., Murabito, J.M., Ong, K.K., Murray, A., 2010. Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. Nat. Genet. 42, 1077–1085.

Farmer, A., Breen, G., Brewster, S., Craddock, N., Gill, M., Korszun, A., Maier, W., Middleton, L., Mors, O., Owen, M., Perry, J., Preisig, M., Rietschel, M., Reich, T., Jones, L., Jones, I., McGuffin, P., 2004. The Depression Network (DeNT) Study: methodology and sociodemographic characteristics of the first 470 affected sibling pairs from a large multi-site linkage genetic study. BMC Psychiatry 4, 42.

Farmer, A., Korszun, A., Owen, M.J., Craddock, N., Jones, L., Jones, I., Gray, J., Williamson, R.J., McGuffin, P., 2008. Medical disorders in people with recurrent depression. Br. J. Psychiatry 192, 351–355.
Farmer, A., Korszun, A., Owen, M.J., Craddock, N., Jones, L., Jones, I., Gray, J., Williamson, R.J., McGuffin, P., 2008. Medical disorders in people with recurrent depression. Br. J. Psychiatry 192, 351–355.
Forty, L., Ulanova, A., Jones, L., Jones, I., Gordon-Smith, K., Fraser, C., Farmer, A., McGuffin, P., Lewis, C.M., Hosang, G.M., Rivera, M., Craddock, N., 2014. Comorbid medical illness in bipolar disorder. Br. J. Psychiatry 205, 465–472.
Frayling, T.M., Timpson, N.J., Weedon, M.N., Zeggini, E., Freathy, R.M., Lindgren, C.M., Perry, J.R., Elliott, K.S., Lango, H., Rayner, N.W., Shields, B., Harries, L.W., Barrett, J.C., Ellard, S., Groves, C.J., Knight, B., Patch, A.M., Ness, A.R., Ebrahim, S., Lawlor, D.A., Ring, S.M., Ben-Shlomo, Y., Jarvelin, M.R., Sovio, U., Bennett, A.J., Melzer, D., Ferrucci, L., Loos, R.J., Barroso, I., Wareham, N.J., Karpe, F., Owen, K.R., Cardon, L. R., Walker, M., Hitman, G.A., Palmer, C.N., Doney, A.S., Morris, A.D., Smith, G.D., Hattersley, A.T., McCarthy, M.I., 2007. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316, 889–894.
Gebhardt, S., Haberhausen, M., Heinzel-Gutenbrunner, M., Gebhardt, N., Remschmidt, H., Krieg, J.C., Hebebrand, J., Theisen, F.M., 2009. Antipsychotic-induced body weight gain: predictors and a systematic categorization of the long-term weight course. J. Psychiatry Res. 43, 620–626.
Hung, C.F., Breen, G., Czamara, D., Corre, T., Wolf, C., Kloiber, S., Bergmann, S., Craddock, N., Gill, M., Holsboer, F., Jones, L., Jones, I., Korszun, A., Kutalik, Z., Lucae, S., Maier, W., Mors, O., Owen, M.J., Rice, J., Rietschel, M., Uher, R., Vollenweider, P., Waeber, G., Craig, I.W., Farmer, A.E., Lewis, C.M., Muller-Myhsok, B., Preisig, M., McGuffin, P., Rivera, M., 2015. A genetic risk score combining 32 SNPs is associated with body mass index and improves obesity prediction in people with major depressive disorder. BMC Med. 13, 86.
Hung, C.F., Rivera, M., Craddock, N., Owen, M.J., Gill, M., Korszun, A., Maier, W., Mors, O., Preisig, M., Rice, J.P., Rietschel, M., Jones, L., Middleton, L., Aitchison, K. J., Davis, O.S., Breen, G., Lewis, C., Farmer, A., McGuffin, P., 2014. Relationship between obesity and the risk of clinically significant depression: Mendelian randomisation study. Br J. Psychiatry 205, 24–28.
Kim, S.F., Huang, A.S., Snowman, A.M., Teuscher, C., Snyder, S.H., 2007. Antipsychotic drug-induced weight gain mediated by histamine H 1 receptor-linked activation of hypothalamic AMP-kinase. PNAS 104, 3456–3459.
Kovacs, K.A., Steullet, P., Steinmann, M., Do, K.Q., Magistretti, P.J., Halfon, O., Cardinaux, J.R., 2007. TORC1 is a calcium- and cAMP-sensitive coincidence detector involved in hippocampal long-term synaptic plasticity. Proc. Natl. Acad. Sci. USA 104, 4700–4705.
Lewis, C.M., Ng, M.Y., Butler, A.W., Cohen-Woods, S., Uher, R., Pirlo, K., Weale, M.E., Schosser, A., Paredes, U.M., Rivera, M., Craddock, N., Owen, M.J., Jones, L., Jones, I., Korszun, A., Aitchison, K.J., Shi, J., Quinn, J.P., Mackenzie, A., Vollenweider, P., Waeber, G., Heath, S., Lathrop, M., Muglia, P., Barnes, M.R., Whittaker, J.C., Tozzi, F., Holsboer, F., Preisig, M., Farmer, A.E., Breen, G., Craig, I.W., McGuffin, P., 2010. Genome-wide association study of major recurrent depression in the U.K. population. Am J. Psychiatry 167, 949–957.
Luppino, F.S., de Wit, L.M., Bouvy, P.F., Stijnen, T., Cuijpers, P., Penninx, B.W., Zitman, F.G., 2010. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch. Gen. Psychiatry 67, 220–229.
Marques-Vidal, P., Bochud, M., Mooser, V., Paccaud, F., Waeber, G., Vollenweider, P., 2009. Obesity markers and estimated 10-year fatal cardiovascular risk in Switzerland. Nutr. Metab. Cardiovasc Dis. 19, 462–468.
Mastronardi, C., Paz-Filho, G.J., Valdez, E., Maestre-Mesa, J., Licinio, J., Wong, M.L., 2011. Long-term body weight outcomes of antidepressant-environment interactions. Mol. Psychiatry 16, 265–272.
McGuffin, P., Katz, R., Aldrich, J., 1986. Past and present state examination: the assessment of'lifetime ever' psychopathology. Psychol. Med. 16, 461–465.
McGuffin, P., Knight, J., Breen, G., Brewster, S., Boyd, P.R., Craddock, N., Gill, M., Korszun, A., Maier, W., Middleton, L., Mors, O., Owen, M.J., Perry, J., Preisig, M., Reich, T., Rice, J., Rietschel, M., Jones, L., Sham, P., Farmer, A.E., 2005. Whole genome linkage scan of recurrent depressive disorder from the depression network study. Hum. Mol. Genet. 14, 3337–3345.
Milaneschi, Y., Lamers, F., Mbarek, H., Hottenga, J.J., Boomsma, D.I., Penninx, B.W., 2014. The effect of FTO rs9939609 on major depression differs across MDD subtypes. Mol. Psychiatry 19, 960–962.
Minokoshi, Y., Alquier, T., Furukawa, N., Kim, Y.B., Lee, A., Xue, B., Mu, J., Foufelle, F., Ferre, P., Birnbaum, M.J., Stuck, B.J., Kahn, B.B., 2004. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. Nature 428, 569–574.
Nurnberger Jr., J.I., Blehar, M.C., Kaufmann, C.A., York-Cooler, C., Simpson, S.G., Harkavy-Friedman, J., Severe, J.B., Malaspina, D., Reich, T., 1994. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch. Gen. Psychiatry 51, 849–859.
Penninx, B.W., Beekman, A.T., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., Cuijpers, P., De Jong, P.J., Van Marwijk, H.W., Assendelft, W.J., Van Der Meer, K., Verhaak, P., Wensing, M., De Graaf, R., Hoogendijk, W.J., Ormel, J., Van Dyck, R., Consortium, N.R., 2008. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. Int. J. Methods Psychiatr. Res. 17, 121–140.
Preisig, M., Fenton, B.T., Matthey, M.L., Berney, A., Ferrero, F., 1999. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of the French version. Eur. Arch. Psychiatry Clin. Neurosci. 249, 174–179.
Preisig, M., Waeber, G., Vollenweider, P., Bovet, P., Rothen, S., Vandeleur, C., Guex, P., Middleton, L., Waterworth, D., Mooser, V., Tozzi, F., Muglia, P., 2009. The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. BMC Psychiatry 9, 9.
Prentice, A.M., Jebb, S.A., 2001. Beyond body mass index. Obes. Rev. 2, 141–147.
Qi, L., Kang, K., Zhang, C., van Dam, R.M., Kraft, P., Hunter, D., Lee, C.H., Hu, F.B., 2008. Fat mass-and obesity-associated (FTO) gene variant is associated with obesity: longitudinal analyses in two cohort studies and functional test. Diabetes 57, 3145–3151.
Rivera, M., Cohen-Woods, S., Kapur, K., Breen, G., Ng, M.Y., Butler, A.W., Craddock, N., Gill, M., Korszun, A., Maier, W., Mors, O., Owen, M.J., Preisig, M., Bergmann, S., Tozzi, F., Rice, J., Rietschel, M., Rucker, J., Schosser, A., Aitchison, K.J., Uher, R., Craig, I.W., Lewis, C.M., Farmer, A.E., McGuffin, P., 2012. Depressive disorder moderates the effect of the FTO gene on body mass index. Mol. Psychiatry 17, 604–611.
Rosenbaum, M., Nicolson, M., Hirsch, J., Heymsfield, S.B., Gallagher, D., Chu, F., Leibel, R.L., 1996. Effects of gender, body composition, and menopause on plasma concentrations of leptin. J. Clin. Endocrinol. Metab. 81, 3424–3427.
Samaan, Z., Anand, S.S., Zhang, X., Desai, D., Rivera, M., Pare, G., Thabane, L., Xie, C., Gerstein, H., Engert, J.C., Craig, I., Cohen-Woods, S., Mohan, V., Diaz, R., Wang, X., Liu, L., Corre, T., Preisig, M., Kutalik, Z., Bergmann, S., Vollenweider, P., Waeber, G., Yusuf, S., Meyre, D., 2013. The protective effect of the obesity-associated rs9939609A variant in fat mass- and obesity-associated gene on depression. Mol. Psychiatry 18, 1281–1286.
Scuteri, A., Sanna, S., Chen, W.M., Uda, M., Albai, G., Strait, J., Najjar, S., Nagaraja, R., Orru, M., Usala, G., Dei, M., Lai, S., Maschio, A., Busonero, F., Mulas, A., Ehret, G. B., Fink, A.A., Weder, A.B., Cooper, R.S., Galan, P., Chakravarti, A., Schlessinger, D., Cao, A., Lakatta, E., Abecasis, G.R., 2007. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet. 3, 1200–1210.
Sham, P.C., Sterne, A., Purcell, S., Cherny, S., Webster, M., Rijsdijk, F., Asherson, P., Ball, D., Craig, I., Eley, T., Goldberg, D., Gray, J., Mann, A., Owen, M., Plomin, R., 2000. GENESiS: creating a composite index of the vulnerability to anxiety and depression in a community-based sample of siblings. Twin Res. 3, 316–322.
Uher, R., Huezo-Diaz, P., Perroud, N., Smith, R., Rietschel, M., Mors, O., Hauser, J., Maier, W., Kozel, D., Henigsberg, N., Barreto, M., Placentino, A., Dernovsek, M.Z., Schulze, T.G., Kalember, P., Zobel, A., Czerski, P.M., Larsen, E.R., Souery, D., Giovannini, C., Gray, J.M., Lewis, C.M., Farmer, A., Aitchison, K.J., McGuffin, P., Craig, I., 2009. Genetic predictors of response to antidepressants in the GENDEP project. Pharm. J. 9, 225–233.
Willemsen, G., de Geus, E.J., Bartels, M., van Beijsterveldt, C.E., Brooks, A.I., Estourgie-van Burk, G.F., Fugman, D.A., Hoekstra, C., Hottenga, J.J., Kluft, K., Meijer, P., Montgomery, G.W., Rizzu, P., Sondervan, D., Smit, A.B., Spijker, S., Suchiman, H.E., Tischfield, J.A., Lehner, T., Slagboom, P.E., Boomsma, D.I., 2010. The Netherlands Twin Register biobank: a resource for genetic epidemiological studies. Twin Res. Hum. Genet. 13, 231–245.
Wing, J.K., Babor, T., Brugha, T., Burke, J., Cooper, J.E., Giel, R., Jablenski, A., Regier, D., Sartorius, N., 1990. SCAN. Schedules for clinical assessment in neuropsychiatry. Arch. Gen. Psychiatry 47, 589–593.
Wu, Z., Huang, X., Feng, Y., Handschin, C., Gullicksen, P.S., Bare, O., Labow, M., Spiegelman, B., Stevenson, S.C., 2006. Transducer of regulated CREB-binding proteins (TORCs) induce PGC-1alpha transcription and mitochondrial biogenesis in muscle cells. Proc. Natl. Acad. Sci. USA 103, 14379–14384.

Prediction of early weight gain during psychotropic treatment using a combinatorial model with clinical and genetic markers

Frederik Vandenberghe[a], Núria Saigí-Morgui[a], Aurélie Delacrétaz[a], Lina Quteineh[a], Séverine Crettol[a], Nicolas Ansermot[a], Mehdi Gholam-Rezaee[b], Armin von Gunten[c], Philippe Conus[d] and Chin B. Eap[a,e]

Background **Psychotropic drugs can induce significant (>5%) weight gain (WG) already after 1 month of treatment, which is a good predictor for major WG at 3 and 12 months. The large interindividual variability of drug-induced WG can be explained in part by genetic and clinical factors.**

Aim **The aim of this study was to determine whether extensive analysis of genes, in addition to clinical factors, can improve prediction of patients at risk for more than 5% WG at 1 month of treatment.**

Methods **Data were obtained from a 1-year naturalistic longitudinal study, with weight monitoring during weight-inducing psychotropic treatment. A total of 248 Caucasian psychiatric patients, with at least baseline and 1-month weight measures, and with compliance ascertained were included. Results were tested for replication in a second cohort including 32 patients.**

Results **Age and baseline BMI were associated significantly with strong WG. The area under the curve (AUC) of the final model including genetic (18 genes) and clinical variables was significantly greater than that of the model including clinical variables only (AUC_{final}: 0.92, $AUC_{clinical}$: 0.75, $P < 0.0001$). Predicted accuracy increased by 17% with genetic markers ($Accuracy_{final}$: 87%), indicating that six patients must be genotyped to avoid one misclassified patient. The validity of the final model was confirmed in a replication cohort. Patients predicted before treatment as having more than 5% WG after 1 month of treatment had 4.4% more WG over 1 year than patients predicted to have up to 5% WG ($P \leq 0.0001$).**

Conclusion **These results may help to implement genetic testing before starting psychotropic drug treatment to identify patients at risk of important WG.** ***Pharmacogenetics and Genomics*** **00:000–000** **Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.**

Pharmacogenetics and Genomics 2016, **00**:000–000

Keywords: atypical antipsychotics, genetic risk prediction, mirtazapine, mood stabilizers, weight gain, weight monitoring

[a]Unit of Pharmacogenetics and Clinical Psychopharmacology, Department of Psychiatry, Centre for Psychiatric Neuroscience, [b]Department of Psychiatry, Center for Psychiatric Epidemiology and Psychopathology, [c]Department of Psychiatry, Service of Old Age Psychiatry, [d]Department of Psychiatry, Service of General Psychiatry, Lausanne University Hospital, Hospital of Cery, Prilly and [e]Department of Pharmaceutical Sciences, School of Pharmacy, University of Geneva, University of Lausanne, Geneva, Switzerland

Correspondence to Chin B. Eap, PhD, Hospital of Cery, 1008 Prilly, Lausanne, Switzerland
Tel: +41 21 314 26 04; fax: +41 21 31424 44; e-mail: chin.eap@chuv.ch

Received 26 June 2016 **Accepted** 16 September 2016

Introduction

Overweight and obesity are major public health problems of the current decade, with a prevalence of obesity (BMI $\geq 30\ kg/m^2$) in the general population ranging from 20 to 23% in Europe [1] and reaching 35% in the US [2]. In the psychiatric population, an even higher prevalence of obesity is reported, reaching 49 and 55% for bipolar and schizophrenic patients, respectively [3]. In line with obesity-related problems, the psychiatric population have a quadrupled and doubled incidence of type 2 diabetes mellitus (T2DM) and hypertension, respectively, compared with healthy controls [4]. This high prevalence of metabolic disorders can be explained, in addition to the effects of the psychiatric illness itself, by the use of psychotropic drugs such as most atypical and also some classical antipsychotics, mood stabilizers (e.g. valproate and lithium), and some antidepressants (e.g. mirtazapine) known to induce significant weight gain (WG) [5,6]. The exact mechanism of psychotropic-induced weight gain (PIWG) is only partially understood, although several clinical and individual factors have been shown to be associated, such as sex (women being at higher risk than men), low baseline BMI, young age, first episode, or non-Caucasian ethnicities [5,7–9].

Genetic associations with BMI have been investigated widely in general as well as in psychiatric populations. Currently, genome-wide association studies (GWAS) have highlighted 32 single-nucleotide polymorphism (SNPs) associated with BMI in cohorts of up to 240 000 patients [10]. However, despite the increasing number of

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (*www.pharmacogeneticsandgenomics.com*).

Previously presented in part at the 168th annual meeting of the American Psychiatric Association, 16–20 May 2015, Toronto, Canada.

Previously presented in part at the 12th World Congress of Biological Psychiatry, 14–18 June 2015, Athens, Greece.

1744-6872 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/FPC.0000000000000249

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

SNPs discovered, the explained BMI variance in the general population remains low (1.45%), reflecting the complexity of mechanisms implicated in WG and the concomitant involvement of many environmental factors [10]. With respect to psychiatric patients, a high inter-individual variability of PIWG is also observed and may be explained in part by genetic variability. Thus, PIWG was found to be heritable as shown in a study including siblings [11]. In addition, several SNPs were found to be associated with PIWG, suggesting that there are, similar to the general population, many genetic contributions to WG. Because second-generation antipsychotics interact with serotonin and dopamine systems, several candidate gene studies were carried out on SNPs located in *serotonin HT_{2C} receptor*, *dopamine D_2 receptor*, or *histamine H_1 receptor* genes [12]. Some discrepant results were published, which can be explained by methodological issues such as a lack of multiple testing correction, population stratification, insufficient sample size, or inappropriate statistical analysis [13]. However, promising results were obtained for other genes [12,14], which may contribute toward the understanding of PIWG mechanisms. Indeed, SNPs located in *CRTC1*, *PCK1*, *MCHR2*, *and HSD11β1* genes were found to be associated with BMI and replicated in three psychiatric cohorts [14–17]. Although some of these SNPs were associated significantly with BMI in general population-based cohorts, effect sizes were higher in psychiatric cohorts, suggesting an important interaction between gene and environmental factors (e.g. psychiatric illness, pharmacological treatment, and lifestyle).

WG can be fast and may occur during the first month of treatment, underlining the importance of monitoring metabolic parameters directly when the drug is introduced and on a regular basis during treatment. Predictive calculations carried out during clinical trials have shown that patients with a rapid WG during the first month of treatment are at a higher risk of having a more significant WG in the long-term [18–20]. Furthermore, we recently showed that more than 5% WG during the first month of treatment is a good predictor for major WG at 3 (>15%) and 12 months (>20%), irrespective of the WG-inducing psychotropic drug prescribed [21]. However, detection of patients at high risk for early WG, even before the start of the psychotropic treatment, would be of high clinical relevance for a personalized prescription. In the present study, we sought to determine, in a psychiatric cohort with compliance ascertained by therapeutic drug monitoring, how clinical risk factors combined with an extensive analysis of genes previously identified to be associated with BMI using GWAS or candidate gene approaches may enable detection of patients at risk for more than 5% WG after 1 month of psychotropic drug treatment. The results obtained were then tested for replication in a second independent psychiatric cohort.

Methods

Patient selection

Patients were selected from a previously published longitudinal observational study on the basis of our clinical guideline requiring a metabolic follow-up after starting with or switching to clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, lithium, valproate, and/or mirtazapine [22]. Detailed patient selection criteria have been previously published [21], with the exception of the criteria mentioned below. Patients were included in the analysis only when compliance was confirmed by therapeutic drug monitoring at the 1-month visit [or at 3 months if no plasma was available at 1 month ($n=40$)], with a minimal follow-up duration of 1 month and with Caucasian ethnicity. Patients were considered compliant when drug plasma concentrations were higher than 10% of the lower value of the recommended therapeutic range [23].

Because of the naturalistic design of the study, the 1-month visit could be performed at variable times, but only data from patients with a visit between 15 and 45 days were retained. All clinical chemistry parameters were determined on plasma samples drawn in the morning under fasting conditions as published previously [21].

Patients from the discovery cohort were included between 1 January 2007 and 8 April 2013. Ethnicity was assessed by patient's reported ethnicity and confirmed by genotyping using principal component analysis with the EIGENSTRAT algorithm implemented in GCTA software [24]. The majority of the variance was explained by the two first vectors, and Caucasian ethnicity was arbitrarily selected when pca1 less than 0.005 and pca2 at least 0.02, values that yielded the highest concordance with the patient's reported ethnicity (see Supplementary Fig., Supplemental digital content 1, *http://links.lww.com/FPC/B89*).

The replication cohort was composed of patients included from 9 April 2013 to 1 December 2014. No principal component analysis could be carried out on these patients; thus, ethnicity was based on the patient's reported ethnicity.

The study was approved by the Ethics Committee of the Lausanne University Hospital and written informed consent for genetic analysis was obtained from all participants.

SNP selection and genotyping

Twenty-three SNPs significantly associated with T2DM (GWAS-T2DM; $P<5\times10^{-8}$) and 32 SNPs significantly associated with BMI (GWAS-BMI; $P<5\times10^{-8}$), discovered by a GWAS approach in the general population samples, were included [10,25]. Finally, 34 SNPs selected from a literature review investigating antipsychotic induced WG during the first 3 months of treatment were

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

also included if published *P*-values were lower than 0.1 (see Supplementary Table, Supplemental digital content 2, *http://links.lww.com/FPC/B90*).

Genomic DNA was extracted from EDTA blood samples using the FlexiGene DNA extraction kit (Qiagen, Hombrechtikon, Switzerland) according to the manufacturer's protocol. All patients from the discovery cohort were genotyped on a MetaboChip array and processed on an iScan equipped platform (Illumina, San Diego, California, USA). Only SNPs of interest (i.e. from genes previously identified to be associated with BMI and T2DM using GWAS or candidate gene approaches) were included in the present study. Quality control of the SNPs investigated was assessed by the call rate (>96%), GenCall score (>0.15), and matched sex. SNPs were extracted from the database using GenomeStudio software (version 2011.1; Illumina).

Patients included in the replication cohort were genotyped by KBioscience Institute in the UK using the fluorescence-based competitive allele-specific PCR technology (KASP, Teddington, Middlesex, UK). Details on this technology are available at: *http://www.lgcgenomics.com/genotyping/kasp-genotyping-chemistry*.

Predictive models

Logistic regression analyses were carried out to investigate the influence of the selected SNPs on early WG. To facilitate the understanding of the calculated odd ratios, age, illness duration, and baseline BMI were categorized by each 10 years (age/10, years/10, and BMI/10, respectively). Because of a small number and an unequal distribution (noninterventional study) of each psychotropic medication, drugs were categorized as having low (amisulpride, aripiprazole), medium (quetiapine, risperidone, lithium, mirtazapine), and high (clozapine, olanzapine, and valproate) potential for inducing WG. SNPs, coded as having an additive effect, were considered in the logistic model through a step-wise model selection on the basis of Akaike Information Criterion (AIC), which minimizes the distance between the fitted and the true model if such a model exists [26]. Some variables were not significantly influential on the dependent variable (>5% WG), but we retained them in the model as advised by the AIC to improve the general quality of the fitted model. Receiver operating characteristic (ROC) analyses were used to compare the predictive power of a model including only clinical (and demographic) data with a model containing both clinical and genetic data [27]. The area under the curve (AUC) of a ROC curve summarizes the probabilities that the model will correctly classify a patient with more than 5% WG as a positive case and inversely a patient with lesser than or equal to 5% WG as a negative case. An ideal test will yield an AUC of 1 and a random test will yield an AUC of 0.5, a test with an AUC of 0.75 being considered as informative enough and useful [28]. AUCs of the different models were compared using a bootstrap test as published previously (P_{AUC}) [29]. Besides AUC tests, likelihood ratio tests were used to compare the model including only the clinical variables (nested model) and the model containing clinical and selected SNPs (P_{LRT}). Median and 95th percentiles (95th) of accuracy (percentage of correctly classified cases among all patients), specificity (percentage of correctly predicted patients with ≤5% WG among all patients with ≤5% WG in reality), sensitivity (percentage of correctly predicted patients with >5% WG among all patients with >5% WG), negative predictive value (NPV, percentage of patients with ≤5% WG among patients who were predicted a ≤5% WG), positive predictive value (PPV, percentage of patients with >5% WG among patients who were predicted a >5% WG), and AUC were determined using 10 000 bootstraps. Because the *P*-value is influenced by the sample size, and thus in the present case by the number of bootstraps, accuracy, specificity, sensitivity, PPV, and NPV were considered different if their median values lay outside the 95th range of the compared group. *P*-values were not corrected for multiple testing because SNPs were selected on an a priori basis and the AIC method was used to fit the best model. Because of the small sample size, no subanalyses were carried out for each medication or demographic parameters (e.g. sex, age).

Replication analysis

The statistical model developed on the discovery cohort was used to predict more than 5% WG. To compare the model performance, predictive statistics obtained in the replication cohort were compared with the previous model.

Evolution of weight over 1 year

To explore the evolution of WG over 1 year between patients with an observed or a predicted up to 5% WG and more than 5% WG, a Generalized Additive Mixed Model (GAMM) was fitted on the discovery and replication cohort combined together. To be more robust in inferences, a linear mixed-effect model was also fitted on the same data to reinforce the results of GAMM.

Observations made at 1–3, 6, 9, and 12 months were used to fit the model. Predictions made by the final model including both clinical and genetic variables were used to construct the grouping variable. The effect of time on WG was not considered linear, but was better represented by a smooth semiparametric curve (with cubic regression spline basis). GAMMs were fitted separately for each subgroup (>5% WG and ≤5% WG) to provide the possibility of capturing the WG trend without restraint at each subgroup (otherwise, a parallel trend in time would have been imposed on all subgroups). These models were not adjusted for multiple comparisons, covariates, or cofactors as they were used only to explore the data and the adequacy of the final model.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Afterwards, confirmatory analyses were carried out by fitting a linear mixed-effect model ['nlme' package of R [30]] adjusted for age, sex, time, and baseline BMI. The fitted linear mixed-effect model [31] had a random effect at the patient level. To be more robust in inferences, a bootstrap analysis [32] 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 for residuals). Results were based on 10 000 bootstrap replicates at the patient level (patients were considered to be independently recruited) and increasing the number of bootstraps did not influence the uncertainty of estimated parameters considerably.

Evaluation of the benefit of pharmacogenetic screening

The number needed to genotype, defined as the number of patients to genotype to detect one misclassified case by using only clinical information, was determined [33]. The calculation method is based on the inverse of the difference between the accuracy of the model including both clinical and genetic data and the accuracy of the model including clinical data only.

All tests were two sided and *P*-values up to 0.05 were considered statistically significant. All statistical analyses were carried out using R software (version 2.15.2; Teddington, Middlesex, UK).

Results

Demographics of the discovery cohort

A total of 248 patients were included (see Supplementary Fig., Supplemental digital content 3, *http://links.lww.com/FPC/B91*); of these, 190 patients were present in the previously published study on the less than 5% threshold as a predictor of long-term WG [21] and 58 additional patients also corresponding to the present inclusion criteria. At baseline, 22% of the patients were overweight (25–30 kg/m^2) and 14% were obese (≥30 kg/m^2). Patients with a more than 5% WG after 1 month of treatment (56/248, 23%) were significantly younger [median (interquartile range (IQR): 38 (27) years] than patients with up to 5% WG [49 (45) years, $P=0.03$, Table 1], in agreement with young age being a risk factor for important WG [9]. A lower prevalence of obese patients was observed in the group of more than 5% WG (5 vs. 16%, $P=0.05$), in agreement with the literature in which a low BMI has been reported to be a risk factor for important WG [7] and inversely there were fewer patients with initial BMI less than 25 kg/m^2 among the up to 5% WG than among the more than 5% WG patients (60 vs. 79%, $P=0.01$). Abdominal obesity and hypo HDL-cholesterolemia were more prevalent in the up to 5% WG group. No significant differences in other demographic variables were found between the two groups. Psychotic disorders [(F200–F249) and (F28–F29)] were the most frequent diagnosis (31%) and risperidone was the most frequently prescribed psychotropic drug (40%). A higher increase in triglycerides and decrease in HDL-cholesterol between up to 5% WG and 5% WG patients were observed between baseline and 3 months [median (IQR) Δmmol/l triglycerides: 0.1 (0.6) vs. 0.3 (1.1), $P=0.04$; Δmmol/l HDL-cholesterol: 0 (0.3) vs. −0.1 (0.2), $P=0.03$] as well as between baseline and 12 months [Δmmol/l triglycerides: −0.1 (0.5) vs. 1.3 (3), $P\leq0.001$; Δmmol/l HDL-cholesterol: −0.1 (0.3) vs. −0.3 (0.4), $P=0.005$]. Further details are presented in Table 1.

Genotyping results

Proxy ($r^2>0.75$) were searched for 20 SNPs that were not available in the MetaboChip (Teddington, Middlesex, UK) (for each missing SNP, a proxy was found). Two SNPs from GWAS-T2DM, one SNP from the GWAS-BMI, and three SNPs from the gene candidate studies deviated from Hardy–Weinberg equilibrium and were excluded from further analysis (see Supplementary Table, Supplemental digital content 2, *http://links.lww.com/FPC/B90*, which are presented in bold). The minor allele frequencies ranged from 3 to 49% and were in agreement with the 1000 Genome Project Phase 1 (data not shown).

Multivariate analysis and prediction model

Clinical model

Low baseline BMI was a significant risk factor for more than 5% WG. No significant associations were observed between age, illness duration, polymedication, sex, and the type of newly prescribed psychotropic drug and more than 5% WG at 1 month (Table 2, left column).

Genetic models

GWAS-T2DM SNPs: four of the 21 SNPs were retained after AIC selection. None of the SNPs selected were associated significantly with WG at 1 month (see Supplementary Table, Supplemental digital content 4, *http://links.lww.com/FPC/B92*). As presented in Table 3, inclusion of these four SNPs did not increase accuracy and AUC.

GWAS-BMI SNPs: the model based on AIC retained 12 SNPs of the initial set of 31 SNPs. The three most significant SNPs were *ZNF608 rs6864049*, *GPRC5B*, *IQCK rs12444979*, and *TMEM160*, *ZC3H4 rs3810291* (see Supplementary Table, Supplemental digital content 5, *http://links.lww.com/FPC/B93*, which shows all SNPs). AUC increased significantly on including genetic data [$AUC_{clinical}$ (95th) = 0.75 (0.68–0.82), $AUC_{clinical/GWAS}$ (95th) = 0.88 (0.82–0.93), $P_{AUC}=0.0002$]. The Likelihood ratio test between the two models indicated that adding genetic data improved the goodness of fit ($P_{LRT}<0.001$), and thus that the observed difference of AUC might not be driven by a higher number of variables included. The accuracy of the prediction with genetic and clinical data (Table 3) is modestly increased compared with the model

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 1 **Demographic characteristics of the discovery cohort**

	All ($n=248$)	First month weight gain ≤ 5% ($n=192$)	First month weight gain > 5% ($n=56$)	P^a
Age [median (IQR)] (years)	46 (41)	49 (45)	38 (27)	**0.03**
Men [*n*/*N* (%)]	112/248 (45)	84/192 (44)	28/56 (50)	0.4
Smoking [*n*/*N* (%)]	51/107 (48)	41/85 (48)	10/22 (45)	1
Illness duration [median (IQR)] (years)	4 (10)	4 (10)	4 (9)	0.6
One-month visit [median (IQR)] (days)	31 (6)	30 (6)	31 (5)	0.6
One-month weight gain [median (IQR)] (%)	1.4 (5.8)	0 (4)	6.7 (3.2)	**< 0.001**
Metabolic traits prevalence at baseline [*n*/*N* (%)]				
BMI				
< 25 kg/m^2	159/248 (64)	115/192 (60)	44/56 (79)	**0.01**
25–30 kg/m^2	55/248 (22)	46/192 (24)	9/56 (16)	0.3
≥ 30 kg/m^2	34/248 (14)	31/192 (16)	3/56 (5)	**0.05**
Waist circumference (men ≥ 94 cm, women ≥ 80 cm)	112/213 (53)	94/167 (56)	18/46 (39)	**0.05**
HDL-cholestrol (men ≤ 1.03 mmol/l, women ≤ 1.29 mmol/l)	36/151 (24)	32/115 (28)	4/36 (11)	**0.04**
Triglyceridemia ≥ 1.7 mmol/l or lipid-lowering treatment	42/159 (26)	34/122 (28)	8/37 (22)	0.5
Fasting glucose ≥ 5.6 mmol/l or antidiabetic treatment	33/156 (21)	26/119 (22)	7/37 (19)	0.8
Blood pressure ≥ 130/85 mmHg or antihypertensive treatment	35/216 (16)	28/165 (17)	7/51 (14)	0.7
Metabolic syndrome[b]	20/121 (17)	18/91 (20)	2/30 (7)	0.2
Metabolic evolution at 3 months of treatment				
Weight gain [median (IQR)] (%)	3.7 (8.7)	2.6 (7.1)	11 (6.8)	**< 0.001**
Waist circumference [median (IQR)] (Δcm)	3 (9)	2 (9)	7.5 (7.5)	**0.01**
HDL-cholestrol [median (IQR)] (Δmmol/l)	0 (0.3)	0 (0.3)	−0.1 (0.2)	**0.03**
Triglyceridemia, [median (IQR)] (Δmmol/l)	0.1 (0.7)	0.1 (0.6)	0.3 (1.1)	**0.04**
Fasting glucose [median (IQR)] (Δmmol/l)	0 (0.8)	0 (0.8)	0.1 (0.5)	0.5
Metabolic evolution at 12 months of treatment				
Weight gain [median (IQR)] (%)	6.6 (12.5)	5.4 (10.5)	12.8 (16.6)	**0.02**
Waist circumference [median (IQR)] (Δcm)	3 (9)	3 (8)	5 (12)	0.8
HDL-cholestrol [median (IQR)] (Δmmol/l)	−0.2 (0.4)	−0.1 (0.3)	−0.3 (0.4)	**0.005**
Triglyceridemia [median (IQR)] (Δmmol/l)	0.1 (0.8)	−0.1 (0.5)	1.3 (3)	**< 0.001**
Fasting glucose [median (IQR)] (Δmmol/l)	0.2 (0.8)	0 (0.7)	0.6 (1.1)	**0.05**
Diagnosis [*n*/*N* (%)]				
Bipolar disorder	49/248 (20)	41/192 (21)	8/56 (14)	0.3
Depression	39/248 (16)	29/192 (15)	10/56 (18)	0.8
Organic disorders	23/248 (9)	20/192 (10)	3/56 (5)	0.4
Psychotic disorders	76/248 (31)	54/192 (28)	22/56 (39)	0.2
Schizoaffective disorder	18/248 (7)	13/192 (7)	5/56 (9)	0.8
Other	43/248 (17)	35/192 (18)	8/56 (14)	0.6
Medication [*n*/*N* (%)]				
Amisulpride	21/248 (8)	14/192 (7)	7/56 (13)	0.3
Aripiprazole	16/248 (6)	13/192 (7)	3/56 (5)	0.9
Clozapine	17/248 (7)	14/192 (7)	3/56 (5)	0.8
Lithium	18/248 (7)	13/192 (7)	5/56 (9)	0.8
Mirtazapine	15/248 (6)	12/192 (6)	3/56 (5)	1
Olanzapine	29/248 (12)	16/192 (8)	13/56 (23)	**0.005**
Quetiapine	31/248 (13)	25/192 (13)	6/56 (11)	0.8
Risperidone	98/248 (40)	83/192 (43)	15/56 (27)	**0.04**
Valproate	3/248 (1)	2/192 (1)	1/56 (2)	1
Polymedication [*n*/*N* (%)][c]	119/248 (48)	97/192 (51)	22/56 (39)	0.2
Comedication possibly inducing weight gain [*n*/*N* (%)][d]	33/248 (13)	22/192 (11)	11/56 (20)	0.1

HDL, high-density lipoprotein; IDF, intermediate distribution frame; IQR, interquartile range; WG, weight gain.

[a]*P*-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between both groups. Significant ($P<0.05$) and borderline ($P=0.05$-0.1) values are presented in bold.

[b]Metabolic syndrome is present if: presence of central obesity (waist circumference: male ≥ 94 cm, female ≥ 80 cm) and at least two other following factors: triglycerides ≥ 1.7 mmol/l or lipid-lowering treatment; glucose of at least 5.6 mmol/l or type 2 diabetes treatment; blood pressure at least 130/85 mmHg or treatment for hypertension; HDL-cholesterol male up to 1.03 mmol/l, female up to 1.29 mmol/l (IDF definition).

[c]Presence of more than one WG-inducing drug (amisulpride, aripiprazole, clozapine, lithium, mirtazapine, olanzapine, quetiapine, risperidone, valproate).

[d]Exhaustive list: pioglitazone, rosiglitazone, cinnarizine, levocetirizine, chlormadinone, desogestrel, ethinylestradiol, estradiol, gestodene, levonorgestrel, medroxyprogesterone, norelgestromin, carbamazepine, chlorprothixene, clomipramine, flupentixol, mianserine, pregabalin, zuclopenthixol.

with clinical data alone [$\text{Accuracy}_{\text{clinical}}$ (95th) = 70 (54–83), $\text{Accuracy}_{\text{clinical/GWAS}}$ (95th) = 83 (72–90)].

Candidate gene SNPs: 31 SNPs from candidate gene studies were included in the logistic model. After AIC selection, 9 SNPs were retained. The three most significant SNPs were *ADIPOQ rs17300539*, *INSIG2 rs17587100*, and *FAAH rs324420* (see Supplementary Table, Supplemental digital content 6, *http://links.lww.com/FPC/B94*, which shows all SNPs). The nine selected SNPs increased the predictive power significantly [$\text{AUC}_{\text{clinical}}$ (95th) = 0.75 (0.68–0.82), $\text{AUC}_{\text{clinical/candidate gene}}$ (95th) = 0.85 (0.79–0.91), $P_{\text{AUC}}=0.01$]. The Likelihood ratio test confirms that the model containing genetic and clinical data should be preferred to the model including only clinical variables ($P_{\text{LRT}}<0.001$). Despite an increase in AUC, inclusion of genetic data did not increase the accuracy of the prediction.

Final model

Retained SNPs from the candidate gene (nine SNPs) and GWAS-BMI models (12 SNPs) were included together in

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 2 Final logistic model

	Clinical model		Final model	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
Intercept	15.2 (1.8–141)	0.01	0 (0–0.1)	0.003
Personal				
Age (years/10)	1 (0.9–1)	0.2	0.8 (0.6–1)	0.04
Baseline BMI [(kg/m^2)/10]	0.9 (0.8–1)	0.003	0.2 (0.1–0.4)	0.0004
Male	1 (0.5–2)	1	1.1 (0.5–2.5)	0.8
Psychiatric illness				
Schizoaffective vs. psychotic disorders	1.4 (0.4–5.1)	0.6	3 (0.5–16)	0.2
Bipolar vs. psychotic disorders	0.9 (0.3–2.6)	0.9	0.9 (0.3–3)	0.8
Depression vs. psychotic disorders	1.3 (0.5–3.7)	0.6	1.7 (0.5–5.8)	0.4
Organic vs. psychotic disorders	0.5 (0.1–2.6)	0.5	0.5 (0.1–3)	0.4
Other vs. psychotic disorders	0.7 (0.2–1.7)	0.4	0.4 (0.1–1.4)	0.2
Illness duration (years/10)	1 (1–1)	0.9	1.1 (0.7–1.7)	0.7
Medication				
Medium vs. low weight gain inducer[a]	0.5 (0.2–1.3)	0.2	0.3 (0.1–1.1)	0.07
High vs. low weight gain inducer[b]	1.2 (0.4–3.5)	0.7	0.9 (0.3–3.6)	0.9
Polymedication (yes)[c]	0.7 (0.3–1.3)	0.3	0.6 (0.3–1.4)	0.3
Genetic, rs number (risk allele)				
ADIPOQ rs17300539 (G)	–	–	4.9 (1.7–17)	0.007
BDNF rs10835187 (C)	–	–	1.7 (1–3.2)	0.07
DRD2 rs6277 (G)	–	–	1.8 (1–3.2)	0.05
FAAH rs324420 (A)	–	–	3.2 (1.5–7.5)	0.005
GPRC5B, IQCK rs12444979 (T)	–	–	3.5 (1.6–8.3)	0.003
INSIG2 rs17587100 (C)	–	–	5.2 (1.2–33.9)	0.05
LRP1B rs2890652 (C)	–	–	1.8 (0.9–3.9)	0.1
LRRN6C rs10968576 (A)	–	–	1.7 (0.8–3.7)	0.1
MC4R rs10871777 (A)	–	–	1.7 (0.9–3.5)	0.1
MTCH2, NDUFS3, CUGBP1 rs3817334 (C)	–	–	1.7 (0.9–3.2)	0.1
MTHFR rs1801131 (G)	–	–	1.8 (1–3.4)	0.08
NRXN3 rs10150332 (T)	–	–	2.2 (1–5.7)	0.08
PPARG rs2197423 (G)	–	–	3 (1.2–8.7)	0.03
RPL27A, TUB rs11041999 (T)	–	–	1.6 (0.9–3)	0.1
SEC16B rs543874 (G)	–	–	2 (1–4.4)	0.07
SH2B1, APOB48R, SULT1A2, AC138894.2, ATXN2L, TUFM rs7359397 (T)	–	–	1.6 (0.8–3)	0.2
TMEM160, ZC3H4 rs3810291 (G)	–	–	2.2 (1.2–4.3)	0.02
ZNF608 rs6864049 (A)	–	–	2.8 (1.5–5.5)	0.002

CI, confidence interval; OR, odds ratio.
[a]Valproate, mirtazapine, quetiapine, and risperidone versus amisulpride and aripiprazole.
[b]Clozapine, olanzapine, and lithium versus amisulpride and aripiprazole.
[c]Presence of more than one psychotropic-induced weight gain.

one final logistic model. Using the AIC model selection, 18 SNPs were retained in the final model (Table 2, right column see Supplementary Equation, Supplemental digital content 7, *http://links.lww.com/FPC/B95*, which shows the model equation), with the three most significant ones being *ZNF608 rs6864049*, *GPRC5B-IQCK rs12444979*, and *FAAH rs324420*. AUC of the final model was significantly increased ($AUC_{clinical}$: 0.75; AUC_{final}: 0.92; $P_{AUC} < 0.001$) as well as the goodness of fit compared with the model containing only clinical data ($P_{LRT} < 0.001$). An increase in accuracy, NPV, and PPV was also observed (Table 3). An increase in predicted risk, as shown in Fig. 1 (left), was observed for 46 patients with more than 5% WG (crosses) and 45 patients with up to 5% WG (black dots), whereas 10 patients with more than 5% WG and 147 patients with up to 5% WG showed a decrease in their predicted risk after inclusion of genetic data. The distribution of predicted risk (Fig. 1, right) indicates that 80% of up to 5% WG patients (gray bar) have a less than 20% predicted risk of having a less than 5% WG.

Replication cohort

A small sample of 32 newly included patients with compliance ascertained was used as a replication cohort. These patients were significantly younger than those in the discovery cohort [median (IQR) age: 33 (20) vs. 46 (41) years old, $P = 0.02$]. No other differences were observed between the two cohorts, except for aripiprazole, lithium, and olanzapine, which were prescribed more in the replication cohort, and risperidone, which was prescribed more in the discovery cohort (see Supplementary Table, Supplemental digital content 8, *http://links.lww.com/FPC/B96*). Comedication possibly inducing WG was also more frequent in the discovery cohort.

The discovery model was used to predict more than 5% WG for the 32 patients in the replication cohort (see Supplementary Table, Supplemental digital content 9, *http://links.lww.com/FPC/B97*, which presents prediction results for each patient). ROC curves calculated with the clinical and genetic-based model were similar between the two cohorts (see Supplementary Fig., Supplemental digital

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 3 Predictive statistics

Logistic models	TN (%)	TP (%)	FN (%)	FP (%)	Accuracy % (95th)[a]	SP % (95th)[a]	SE % (95th)[a]	NPV % (95th)[a]	PPV % (95th)[a]	AUC (95th)[a]	*P*-value[b]
Clinical	115 (46)	40 (16)	16 (6)	77 (31)	70 (54–83)	69 (43–91)	76 (48–96)	**91 (84–96)**	41 (30–64)	0.75 (0.68–0.82)	
Model including clinical and genetic data:											
GWAS-diabetes	149 (60)	32 (13)	24 (9)	43 (17)	78 (64–88)	77 (50–94)	75 (52–93)	**91 (85–97)**	49 (33–74)	0.80 (0.73–0.86)	0.1689
GWAS-BMI	154 (62)	43 (17)	13 (5)	38 (15)	**83 (72–90)**	83 (66–94)	84 (67–96)	95 (90–98)	58 (42–79)	**0.88 (0.82–0.93)**	0.0002
Candidate gene	164 (66)	38 (15)	18 (7)	28 (11)	81 (68–89)	81 (61–94)	80 (62–95)	93 (88–98)	55 (39–76)	**0.85 (0.79–0.91)**	0.01
Final	155 (63)	47 (19)	9 (4)	37 (15)	**87 (77–94)**	87 (72–96)	87 (74–97)	**97 (92–99)**	**67 (48–87)**	**0.92 (0.87–0.96)**	<0.0001
Replication cohort[c]	15 (46)	8 (28)	0 (0)	9 (25)	72	63	100	100	47	0.89	

In bold are the parameters lying beyond the corresponding 95th calculated in the clinical model, which is considered different.
AUC, area under the curve; FN, false negative (*n*); GWAS, genome-wide association studies; NPV, negative predictive value; PPV, positive predictive value; SE, sensibility; SP, specificity; TN, true negative (*n*); TP, true positive (*n*).
[a]Median and 95th percentiles for each parameter were determined using 10 000 bootstraps.
[b]*P*-value were calculated between the AUC of the model containing clinical data and the model containing clinical and genetic data. 2000 bootstraps were used for the analysis.
[c]Because of the very small sample size, no bootstrap could be performed and thus no percentiles were obtained.

content 10, *http://links.lww.com/FPC/B98* $AUC_{replication} = 0.9$; $P_{AUC} = 0.9$). Accuracy, specificity, sensitivity, NPV, and PPV lay outside of the 95th interval (Table 3), which may be explained, in part, by the small size of the replication cohort. There was no difference in the predicted risk between the two cohorts when comparing patients with up to 5% WG ($P = 0.2$) and more than 5% WG ($P = 0.1$, see Supplementary Fig., Supplemental digital content 11, *http://links.lww.com/FPC/B99*).

Validation for long-term weight changes

GAMM prediction of WG over the first year is represented in Fig. 2 (see Supplementary Fig., Supplemental digital content 12, *http://links.lww.com/FPC/B100*, which presents raw data). Patients with more than 5% WG after 1 month of treatment (left plot, red line) had a stronger WG during the first year of treatment than patients with up to 5% WG (green line; linear mixed model controlled by several confounders: $\beta = 7.8\%$; $P_{adjusted} < 0.0001$; see Supplementary Table, Supplemental digital content 13, *http://links.lww.com/FPC/B101*).

Patients predicted before treatment to have more than 5% or up to 5% WG after 1 month of treatment, on the basis of clinical and genetic data, are shown on the right plot (Fig. 2). The difference in WG between the two predicted groups was significant after 1 year ($\beta = 4.4\%$; $P_{adjusted} < 0.0001$; see Supplementary Table, Supplemental digital content 13, *http://links.lww.com/FPC/B101*).

Number needed to genotype

Accuracy (i.e. percentage of correctly classified cases) increased by 17% (from 70 to 87%) with the final model including clinical and genetic data compared with the clinical model alone. In other words, six patients have to be genotyped to detect one patient misclassified after using only clinical parameters.

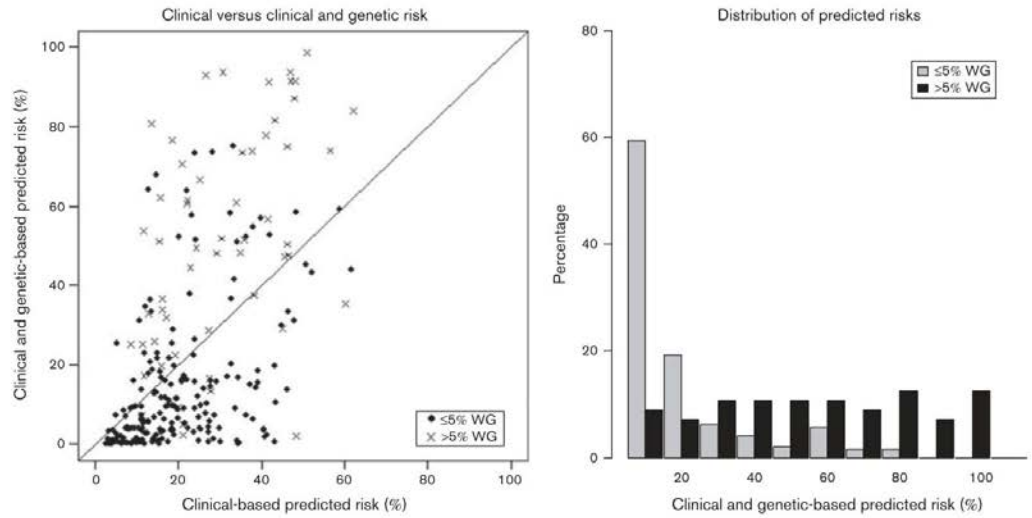
Discussion

A fast (after 1 month) and important (>5%) WG following treatment with WG-inducing psychotropic drugs has been shown to be a good predictor for significant long-term weight changes [21], highlighting the need to regularly monitor WG during psychotropic treatment [3,22]. Thus, detection of patients at risk even before starting the treatment could be useful for a personalized prescription to minimize PIWG and long-term metabolic consequences.

Several clinical variables such as young age, low BMI, or female sex are known risk factors for PIWG [34]. In the present study, we showed that a combination of genetic data resulting from an extensive genetic analysis of patients in addition to clinical risk factors could improve the ability to detect patients at increased risk before starting a pharmacological treatment with WG-inducing psychotropic drugs. We confirmed that baseline BMI and age were associated significantly with more than 5% WG

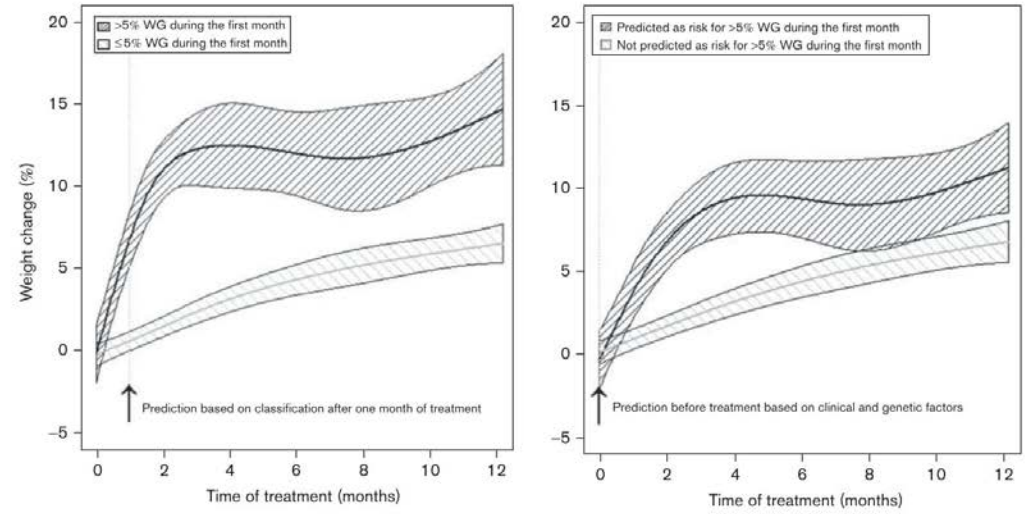
Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Fig. 1



Left scatter plot indicates the predicted risk change between the model with only clinical variables and the model including both clinical and genetic variables. The dots above the diagonal line indicate that adding genetic variables increases the predicted risk of more than 5% WG and the dots below the diagonal line indicate a decrease of more than 5% WG predicted risk after adding genetic variables. The right bar plot represents the distribution of more than 5% WG and up to 5% WG cases according to the predicted risk. WG, weight gain.

Fig. 2



Generalized additive mixed-model prediction of weight over 1 year. The left plot represents weight changes in patients having more than 5% WG (black) or up to 5% WG (grey) after 1 month following the introduction of weight gain-inducing psychotropic drugs. The right plot represent the prediction before treatment of 5% WG in patients after 1 month on the basis of clinical and genetic data more than 5% WG (dark) or up to 5% WG (grey). 95% confidence interval is represented by the shaded area. WG, weight gain.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

(Table 2, right column), underlining the vulnerability of young patients (children and adolescents) to PIWG [7,9, 35]. No significant influence of medication, neither analyzed separately (data not shown) nor clustered as a function of their potential WG magnitude (amisulpride, aripiprazole vs. risperidone, quetiapine, mirtazapine, lithium vs. clozapine, olanzapine, and valproate), was observed in the multivariate analysis. This could be explained by the combined effect of present and past treatment as most patients were not drug naive. However, a higher proportion of olanzapine prescription was observed in more than 5% WG group, in agreement with the fact that olanzapine is one of the most potent WG-inducing antipsychotics.

The model combining clinical and genetic data selected from T2DM-GWAS showed no significant AUC increase compared with the clinical model alone. This could first be explained by the short duration of treatment examined in the present study, which decreases the possible influence of genes associated with diabetes. In addition, T2DM is likely to involve essentially different genes, with different biological pathways than WG. This conclusion is supported by a review concluding that there is, to date, a limited shared genetic etiology between type 2 diabetes and obesity [36].

In addition to clinical data, the final model contains 18 SNPs from candidate gene studies investigating PIWG during the first 3 months of treatment and from a GWAS investigating BMI in general populations. Although several SNPs were not individually significantly associated with BMI, retaining them in the final model using AIC selection significantly improved the fit, suggesting gene–gene interactions. Considering genetic variants that were most significantly associated with fast and important WG, *ADIPOQ rs17300539*, located in the promoter region, was found to be associated strongly with low adiponectin levels [37]. It could thus be associated with metabolic disorders, although discrepant results have been published in two meta-analyses investigating obesity and T2DM [38,39]. The *FAAH rs324420* SNP is located in the fatty acid amide hydrolase locus, and the present result is in agreement with a study investigating PIWG [40]. It is noteworthy that besides associations with metabolic traits, *FAAH* belongs to the endocannabinoid system and was also related to several psychiatric disorders [41,42] underlying possible common risk factors between psychiatric and metabolic disorders. The same remark also applies to *GPRC5B*, *IQCK rs12444979*, which was found to be associated with attention-deficit/hyperactivity disorder and BMI [43].

Adding SNPs selected from GWAS investigating BMI [10] to the model containing only clinical data or the model containing SNPs from gene candidate studies increased the predictive power of the model significantly. In addition, only the final model resulted in an increase in NPV and PPV compared with the clinical model alone. It is noteworthy that patients with more than 5% WG at 1 month (i.e. those misclassified and those correctly predicted to develop > 5% WG) did have significant WG over the first year of treatment compared with the patients predicted as not being at risk for 5% WG, underlining the importance of an early WG and the 5% threshold for predicting long-term weight changes [21].

Several limitations of the present study need to be acknowledged. First, most of the patients were not drug naive, and thus possibly already experienced major WG during previous pharmacological treatments. However, nondrug-naive psychiatric patients represent the majority of cases in clinical practice, which should strengthen the validity of our results under real-world conditions. Second, although the choice of genes included in the present study is already extensive, it is almost certain that other genes will be discovered in the future to be associated with PIWG, in particular, by using exome or whole-genome sequencing. However, the present model already reaches 87% accuracy, and although it can be increased, 100% accuracy will most probably never be achieved even after adding more genetic information. Third, the present results are valid only for predicting more than 5% WG after a short (1 month) period of treatment. However, consequences on weight and other metabolic features have been shown for 1-year treatment. Because of the naturalistic condition of the study, it is not known whether some patients, in particular those with a high WG, decreased their caloric intake and/or increased their physical activity following recommendations provided by their treating physicians and/or nurses. Because of the lack of data on the individual effect of each SNP, an unweighted approach was used, which might overestimate or underestimate the effect of certain SNPs. Fourth, the present results should be interpreted with caution considering the small sample size of the replication cohort. To validate the present results as well as to develop a weighted model, replications in other psychiatric cohorts, using retrospective as well as prospective designs, are needed. In addition, analysis and validation of the model in patients with specific diagnosis and with specific drugs should be carried out in the future.

The strengths of the present study include its naturalistic setting and a longitudinal design, with weight having been monitored at introduction and after regular time intervals. Moreover, therapeutic drug monitoring was used to assess compliance, which is an important issue in psychiatry. Indeed, major WG is a strong risk factor for poor or noncompliance, possibly leading to false evaluation of the patients (no WG because of noncompliance). To our knowledge, the present study is the most thorough genetic study carried out in psychiatric patients for predicting WG during psychotropic treatment, with the validity of the model confirmed in a replication cohort.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Conclusion

This study explores the potential role of known SNPs in identifying patients at risk of a rapid WG during the first month of treatment, which is an important issue for long-term WG and for its consequences on quality of life and general health. Extensive genetic analysis increases the accuracy, PPV, and NPV to detect at-risk patients compared with clinical risk factors alone, such as age and baseline BMI. Future studies should be carried out to replicate the present results in a larger cohort and to investigate prospectively the implementation of this predictive test in routine practice. If replicated, considering that only 6 patients need to be genotyped to avoid one misclassified patient by using only clinical information, the use of genetic information should be considered. The combined use of genetic and clinical data could help the clinician to identify patients at high risk for a rapid WG. Such patients should be prescribed, whenever possible, psychotropic drugs with low potential for WG combined with a close monitoring of metabolic parameters. However, such tests should be used in addition to a monitoring program of weight and other metabolic parameters during PIWG treatment, which is, to date, the best way to detect and, if possible, to prevent metabolic complications related to psychotropic treatment.

Acknowledgements

The authors are grateful to all participating psychiatrists and medical staff who were involved in the metabolic monitoring program.

C.B.E. has received research support from Takeda and The Roche Transplantation Research Foundation in the past 3 years.

Professor C.B. Eap had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; C.B. Eap: study concept and design; F. Vandenberghe, N. Saigí-Morgui, A. Delacrétaz, A. von Gunten, P. Conus: acquisition of data; F. Vandenberghe, M. Gholam-Rezaee:analysis and interpretation; F. Vandenberghe: drafting of the manuscript; F. Vandenberghe, M. Gholam-Rezaee: statistical analysis; S. Crettol, N. Ansermot, A. von Gunten, P. Conus: administrative, technical, or material support. All authors critical revised the manuscript for important intellectual content.

This work has been funded in part by the Swiss National Research Foundation (C.B.E. and P.C.: 320030-120686 and 324730-144064).

Conflicts of interest

C.B.E. received honoraria for conferences or teaching CME courses from Advisis, Astra Zeneca, Lundbeck, MSD, Otsuka; Sandoz, Servier, and Vifor-Pharma in the past 3 years. A. von Gunten received honoraria for a conference and a workshop, not related to this study, organized by Vifor and Bayer Schering within the previous 3 years. For the remaining authors there are no conflicts of interest.

References

1 World Health Organization. The challenge of obesity - quick statistics. 2015 [cited 2015 April]. Available at: *http://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity/data-and-statistics*. [Accessed April 2015].
2 Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity among adults: United States, 2011-2012. *NCHS Data Brief* 2013. 1–8.
3 De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry* 2009; **24**:412–424.
4 Goff DC, Cather C, Evins AE, Henderson DC, Freudenrich O, Copeland PM, *et al*. Medical morbidity and mortality in schizophrenia: guidelines for psychiatrists. *J Clin Psychiatry* 2005; **66**:183–194.
5 Allison DB, Mentore JL, Heo M, Chandler LP, Capelleri JC, Infante MC, *et al*. Antipsychotic- induced weight gain a comprehensive research synthesis. *Am J Psychiatry* 1999; **156**:1686–1696.
6 Laimer M, Kramer-Reinstadler K, Rauchenzauner M, Lechner-Schoner T, Strauss R, Engl J, *et al*. Effect of mirtazapine treatment on body composition and metabolism. *J Clin Psychiatry* 2006; **67**:421–424.
7 Russell JM, Mackell JA. Bodyweight gain associated with atypical antipsychotics: epidemiology and therapeutic implications. *CNS drugs* 2001; **15**:537–551.
8 Choong E, Bondolfi G, Etter M, Jermann F, Aubry JM, Bartolomei J, *et al*. Psychotropic drug induced weight gain and other metabolic complications in a Swiss Psychiatric population. *J Psychiatr Res* 2012; **46**:540–548.
9 Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 2009; **302**:1765–1773.
10 Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, *et al*. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010; **42**:937–948.
11 Gebhardt S, Theisen FM, Haberhausen M, Heinzel-Gutenbrunner M, Wehmeier PM, Krieg JC, *et al*. Body weight gain induced by atypical antipsychotics: an extension of the monozygotic twin and sib pair study. *J Clin Pharm Ther* 2010; **35**:207–211.
12 Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Muller DJ. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Mol Psychiatry* 2012; **17**:242–266.
13 Li A, Meyre D. Challenges in reproducibility of genetic association studies: lessons learned from the obesity field. *Int J Obes (Lond)* 2013; **37**:559–567.
14 Choong E, Quteineh L, Cardinaux JR, Gholam-Rezaee M, Vandenberghe F, Dobrinas M, *et al*. Influence of CRTC1 polymorphisms on body mass index and fat mass in psychiatric patients and in the general adult population. *JAMA Psychiatry* 2013; **70**:1011–1019.
15 Quteineh L, Vandenberghe F, Saigi Morgui N, Delacretaz A, Choong E, Gholam-Rezaee M, *et al*. Impact of HSD11B1 polymorphisms on BMI and components of the metabolic syndrome in patients receiving psychotropic treatments. *Pharmacogenet Genomics* 2015; **25**:246–258.
16 Saigi Morgui N, Vandenberghe F, Delacrétaz A, Quteineh L, Choong E, Gholam-Rezaee M, *et al*. Association of PCK1 with body mass index and other metabolic features in patients with psychotropic treatments. *J Clin Psychopharmacol* 2015; **35**:544–552.
17 Delacrétaz A, Preisig M, Vandenberghe F, Saigi Morgui N, Quteineh L, Choong E, *et al*. Influence of MCHR2 and MCHR2-AS1 genetic polymorphisms on body mass index in psychiatric patients and in subjects from the general population with present or past atypical depression. *PLoS ONE* 2015; **10**:e0139155.
18 Hoffmann VP, Case M, Stauffer VL, Jacobson JG, Conley RR. Predictive value of early changes in triglycerides and weight for longer-term changes in metabolic measures during olanzapine, ziprasidone or aripiprazole treatment for schizophrenia and schizoaffective disorder post hoc analyses of 3 randomized, controlled clinical trials. *J Clin Psychopharmacol* 2010; **30**:656–660.
19 Lipkovich I, Citrome L, Perlis R, Deberdt W, Houston JP, Ahl J, *et al*. Early predictors of substantial weight gain in bipolar patients treated with olanzapine. *J Clin Psychopharmacol* 2006; **26**:316–320.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

20 Lipkovich I, Jacobson JG, Hardy TA, Hoffmann VP. Early evaluation of patient risk for substantial weight gain during olanzapine treatment for schizophrenia, schizophreniform, or schizoaffective disorder. *BMC psychiatry* 2008; **8**:78.

21 Vandenberghe F, Gholam-Rezaee M, Saigi-Morgui N, Delacrétaz A, Choong E, Solida-Tozzi A, *et al.* Importance of early weight gain changes to predict long term weight gain during psychotropic drug treatment. *J Clin Psychiatry* 2015; **76**:e1417–e1423.

22 Choong E, Solida A, Lechaire C, Conus P, Eap CB. Suivi du syndrome métabolique induit par les antipsychotiques atypiques: recomendations et perspectives pharmacogénétiques. *Rev Med Suisse* 2008; **4**:1994–1999.

23 Hiemke C, Baumann P, Bergemann N, Conca A, Dietmaier O, Egberts K, *et al.* AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry* 2011; **44**:195–235.

24 Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet* 2011; **88**:76–82.

25 Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, *et al.* Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet* 2010; **42**:579–589.

26 Venables WN, Ripley BD. *Modern applied statistics with S*. New York: Springer; 2002.

27 Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, Müller M. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011; **12**:77.

28 Janssens AC, Moonesinghe R, Yang Q, Steyerberg EW, van Duijn CM, Khoury MJ. The impact of genotype frequencies on the clinical validity of genomic profiling for predicting common chronic diseases. *Genet Med* 2007; **9**:528–535.

29 Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983; **148**:839–843.

30 Pinheiro J, Bates D, DebRoy S, Sarkar D. the R Development Core Team. nlme: linear and nonlinear mixed effects models. R package version 3.1-108. 2013.

31 Pinheiro JC, Bates DM. *Mixed-effects models in S and S-PLUS*. New York: Springer; 2000.

32 Davison AC, Hinkley DV. *Bootstrap methods and their application*. Cambridge, NY: Cambridge University Press; 1997. pp. 1–592.

33 International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, *et al.* Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009; **360**:753–764.

34 De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* 2012; **8**:114–126.

35 De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: a systematic review of randomized, placebo controlled trials and guidelines for clinical practice. *Eur Psychiatry* 2011; **26**:144–158.

36 Grarup N, Sandholt CH, Hansen T, Pedersen O. Genetic susceptibility to type 2 diabetes and obesity: from genome-wide association studies to rare variants and beyond. *Diabetologia* 2014; **57**:1528–1541.

37 Hivert MF, Manning AK, McAteer JB, Florez JC, Dupuis J, Fox CS, *et al.* Common variants in the adiponectin gene (ADIPOQ) associated with plasma adiponectin levels, type 2 diabetes, and diabetes-related quantitative traits: the Framingham Offspring Study. *Diabetes* 2008; **57**:3353–3359.

38 Han LY, Wu QH, Jiao ML, Hao YH, Liang LB, Gao LJ, *et al.* Associations between single-nucleotide polymorphisms (+45 T > G, +276 G > T, −11377C > G, −11391 G > A) of adiponectin gene and type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetologia* 2011; **54**:2303–2314.

39 Lu JF, Zhou Y, Huang GH, Jiang HX, Hu BL, Qin SY. Association of ADIPOQ polymorphisms with obesity risk: a meta-analysis. *Hum Immunol* 2014; **75**:1062–1068.

40 Monteleone P, Milano W, Petrella C, Canestrelli B, Maj M. Endocannabinoid Pro129Thr FAAH functional polymorphism but not 1359 G/A CNR1 polymorphism is associated with antipsychotic-induced weight gain. *J Clin Psychopharmacol* 2010; **30**:441–445.

41 Ando T, Tamura N, Mera T, Morita C, Takei M, Nakamoto C, *et al.* Association of the c.385C > A (p.Pro129Thr) polymorphism of the fatty acid amide hydrolase gene with anorexia nervosa in the Japanese population. *Mol Genet Genomic Med* 2014; **2**:313–318.

42 Monteleone P, Bifulco M, Maina G, Tortorella A, Gazzerro P, Proto MC, *et al.* Investigation of CNR1 and FAAH endocannabinoid gene polymorphisms in bipolar disorder and major depression. *Pharmacol Res* 2010; **61**:400–404.

43 Albayrak O, Putter C, Volckmar AL, Cichon S, Hoffmann P, Nothen MM, *et al.* Common obesity risk alleles in childhood attention-deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet* 2013; **162B**: 295–305.

Copyright © 2016 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.