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

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## Abstract

**Objectives:** Dyslipidemia represents a major health issue in psychiatry. We determined whether weighted polygenic risk scores (wPRS) combining multiple Single Nucleotide Polymorphisms (SNPs) associated with lipid levels in the general population are associated with lipid levels (high density lipoproteins (HDL), low density lipoproteins (LDL), total cholesterol (TC) and triglycerides (TG)) and/or dyslipidemia in patients receiving weight gain-inducing psychotropic drugs. We also determined whether genetics improve the predictive power of dyslipidemia. **Methods:** The influence of wPRS on lipid levels was firstly assessed in a discovery psychiatric sample (n=324) and was then tested for replication in an independent psychiatric sample (n=148). The contribution of genetic markers to predict dyslipidemia was evaluated in the combined psychiatric sample. **Results:** wPRS 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 TG levels (0.20, 0.32 and 0.26 mmol/l;  $p \leq 0.004$ ) and significantly lower HDL levels (0.13 mmol/l;  $p < 0.0001$ ) compared to 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 ( $p = 0.08$ ). **Conclusions:** Population-based wPRS have thus significant effects on lipid levels in the psychiatric population. As genetics improved the predictive power of dyslipidemia development, only 24 patients should be genotyped in order 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.

## Introduction

Cardiovascular diseases have become a major public health burden, its prevalence increasing considerably over the last 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, e.g. 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]. While 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) worsens patient metabolic condition (e.g. weight gain and/or alteration of lipid and glucose metabolism) [10,11]. Dyslipidemia, defined as high total-cholesterol and/or LDL-cholesterol and/or triglyceride and/or low HDL-cholesterol levels, constitutes a considerable risk factor for cardiovascular diseases in the psychiatric population as its prevalence was shown to raise as high as 60% [12]. Some factors were associated with psychotropic drug-induced metabolic complications, including female sex, low baseline BMI, young age or non-white ethnicities [13]. Additionally, many genetic susceptibilities as variations in

pharmacodynamic receptors or in energy homeostasis regulating genes were associated with metabolic side effects [14-18]. For instance, previous studies demonstrated the influence of 5HT<sub>2C</sub> serotonin and H<sub>1</sub> 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 (SREBP) pathway [21]. Thus, olanzapine, clozapine and risperidone were shown to promote the up-regulation of SREBP 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]. While several PRS 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 PRS combining multiple risk-associated SNPs from two lipid meta-analyses were associated with dyslipidemia-related traits (high-density lipoproteins (HDL), low-density lipoproteins (LDL), total cholesterol (TC) and triglycerides (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 to models including both clinical and genetic data to examine whether models including genetics could be useful enough to be applied in clinical settings.

## **Material 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, risperidone), mood stabilizers (lithium, valproate) or/and 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 materials. All individuals or their legal representatives signed a written informed consent for genetic analyses. Low HDL-cholesterol, high LDL-cholesterol, high triglyceride and high total cholesterol levels were defined by HDL hypocholesterolemia ( $<1$  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 ESH/ESC guidelines [35].

The discovery sample consisted of 332 patients from the above described cohort with psychotropic treatments starting between 2007 and 31<sup>st</sup> of December, 2010. The replication sample was composed of 140 patients of the same cohort with treatments starting between 1<sup>st</sup> of January 2011 and 2014. Only patients of European ancestry were included in the analysis. More details in supplementary materials.

## **SNP selection, genotyping and construction of the PRS**

### *SNP 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 (Willer et al) [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 (Surakka et al) [27]. Both population-based samples were used to select genetic variants associated with lipid levels. In the present study,  $\beta$ -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 materials. **S1 Figure** describes SNP selection (more details in supplementary materials).

### *Genotyping*

CardioMetaboChip genotyping of European ancestry patients from the Lausanne Psychiatric University Hospital study was performed using the Illumina 200K CardioMetaboChip (Illumina, San Diego, CA) at the iGE3 genomics platform of the

University of Geneva (<http://www.ige3.unige.ch/genomics-platform.php>). More details in supplementary materials.

### *Construction of the PRSs*

One PRS was calculated by taking into account SNPs from each GWAS meta-analysis (i.e. PRS<sub>Willer</sub> and PRS<sub>Surakka</sub>) in association with each lipid phenotype, namely HDL, LDL, TC and TG. In addition, according to their respective inclusion criteria (**S1 Figure**), one PRS was calculated for each lipid phenotype by considering SNPs from both meta-analyses (i.e. PRS<sub>combined</sub>; n=73, 60, 72 and 47 SNPs for HDL, LDL, TC and TG, respectively). More details in supplementary materials.

### **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 (GAMM) were used, adjusting for covariates possibly associated with lipid parameters, i.e. 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 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 TX, USA) and R version 3.2.3 software. P-values  $\leq 0.05$  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 AUC construction and interpretation are available in supplementary material.

### **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 in order 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 **S1 Table**. 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; 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 of demographic nor of clinical characteristics between the two psychiatric samples, except lower baseline levels of TC and LDL in the discovery sample compared to the replication sample (4.7 mmol/l versus 5.2 mmol/l;  $p=0.002$  and 2.6 mmol/l versus 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. **S2-S6 Figures** show the evolution of lipid levels during psychotropic treatment stratified by covariates taken into account in GAMM analyses, i.e. BMI, age, sex, smoking status and psychotropic drug class. More details are available in supplementary material.

### **Influence of PRS 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 **S2-S13 Tables**. In the discovery sample,  $wPRS_{Willer}$  and  $wPRS_{Surakka}$  calculated for each phenotype were significantly associated with HDL, LDL, TC and TG ( $p \leq 0.02$ ) (**S14 Table**). 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 and decreased HDL by 0.02 mmol/l, respectively (**Table 1**;  $p < 0.001$ ,  $p < 0.00001$ ,  $p < 0.0001$

and  $p < 0.00001$ , respectively). Since analyses on  $wPRS_{\text{combined}}$  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  $wPRS_{\text{combined}}$  in the combined psychiatric sample. Details for further analyses are available in supplementary material (**S7-S16 Figures, S15 Table**).

In accordance with previous results, significant differences of the four lipid phenotype levels were observed between percentile groups ( $p \leq 0.004$ ) (**Table 2; Figure 2**). 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 to the others.

#### *Predictive power of models containing clinical and genetic variables*

Predictive powers of models including genetics were not improved compared to models including only clinical variables for any of the four lipid traits, neither in the discovery sample (**S17 Figure a**) nor in the replication sample (**S17 Figure b**). In the combined sample (**Figure 1**), adding genetics to models did not increase AUC for hypertriglyceridemia (AUC = 0.75 versus 0.74;  $p = 0.57$ ) and for LDL-hypercholesterolemia (AUC=0.68 versus 0.66;  $p = 0.41$ ). However, for HDL-hypocholesterolemia, AUC was significantly increased when adding genetics to the clinical model (AUC = 0.76 versus 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 versus 0.70;  $p = 0.08$ ). More details are available in **S16 Table**. Of note, as fasting TG levels may vary considerably following a high-fat diet, more stringent

analyses were also conducted considering hypertiglyceridemia only if patients had at least two abnormal TG values during the psychotropic treatment. This new criterion slightly improved AUC (0.82 versus 0.79;  $p=0.29$ ) but did not reveal any significant AUC increase by adding genetics (data not shown).

**S17 Table** 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 materials (**S18-S20 Figures, S18 Table**).

### 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 (**S19 Table**). Interestingly, wPRS was among the variables having high impact 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 beta values were higher than the percentile 95 of all beta values explained 3.5%, 3.1%, 2.5% and 3.3% of the total lipid variability for HDL, LDL, TC and TG, respectively (**S20 Table**). 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 beta value of 1 for each individual SNPs (**S20 Table**), showing the importance to consider allele effects in a weighted approach. SNPs whose beta values were higher than the percentile 95 of all beta values are lying in well-known

genes involved in the regulation of lipid homeostasis, as for instance in the lipoprotein lipase (*LPL*), in the low-density lipoprotein receptor (*LDLR*) or in the apolipoprotein E (*APOE*) (**S21 Table**).

### Number needed to genotype

To detect whether genotyping would be useful as a routine test, the number needed to genotype 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 RAISE study (Recovery After an Initial Schizophrenia Episode) [12], possibly because of the shorter lifetime exposure to psychotropic treatment in the latter (less than 6 months) than in the present psychiatric sample (around 8 years). On the other hand, in accordance with the latter study [12], only a small proportion of patients (less than 7%) received lipid-lowering agent(s),

corresponding to 14 % of patients with hypercholesterolemia). Of note, 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. On the other hand, the clinical heterogeneity of the present sample also constitutes a 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 to population-based wPRS on lipids may be due to a lower number of patients in our psychiatric sample but also to the use of non-appropriate allele estimates. Thus, population-based estimates could either under- 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 wGRS may help to improve the predictive power of wGRS on dyslipidemia. Unfortunately, such promising variants could not be included in polygenic risk scores because no allele effect ( $\beta$ -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 neither in the drug-free psychiatric population nor in 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 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 wPRS were highly associated with lipid levels in the present 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 to 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]. Based on 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- and/or diagnosis-stratified samples).

Results of the present study should be considered with the following limitations. Firstly, the study was restricted to European patients, which impedes extrapolation to other ethnicities. Secondly, 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. A 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, i.e. patients who did not develop dyslipidemia because they did not take the drug, an important factor to consider in the psychiatric population.

In 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.

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**Table 1. Association of wPRS groups (SNPs selected from both meta-analyses) with lipid traits in GAMM adjusted with age, sex, BMI, medication and smoking status in the discovery, replication and combined sample.**

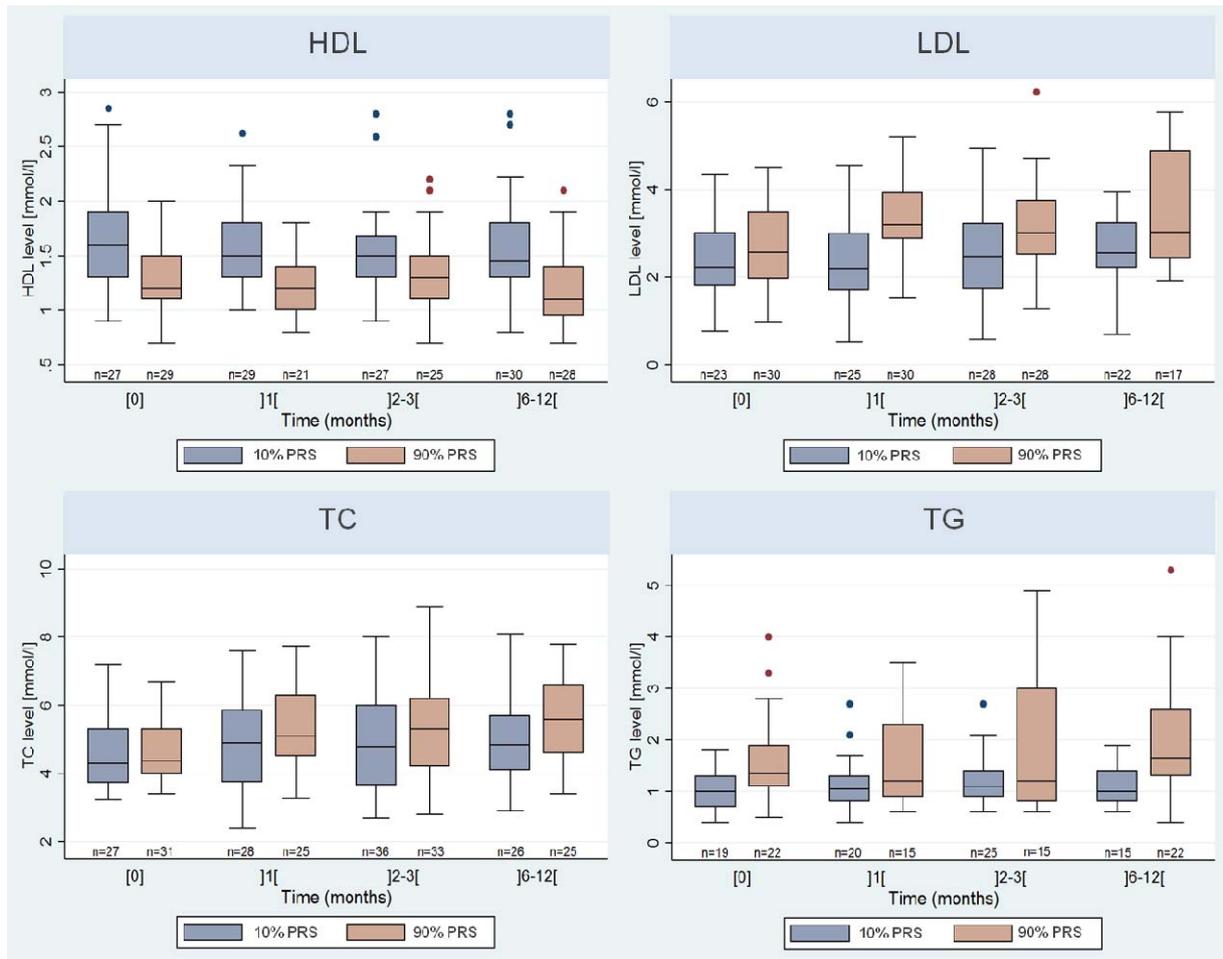
	Phenotype	Number of SNPs	Number of patients	Estimate [95% CI] (mmol/l)	Explained variability [%]	Explained variability by PRS [%]	p-value
<b>Discovery sample</b>	<b>HDL</b>	<b>73</b>	233	0.01 [0.01 - 0.02]	18.32	3.44	<b>&lt;0.001</b>
	<b>LDL</b>	<b>60</b>	211	0.03 [0.01 - 0.05]	15.05	1.85	<b>0.004</b>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

CI: confidence interval. Caucasian patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses. Explained variability [%] refers to models including all variables. Estimates indicate the influence of each additional risk allele on lipid levels (in mmol/l). For instance, each additional risk allele significantly increases LDL by 0.03 mmol/l [0.01-0.05].

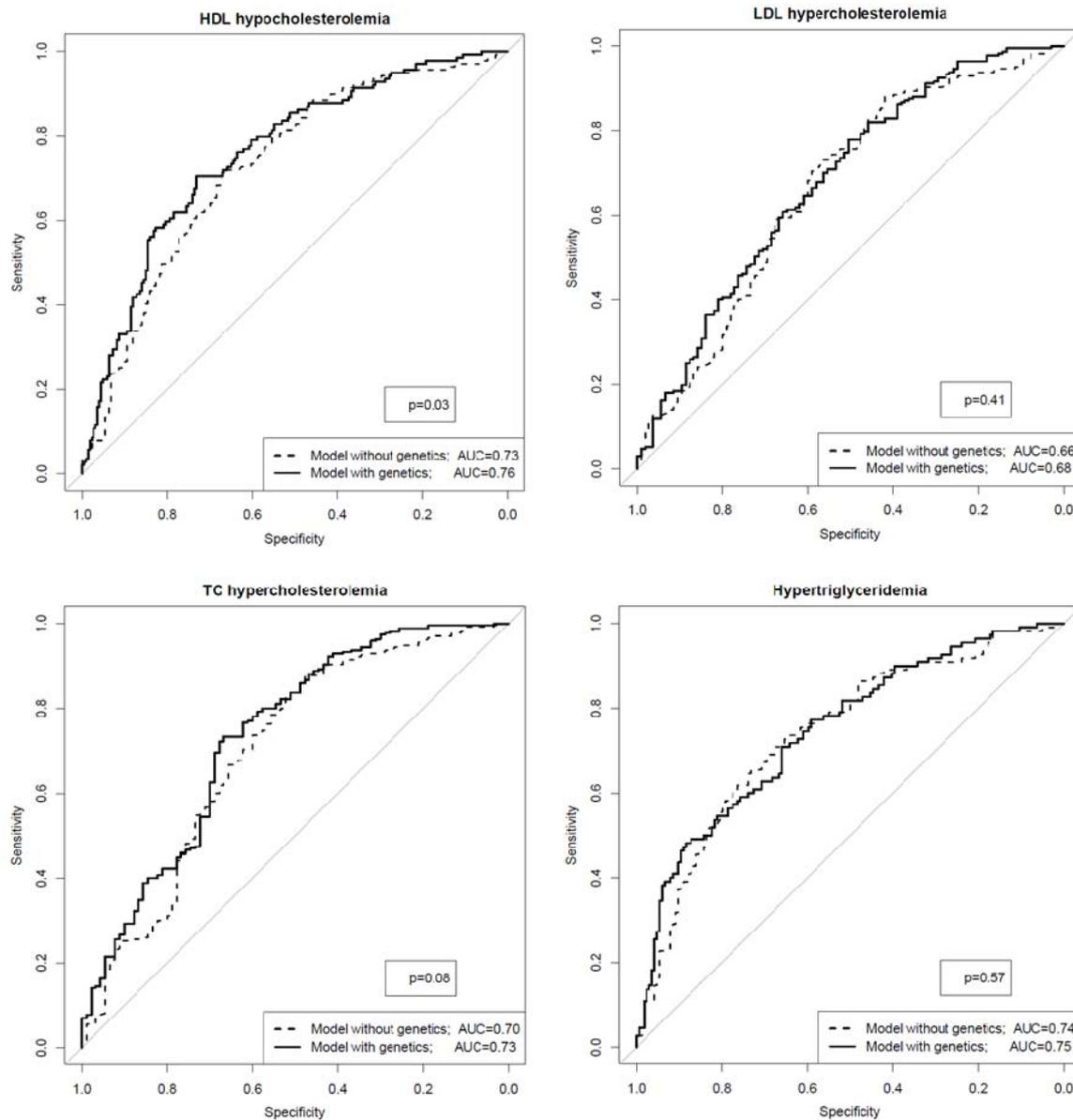
**Table 2. Association of wPRS groups (SNPs selected from both meta-analyses) with lipid traits in GAMM adjusted with age, sex, BMI, medication and smoking status in the combined sample.**

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

CI: confidence interval. GAMM were performed with PRS as a categorical variable with two groups. 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. 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).



**Figure 2. Evolution of lipid variables during psychotropic treatment, according to extreme groups of PRS.** 10% PRS = PRS lower than the 10th percentile. 90% PRS = PRS higher than the 90th percentile. Median, interquartiles and number of observations are indicated for each box. Months were defined as: month [0]: day 0, month ]1[:  $\geq 10$  &  $< 45$  days, month ]2-3[:  $\geq 45$  &  $< 135$  days, month ]6-12[:  $\geq 135$  &  $< 535$  days. Patients taking lipid-lowering medication were excluded. Only fasting patients were included for TG analyses.



**Figure 1: ROC 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, i.e. HDL hypocholesterolemia was defined as  $< 1$  mmol/l and/or prescription of a lipid-lowering agent, high LDL-cholesterol level, i.e. LDL hypercholesterolemia was defined as  $\geq 3$  mmol/l and/or prescription of a lipid-lowering agent, high triglyceride level, i.e. hypertriglyceridemia was defined as  $\geq 2$  mmol/l and/or prescription of a lipid-lowering agent and high total cholesterol level, i.e. hypercholesterolemia was defined as  $\geq 5$  mmol/l and/or prescription of a lipid-lowering agent [53], according to ESH/ESC guidelines [54].

**Table 3: HDL dyslipidemia incidence and number needed to genotype for the discovery, replication and combined samples**

	<b>Dyslipidemia incidence [%]</b>	<b>Sensitivity</b>	<b>Number needed to genotype (NNG)</b>
<b>Discovery sample</b>	7.1	0.63	22
<b>Replication sample</b>	2.9	0.49	70
<b>Combined sample</b>	6.0	0.70	<b>24</b>

NNG calculations were done using sensitivity (reported in the present table) of the best threshold coordinates in each sample for HDL dyslipidemia development.