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Prediction of early weight gain during psychotropic treatment using a combinatorial model with clinical and genetic markers

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ABSTRACT

Background: Psychotropic drugs can induce an important (>5%) weight gain (WG) already after one month of treatment, which is a good predictor for major WG at 3 and 12 months. The large inter-individual variability of drug-induced WG, can be explained in part by genetic and clinical factors.

Aim: To determine if extensive analysis of genes, in addition to clinical factors, can improve prediction of patients at risk for >5% WG at one month of treatment.

Methods: Data were obtained from a one year naturalistic longitudinal study, with weight monitoring during weight-inducing psychotropic treatment. 248 Caucasian psychiatric patients, with at least baseline and one 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 significantly associated 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 6 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 >5% WG after one month of treatment had 4.4% more weight gain over one year than patients predicted to have ≤5% WG ($p\leq0.0001$).

Conclusion: These results may help to implement genetic testing before starting psychotropic drug treatment to identify patients at risk of important WG.

INTRODUCTION

Overweight and obesity are major public health problems of the current decade, with a prevalence of obesity (body mass index (BMI)≥30kg/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, as compared to 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 important 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 gender (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 widely investigated in general as well as psychiatric populations. Currently, genome-wide association studies (GWAS) have highlighted 32 single-nucleotide polymorphism (SNPs) associated with BMI in cohorts of up to 240000 subjects (10). However, despite the increasing number of 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 regard to psychiatric patients, a high interindividual 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, similarly to the general population, many genetic contributions to WG. Because second generation antipsychotics interact with serotonin and dopamine systems, several candidate gene studies were conducted 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 to the understanding of PIWG mechanisms. Indeed, SNPs located in *CRTC1, PCK1, MCHR2, HSD11β1* genes were found to be associated with BMI and replicated in 3 psychiatric cohorts (14-17). Although some of these SNPs were significantly associated 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 made during clinical trials have shown that patients with a rapid WG during the first month of treatment are at a higher risk to have a more important WG on the long term (18-20). Furthermore, we recently showed that a >5% WG during the first month of treatment is a good predictor for major WG at 3 (>15%) and 12 months (>20%), disregarding of the prescribed WG-inducing psychotropic drug (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 allow to detect patients at risk for a>5% WG after one month of psychotropic drug treatment. The obtained results were then tested for replication in a second independent psychiatric cohort.

METHODS

Patient selection:

Patients were selected from a previously published longitudinal observational study based on 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 were 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 one month visit (or at three months if no plasma was available at one month (n=40)), with a minimal follow-up duration of one 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 one 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 in fasting conditions as previously published (21).

Patients from the discovery cohort were included between 01.01.2007 and 08.04.2013. 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<0.005 and pca2>-0.02, values which gave the highest concordance with the patient's reported ethnicity (see Figure, Supplemental Digital Content 1).

The replication cohort was composed of patients included from 09.04.2013 to 01.12.2014. No principal component analysis could be performed on these patients, thus ethnicity was based on 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:

23 SNPs significantly associated with T2DM (GWAS-T2DM; $P<5 \times 10^{-8}$) and 32 SNPs significantly associated with BMI (GWAS-BMI; $P<5 \times 10^{-8}$), 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 three months of treatment were also included if published p-values were lower than 0.1 (see Table, Supplemental Digital Content 2).

Genomic DNA was extracted from EDTA blood samples with 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). 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 investigated SNPs were assessed by the call rate (>96%), GenCall score (>0.15) and matched gender. SNPs were extracted from the database by using GenomeStudio software (version 2011.1, Illumina, San Diego, California).

Patients included in the replication cohort were genotyped by KBioscience Institute in United Kingdom using the fluorescence-based competitive allele-specific PCR technology (KASP™).

Details about 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. In order 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). Due to a small number and an unequal distribution (non-interventional study) of each psychotropic medication, drugs were categorized as 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 based on 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 as their presence in the model was advised by the AIC, we kept them in the model 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 a>5% WG as a positive case and inversely a patient with a ≤5% WG as a negative case. An ideal test will give an AUC of 1 and a random test 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 previously published (p_{AUC}) (29). Beside 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 (95^{th}) of accuracy (percentage of correctly classified cases among all subjects), 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 10000 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 as different if their median values were laying outside the 95^{th} range of the compared group. P-values were not corrected for multiple testing because SNPs were selected on a priori basis and the AIC method was used to fit the best model. Due to the small sample size, no sub-analyses have been conducted for each medication or demographic parameters (e.g. gender, age).

Replication analysis

The statistical model developed on the discovery cohort was used to predict >5% WG. To compare the model performance, predictive statistics obtained in the replication cohort were compared to the previous model.

Evolution of weight over one year

To explore the evolution of WG over one year between patients with an observed or a predicted ≤5% WG and >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 one, two, three, six, nine and 12 months was 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 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 (>5% WG and ≤5% WG) 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.

Afterwards, confirmatory analyses were made by fitting a linear mixed effect model ("nlme" package of R (30)) adjusted for age, sex, time, baseline BMI. The fitted linear mixed effect model (31) had a random effect at the subject 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 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.

Evaluation of benefit of pharmacogenetic screening

The number needed to genotype (NNG), defined as the number of patients to genotype in order to detect one misclassified case by using only clinical information was determined (33). The calculation methodis 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 ≤0.05 were considered as statistically significant. All statistical analyses were carried out using R software (version 2.15.2).

RESULTS

Demographics of the discovery cohort:

248 patients were included (see Figure, Supplemental Digital Content 3), of which 190 patients were present in the previously published study on the >5% threshold as predictor of long term WG (21) and 58 additional patients also corresponding to the present inclusion criteria. At baseline, 22% of the patients were overweighed ([25-30[kg/m^2) and 14% were obese (≥30kg/m^2). Patients having a >5% WG after one month of treatment (56/248, 23%) were significantly younger (median (inter-quartile range (IQR)): 38(27) years) than patients with ≤5% WG (49(45) years, p=0.03, Table 1), in agreement with a young age being a risk factor for important WG (9). A lower prevalence of obese patients was observed in the group of >5% WG (5% versus 16%, p=0.05), in agreement with the literature in which a low BMI being a risk factor for important WG (7) and inversely patients with initial BMI <25kg/m^2 were less frequent in the ≤5% WG than in the >5% WG patients (60% vs 79%, p=0.01). Abdominal obesity and hypo HDL-cholesterolemia were more prevalent in the ≤5% WG group. No significant differences in other demographic variables were found between the two groups. Psychotic disorders ([F200-F249] & [F28-F29]) were the most frequent diagnosis (31%) and risperidone was the most frequently prescribed psychotropic drug (40%). A higher elevation of triglycerides and decrease of HDL-cholesterol between ≤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) and as well as between baseline and 12 months (Δmmol/l triglycerides: -0.1 (0.5) vs 1.3 (3), p≤0.001; 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 (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 Table, Supplemental Digital Content 2, 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 factors for >5% WG. No significant associations were observed between age, illness duration, polymedication, gender and the type of newly prescribed psychotropic drug and >5% WG at one month (table 2, left column).

Genetic models:

GWAS- Type 2 diabetes mellitus SNPs:

Four of the 21 SNPs were retained after AIC selection. None of the selected SNPs were significantly associated with WG at one month (see Table, Supplemental Digital Content 4). As presented in table 3, inclusion of these 4 SNPs did not increase accuracy and AUC.

GWAS-BMI SNPs:

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 Table, Supplemental Digital Content 5, which gives all SNPs). AUC significantly increased by including genetic data ($AUC_{clinical}(95^{th})$=0.75(0.68-0.82), $AUC_{clinical/GWAS}(95^{th})$=0.88(0.82-0.93), p_{AUC}=0.0002). 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 included variables. Accuracy of the prediction with genetic and clinical data (table 3) is modestly increased when compared to the model with clinical data alone ($Accuracy_{clinical}(95^{th})$=70(54-83), $Accuracy_{clinical/GWAS}(95^{th})$=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 3 most significant SNPs were *ADIPOQ rs17300539*, *INSIG2 rs17587100* and *FAAH rs324420* (see Table, Supplemental Digital Content 6, which gives all SNPs). The 9 selected SNPs increased significantly the predictive power ($AUC_{clinical}(95^{th})$=0.75(0.68-0.82), $AUC_{clinical/candidate\ gene}(95^{th})$=0.85(0.79-0.91), p_{AUC}=0.01). Likelihood ratio test confirms that the model containing genetic and clinical data should be preferred to the model including only clinical variables (p_{LRT}<0.001). Despite an increase of AUC, inclusion of genetic data did not increase accuracy of the prediction.

Final model:

Retained SNPs from the candidate gene (9 SNPs) and GWAS-BMI models (12 SNPs) were included together into one final logistic model. Using the AIC model selection, 18 SNPs were retained in the final model (table 2, right column. See Equation, Supplemental Digital Content 7, which gives the model equation), with the 3 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 to the model containing only clinical data (p_{LRT}<0.001). An increase of accuracy, NPV and PPV was also observed (Table 3). An increase of predicted risk, as shown in figure 1 (left), was observed for 46 patients having a >5% WG (red dots) and 45 patients having ≤5% WG (green dots) whereas 10 patients with >5% WG and 147 patients with ≤5% WG have a

decrease of their predicted risk after inclusion of genetic data. Distribution of predicted risk (figure1, right), indicates that 80% of ≤5% WG patients (gray bar) have a less than 20% predicted risk to have a >5% WG.

Replication cohort

A small sample of 32 newly included patients with compliance ascertained was used as replication cohort. These patients were significantly younger than in the discovery cohort (median (IQR) age: 33(20) versus 46(41) years old, p=0.02). No other differences were observed between the two cohorts except for aripiprazole, lithium and olanzapine which were more prescribed in the replication cohort and risperidone which was more prescribed in the discovery cohort (see Table, Supplemental Digital Content 8). Comedication possibly inducing WG was also more frequent in the discovery cohort.

The discovery model was used to predict >5% WG for the 32 patients in the replication cohort (see Table, Supplemental Digital Content 9, which presents prediction results for each patient). ROC curves calculated with the clinical and genetic-based model were similar between the two cohorts (see Figure, Supplemental Digital Content 10, $AUC_{replication}$=0.9; p_{AUC}=0.9). Accuracy, specificity, sensitivity, NPV and PPV layed outside of the 95^{th} interval (Table 3) which may be explained, in part, by the small size of the replication cohort. There was no difference as to the predicted risk between the two cohorts when comparing patients with ≤5% WG (p=0.2) and >5% WG (p=0.1, see Figure, Supplemental Digital Content 11).

Validation for long term weight changes:

GAMM prediction of WG over the first year is represented in figure 2 (see Figure, Supplemental Digital Content 12, which presents raw data). Patients having >5% WG after one month of treatment (left plot, red line) had a stronger WG during the first year of

treatment than patients having ≤5% WG (green line; linear mixed model controlled by several confounders: β=7.8%; $p_{adjusted}$<0.0001; see Table, Supplemental Digital Content 13). Patients predicted before treatment to have >5% or ≤5% WG after one month of treatment, based on clinical and genetic data, are shown on the right plot (figure 2).The difference of WG between the two predicted groups was significant after one year (β=4.4%; $p_{adjusted}$<0.0001; see Table, Supplemental Digital Content 13).

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 as compared to the clinical model alone. In other words, 6 patients have to be genotyped to detect one patient misclassified after using clinical parameters only.

DISCUSSION

A fast (after one month) and important (>5%) WG following treatment with WG inducing psychotropic drugs has been shown to be a good predictor for important 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 gender 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 significantly associated with a >5% WG (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 in function of their potential weight gain 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 naïve. However, a higher proportion of olanzapine prescription was observed in the >5% WG group, in agreement with the fact that olanzapine is one of the most potent WG inducing antipsychotic.

The model combining clinical and genetic data selected from T2DM-GWAS showed no significant AUC increase compared to the clinical model alone. This could first be explained by the short duration of treatment examined in the present study, which diminishes 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 aetiology 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 which were most significantly associated with fast and important WG, *ADIPOQ rs17300539*, located in the promoter region, was found to be strongly associated with low adiponectin levels (37). It could thus be associated with metabolic disorders, although discrepant results have been published intwo 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). Of note, beside 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 significantly the predictive power of the model. In addition, only the final model resulted in an increase of NPV and PPV when compared to the clinical model alone. Of note, patients with >5% WG at one month (i.e. those misclassified and those correctly predicted to develop >5%WG) did have an important WG over the first year of treatment compared to 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. Firstly, most of the patients were not drug naïve, and thus possibly already experienced major WG during previous pharmacological treatments. However, non-drug naïve psychiatric patients represent the majority of cases in clinical practice, which should strengthen the validity of our results in real world conditions. Secondly, 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 reached even after adding more genetic information. Thirdly, the present results are valid only for predicting a >5% WG after a short (1 month) period of treatment. However, consequences on weight and other metabolic features have been demonstrated for one year treatment. Because of the naturalistic condition of the study, it is not known if some patients, in particular those with a high WG, decreased their caloric intake and/or increase their physical activity following recommendations given by their treating physicians and/or nurses. Due to the lack of data on the individual effect of each SNP, an unweighted approach was used, which might over or under-estimate the effect of certain SNPs. Fourthly, 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 performed in the future.

The strengths of the present study include its naturalistic setting, 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 non-compliance, possibly leading to false evaluation of the patients (no WG because of non-compliance). To our knowledge, the present study is the most thorough genetic study performed in psychiatric patients for predicting WG during psychotropic treatment with the validity of the model confirmed in a replication cohort.

In conclusion, this study explores the potential role of known SNPs to identify subjects 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 when compared to clinical risk factors alone, such as age and baseline BMI. Future studies should be performed to replicate the present results in a larger cohort and to investigate prospectively the implementation of this predictive test in a 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 subjects at high risk for a rapid weight gain. Such patients should be prescribed, whenever possible, psychotropic drugs with low potential for weight gain 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.

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Author Contributions:

Prof CB. 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.

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Drafting of the manuscript: F. Vandenberghe

Critical revision of the manuscript for important intellectual content: all authors

Statistical analysis: F. Vandenberghe, M. Gholam-Rezaee

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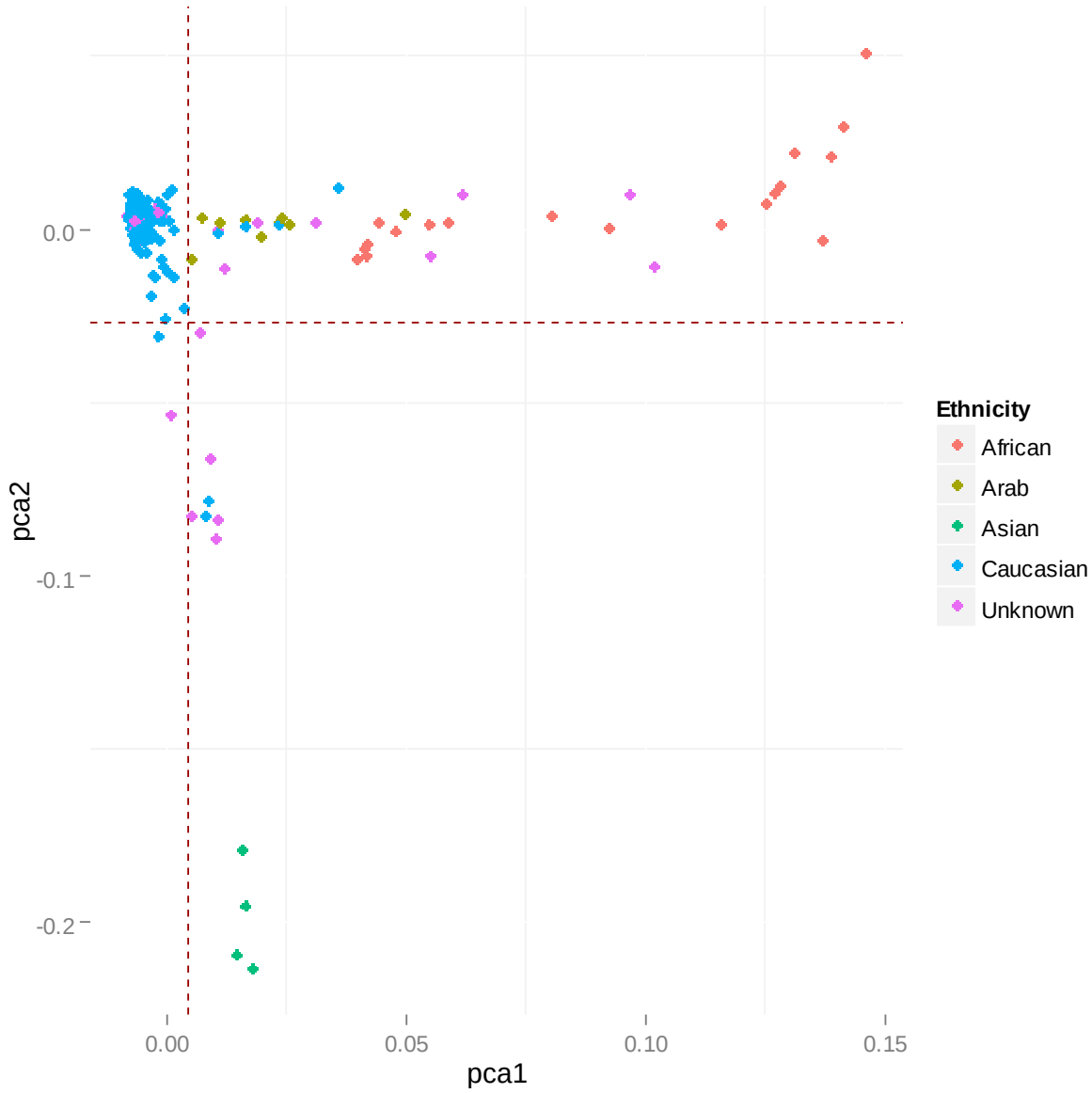

Supplemental Digital Content 1: Principal component analysis versus reported ethnicity.

Supplemental Digital Content 2: Selected SNPs from GWAS and candidate gene studies.

SNP	Gene	Author	Analyzed proxy[a]	Allele[b,d]	MAF-caucasian population (%)[c,d]	MAF-present study (%)	HW p-value[e]
GWAS -Type 2 diabetes mellitus							
rs243021	*BCL11A*			G | A	46	45	0.327
rs10440833	*CDKAL1*		*rs9368222*	C | A	27	28	0.524
rs10965250	*CDKN2A,CDKN2B*			A | G	16	17	0.434
rs1552224	*CENTD2*			A | C	16	12	0.764
rs13292136	*CHCHD9*		*rs4295736*	G | A	7	4	0.327
rs5945326	*DUSP9*			A | G	26	21	**0.000**
rs11642841	*FTO*			C | A	42	38	0.760
rs5015480	*HHEX,IDE*			C | T	45	43	0.771
rs1531343	*HMGA2*			G | C	12	14	0.259
rs7957197	*HNF1A*		*rs7965349*	C | T	19	20	0.586
rs1470579	*IGF2BP2*			C | A	29	35	**0.005**
rs7578326	*IRS1*	Voight et al. 2010(1)		A | G	35	37	0.784
rs849134	*JAZF1*			A | G	47	49	0.664
rs231362	*KCNQ1*			A | G	49	49	0.839
rs972283	*KLF14*		*rs13234407*	G | A	46	45	0.704
rs1387153	*MTNR1B*			C | T	28	31	0.064
rs8042680	*PRC1*		*rs4932182*	A | C	35	36	0.308
rs3802177	*SLC30A8*			G | A	29	26	0.371
rs7903146	*TCF7L2*			T | C	31	39	0.309
rs896854	*TP53INP1*			T | C	46	46	0.294
rs1801214	*WFS1*		*rs10012946*	T | C	37	40	0.866
rs4457053	*ZBED3*			A | G	32	31	0.223
rs11634397	*ZFAND6*			A | G	34	32	0.389
GWAS - BMI							
rs10767664	*BDNF*		*rs2030323*	A | C	24	27	0.740
rs13078807	*CADM2*			A | G	20	20	0.645
rs9816226	*ETV5*			T | A	19	20	**0.034**
rs7138803	*FAIM2*			G | A	34	34	0.108
rs887912	*FANCL*			C | T	27	29	0.166
rs2112347	*FLJ35779, HMGCR*			T | G	38	31	0.724
rs1558902	*FTO*		*rs1421085*	T | C	44	42	0.316
rs10938397	*GNPDA2*			A | G	42	41	0.425
rs12444979	*GPRC5B, IQCK*			C | T	12	14	0.975
rs29941	*KCTD15*			G | A	32	32	0.931
rs2890652	*LRP1B*			C | T	16	18	0.710
rs10968576	*LRRN6C*			A | G	31	26	0.735
rs2241423	*MAP2K5, LBXCOR1*			G | A	23	24	0.939
rs571312	*MC4R*			C | A	23	24	0.721
rs3817334	*MTCH2*			C | T	42	39	0.343
rs4771122	*MTIF3, GTF3A*	Speliotes et al. 2010(2)		G | A	26	24	0.671
rs2815752	*NEGR1*			G | A	37	36	0.107
rs10150332	*NRXN3*			T | C	22	17	0.062
rs206936	*NUDT3, HMGA1*			G | A	20	22	0.443
rs11847697	*PRKD1*		*rs10134820*	C | T	5	4	0.325
rs1555543	*PTBP2*			C | A	42	44	0.356
rs2287019	*QPCTL, GIPR*			C | T	19	18	0.833
rs713586	*RBJ, ADCY3, POMC*			T | C	46	46	0.673
rs4929949	*RPL27A, TUB*		*rs11041999*	T | C	50	50	0.950
rs543874	*SEC16B*			A | G	20	18	0.100
rs7359397	*SH2B1*			C | T	34	36	0.332
rs13107325	*SLC39A8*			C | T	8	6	0.147
rs987237	*TFAP2B*			A | G	20	19	0.263
rs3810291	*TMEM160*			G | A	34	34	0.395
rs2867125	*TMEM18*			C | T	18	17	0.129
rs1514175	*TNNI3K*			A | G	44	41	0.718
rs4836133	*ZNF608*		*rs6864049*	G | A	47	47	0.626
Candidate gene studies - Psychotropic drug - induced weight gain							
rs1045642	*ABCB1*	Kuzman et al, 2008(3)	*rs2235048*	A | G	47	46	0.603
rs2032582	*ABCB1*	Kuzman et al, 2008(3)	*rs4148738*	T | C	45	45	**0.042**
rs17300539	*ADIPOQ*	Jassim et al. 2011(4)		G | A	7	9	0.562
rs4994	*ADRB3*	Ujike et al. 2008(5)	*rs4998*	G | C	8	6	0.220
rs11214601	*ANKK1*	Houston et al. 2012(6)		C | T	14	14	0.679
rs1800497	*ANKK1*	Muller et al. 2012(7)		A | G	18	18	0.568
rs11030101	*BDNF*	Tsai et al. 2011(8)	*rs10835187*	C | T	44	48	0.239
rs1519480	*BDNF*	Zai et al. 2012(9)		T | C	29	29	0.187
rs6265	*BDNF*	Lane et al. 2006(10)		C | T	20	24	0.851
rs10485170	*CNR1*	Tiwari et al. 2010(11)		T | C	10	9	0.186
rs806378	*CNR1*	Tiwari et al. 2010(11)		C | T	27	26	0.670
rs806380	*CNR1*	Tiwari et al. 2010(11)		A | G	33	33	0.849
rs9450902	*CNR1*	Tiwari et al. 2010(11)		C | G	10	9	0.186
rs1079598	*DRD2*	Muller et al. 2012(7)		A | G	14	13	0.211
rs1801028	*DRD2*	Lane et al. 2006(10)		G | C	2	3	0.648
rs2440390	*DRD2*	Houston et al. 2012(6)		T | C	13	13	0.993
rs6277	*DRD2*	Muller et al. 2012(7)		G | A	46	45	0.631
rs324420	*FAAH*	Monteleone et al. 2010(12)		C | A	21	18	0.568
rs6313	*HTR2A*	Ujike et al. 2008(5)		G | A	44	44	0.121
rs518147	*HTR2C*	Godlewska et al. 2009(13)		C | G	33	34	**0.000**
rs17047764	*INSIG2*	Le Hellard et al. 2009(14)		C | G	17	16	0.890
rs17587100	*INSIG2*	Le Hellard et al. 2009(14)		A | C	10	6	0.311
rs4731426	*LEP*	Srivastava et al. 2008(15)		G | C	44	43	0.120
rs7799039	*LEP*	Brandl et al. 2012(16)	*rs10487506*	G | A	46	46	**0.033**
rs1137101	*LEPR*	Ellingrod et al. 2007(17)		A | G	49	39	0.375
rs17782313	*MC4R*	Czerwensky et al. 2013(18)	*rs10871777*	A | G	24	24	0.851
rs489693	*MC4R*	Malhotra et al. 2012(19)		A | C	31	31	0.354
rs1801131	*MTHFR*	Kao et al. 2014(20)		T | G	32	30	0.930
rs16147	*NPY*	Tiwari et al. 2013(21)		T | C	47	48	0.501
rs11624704	*NRXN3*	Hu et al. 2013(22)		A | C	14	13	0.188
rs3754860	*POMC*	Chowdhury et al. 2014(23)	*rs7589318*	G | A	29	26	0.688
rs1801282	*PPARG*	Herken et al. 2009(24)	*rs2197423*	G | A	12	13	0.087
rs10074991	*PRKAA1*	Jassim et al. 2011(4)		A | G	29	32	0.608
rs10789038	*PRKAA2*	Souza et al. 2012(25)		A | G	49	46	0.180

[a]Proxies (R^2>0.75) were selected when the SNP of interest was not available in the Cardiometabochip.

[b]Left allele corresponds to the ancestral allele.

[c]MAF from the 1000 Genome Project Phase 1.

[d]Correspond to the analyzed proxy if used.

[e] P-values in bold when SNPs deviate from Hardy-Weinberg equilibrium.

Abbreviations: MAF=Minor allele frequency; HW=Hardy-Weinberg equilibrium.

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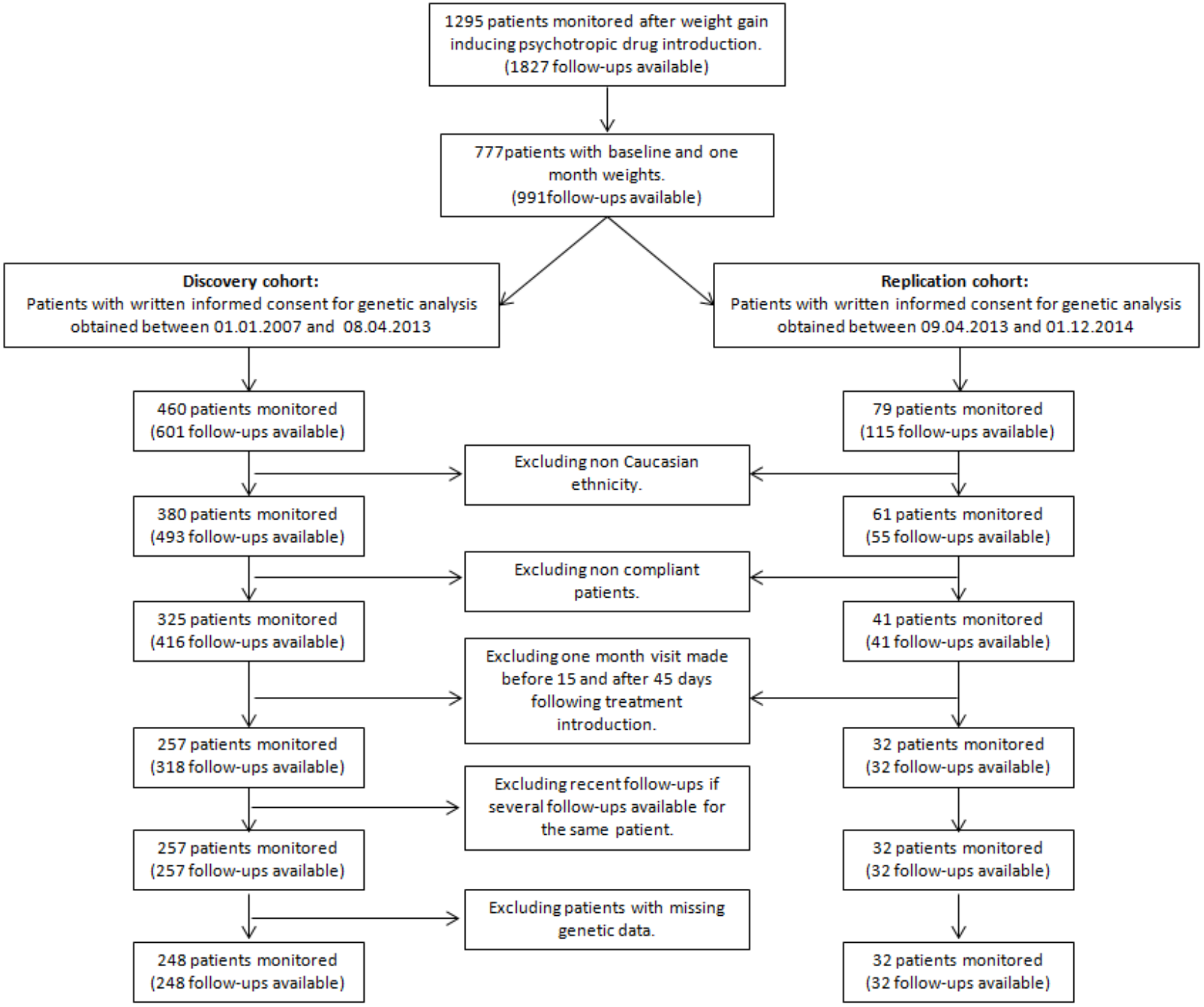


Supplemental Digital Content 3: Patient selection flow chart.

Table1: 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/total n (%)	112/248 (45)	84/192 (44)	28/56 (50)	0.4
Smoking, 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/total n (%)				
BMI < 25 kg/m^2	159/248 (64)	115/192 (60)	44/56 (79)	**0.01**
BMI [25-30[, kg/m^2	55/248 (22)	46/192 (24)	9/56 (16)	0.3
BMI ≥ 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-chol. 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), Δ cm	3 (9)	2 (9)	7.5 (7.5)	**0.01**
HDL-chol., median (IQR), Δ mmol/l	0 (0.3)	0 (0.3)	-0.1 (0.2)	**0.03**
Triglyceridemia, median (IQR), Δ mmol/l	0.1 (0.7)	0.1 (0.6)	0.3 (1.1)	**0.04**
Fasting glucose, median (IQR), Δ mmol/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), Δ cm	3 (9)	3 (8)	5 (12)	0.8
HDL-chol., median (IQR), Δ mmol/l	-0.2 (0.4)	-0.1 (0.3)	-0.3 (0.4)	**0.005**
Triglyceridemia, median (IQR), Δ mmol/l	0.1 (0.8)	-0.1 (0.5)	1.3 (3)	**<0.001**
Fasting glucose, median (IQR), Δ mmol/l	0.2 (0.8)	0 (0.7)	0.6 (1.1)	**0.05**
Diagnosis, n/total 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/total 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[C], n/total n (%)	119/248 (48)	97/192 (51)	22/56 (39)	0.2
Co-medication possibly inducing weight gain[d], n/total n (%)	33/248 (13)	22/192 (11)	11/56 (20)	0.1

[a] p-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between both groups.

[b] Metabolic syndrome is present if: presence of central obesity (Waist circumference : 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 or treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 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.

Table 2: Final logistic model

Variable	Clinical model		Final model	
	OR (IC_{95})	P	OR (IC_{95})	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
Ilness duration (years/10)	1 (1-1)	0.9	1.1 (0.7-1.7)	0.7
Medication				
Medium versus low weight gain inducer[a]	0.5 (0.2-1.3)	0.2	0.3 (0.1-1.1)	0.07
High versus low weight gain inducer[b]	1.2 (0.4-3.5)	0.7	0.9 (0.3-3.6)	0.9
Poly-medication (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

[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.

Supplemental Digital Content 4: Logistic regression results including SNPs related to type 2 diabetes (Voight et al. 2010).

Variable	Estimate (se)	OR (IC_{95})	P
Intercept	-0.695 (1.966)	0.5 (0-19.3)	0.7
Personal			
Age (years/10)	-0.155 (0.097)	0.9 (0.7-1)	0.1
Baseline BMI (kg/m^2)/10	-1.164 (0.399)	0.3 (0.1-0.7)	0.004
Male	-0.032 (0.362)	1 (0.5-2)	0.9
Psychiatric illness			
Schizoaffective vs psychotic disorders	0.688 (0.685)	2 (0.5-7.6)	0.3
Bipolar vs psychotic disorders	-0.097 (0.532)	0.9 (0.3-2.5)	0.9
Depression vs psychotic disorders	0.162 (0.532)	1.2 (0.4-3.3)	0.8
Organic vs psychotic disorders	-0.377 (0.852)	0.7 (0.1-3.4)	0.7
Other vs psychotic disorders	-0.468 (0.522)	0.6 (0.2-1.7)	0.4
Illness duration (years/10)	-0.003 (0.207)	1 (0.7-1.5)	0.9
Medication			
Medium versus low weight gain inducer	-0.686 (0.48)	0.5 (0.2-1.3)	0.2
High versus low weight gain inducer	0.384 (0.56)	1.5 (0.5-4.5)	0.5
Poly-medication (yes)	-0.385 (0.359)	0.7 (0.3-1.4)	0.3
Gene, rs number (risk allele)			
CHCHD9, rs4295736(G)	1.104 (0.8)	3 (0.8-20.4)	0.2
ZBED3, rs4457053(G)	0.376 (0.262)	1.5 (0.9-2.4)	0.2
IRS1, rs7578326(A)	0.376 (0.263)	1.5 (0.9-2.5)	0.2
TCF7L2, rs7903146(T)	0.444 (0.251)	1.6 (1-2.6)	0.08

Table 3: Predictive statistics

Logistic model	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	

[a] Median and 95th percentiles for each parameter were determined by using 10000 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] Due to too small sample size, no bootstrap could be performed and thus no percentiles were obtained.

In bold are the parameters lying out of the corresponding 95th calculated in the clinical model, which is considered as different.

Abbreviations: TN=True negative (n cases); TP=True positive (n cases); FN=False negative (n cases); FP=False positive (n cases); SP=Specificity; SE=Sensibility; NPV=Negative predictive value; PPV=positive predictive value; AUC=Area under the curve.

Supplemental Digital Content 5: Logistic regression results including SNPs related to BMI (Speliotes et al. 2010).

Variable	Estimate (se)	OR (IC_{95})	P
Intercept	-2.05 (1.65)	0.1 (0-3.1)	0.2
Personal			
Age (years/10)	-0.182 (0.105)	0.8 (0.7-1)	0.08
Baseline BMI (kg/m^2)/10	-1.465 (0.462)	0.2 (0.1-0.5)	0.002
Male	-0.041 (0.403)	1 (0.4-2.1)	0.9
Psychiatric illness			
Schizoaffective vs psychotic disorders	0.877 (0.818)	2.4 (0.5-12)	0.3
Bipolar vs psychotic disorders	0.024 (0.602)	1 (0.3-3.3)	1
Depression vs psychotic disorders	0.409 (0.616)	1.5 (0.4-5.1)	0.5
Organic vs psychotic disorders	-0.612 (0.935)	0.5 (0.1-3.2)	0.5
Other vs psychotic disorders	-0.627 (0.57)	0.5 (0.2-1.6)	0.3
Illness duration (years/10)	-0.023 (0.222)	1 (0.6-1.5)	0.9
Medication			
Medium versus low weight gain inducer	-0.966 (0.557)	0.4 (0.1-1.2)	0.08
High versus low weight gain inducer	-0.016 (0.626)	1 (0.3-3.4)	1
Poly-medication (yes)	-0.515 (0.401)	0.6 (0.3-1.3)	0.2
Gene, rs number (risk allele)			
FANCL, rs887912 (T)	0.491 (0.282)	1.6 (0.9-2.9)	0.08
GPRC5B, IQCK rs12444979 (T)	1.095 (0.385)	3 (1.4-6.5)	0.004
LRP1B, rs2890652 (C)	0.573 (0.325)	1.8 (0.9-3.4)	0.08
LRRN6C, rs10968576 (A)	0.485 (0.326)	1.6 (0.9-3.2)	0.1
MTCH2, NDUFS3, CUGBP1 rs3817334 (C)	0.459 (0.294)	1.6 (0.9-2.9)	0.1
MTIF3, GTF3A rs4771122 (G)	0.534 (0.314)	1.7 (0.9-3.2)	0.09
NRXN3, rs10150332 (T)	0.621 (0.384)	1.9 (0.9-4.2)	0.1
RPL27A, TUB rs11041999 (T)	0.402 (0.274)	1.5 (0.9-2.6)	0.1
SEC16B, rs543874 (G)	0.713 (0.361)	2 (1-4.2)	0.05
SH2B1, APOB48R, SULT1A2, AC138894.2, ATXN2L, TUFM, rs7359397 (T)	0.445 (0.294)	1.6 (0.9-2.8)	0.1
TMEM160, ZC3H4 rs3810291 (G)	0.589 (0.283)	1.8 (1-3.2)	0.04
ZNF608, rs6864049 (A)	0.976 (0.29)	2.7 (1.5-4.8)	0.001

Supplemental Digital Content 6: Logistic regression results including SNPs related to antipsychotic induced weight gain.

Variable	Estimate (se)	OR (IC_{95})	P
Intercept	-5.603 (2.262)	0 (0-0.3)	0.01
Personal			
Age (years/10)	-0.183 (0.104)	0.8 (0.7-1)	0.08
Baseline BMI (kg/m^2)/10	-1.565 (0.447)	0.2 (0.1-0.5)	0.0005
Male	-0.03 (0.401)	1 (0.4-2.1)	0.9
Psychiatric illness			
Schizoaffective vs psychotic disorders	0.555 (0.716)	1.7 (0.4-7)	0.4
Bipolar vs psychotic disorders	-0.324 (0.561)	0.7 (0.2-2.1)	0.6
Depression vs psychotic disorders	0.469 (0.581)	1.6 (0.5-5)	0.4
Organic vs psychotic disorders	-0.862 (0.915)	0.4 (0.1-2.4)	0.3
Other vs psychotic disorders	-0.379 (0.546)	0.7 (0.2-2)	0.5
Illness duration (years/10)	-0.062 (0.219)	0.9 (0.6-1.4)	0.8
Medication			
Medium versus low weight gain inducer	-0.987 (0.532)	0.4 (0.1-1.1)	0.06
High versus low weight gain inducer	0.022 (0.61)	1 (0.3-3.4)	1
Poly-medication (yes)	-0.507 (0.374)	0.6 (0.3-1.2)	0.2
Gene, rs number (risk allele)			
ADIPOQ, rs17300539 (G)	1.364 (0.503)	3.9 (1.6-11.5)	0.007
BDNF, rs10835187 (C)	0.402 (0.267)	1.5 (0.9-2.5)	0.1
DRD2, rs6277 (G)	0.559 (0.271)	1.7 (1-3)	0.04
FAAH, rs324420 (A)	0.709 (0.333)	2 (1.1-3.9)	0.03
INSIG2, rs17587100 (C)	1.591 (0.713)	4.9 (1.4-24.3)	0.03
LEPR, rs1137101 (A)	0.408 (0.266)	1.5 (0.9-2.5)	0.1
MC4R, rs10871777 (A)	0.524 (0.31)	1.7 (0.9-3.2)	0.09
MTHFR, rs1801131 (G)	0.57 (0.281)	1.8 (1-3.1)	0.04
PPARG, rs2197423 (G)	0.811 (0.444)	2.3 (1-5.6)	0.07

Supplemental Digital Content 7: Final model equation.

$$\Pr(5\%\ \mathrm{WG} = 1|0) = \frac{1}{1 + e^{-\boldsymbol{\theta}}}$$

$$\begin{aligned}\boldsymbol{\theta} = {} & -6.337 - 0.232 * \left(\frac{\mathrm{age}}{10}\right) - 1.749 * \frac{\mathrm{baselineBMI}}{10} + 0.087 * (0 \text{ if female } |1 \text{ if male}) \\ & + \textbf{diagnostic} + (-1.105 \text{ if medium weight gain inducer}| \\ & - 0.054 \text{ if high weight gain inducer}) + \textbf{genetic}\end{aligned}$$

$$\begin{aligned}\textbf{diagnostic} = {} & (0 \text{ if psychotic disorders} |\ 1.083 \text{ if schizoaffective} \\ & - 0.118 \text{ if bipolar disorders} |\ 0.502 \text{ if depression} | \\ & - 0.783 \text{ if organic} | 0.804 \text{ if other})\end{aligned}$$

$$\begin{aligned}\textbf{genetic} = {} & 1.587 * (1 \text{ if rs17300539=GG} | 2 \text{ if rs17300539=GA} | 3 \text{ if rs17300539=AA}) \\ & + 0.547 * (1 \text{ if rs10835187=CC} | 2 \text{ if rs10835187=CT} | 3 \text{ if rs10835187=TT}) \\ & + 0.569 * (1 \text{ if rs6277=GG} | 2 \text{ if rs6277=GA} | 3 \text{ if rs6277=AA}) \\ & + 1.166 * (1 \text{ if rs324420=AA} | 2 \text{ if rs324420=AC} | 3 \text{ if rs324420=CC}) \\ & + 1.249 * (1 \text{ if rs12444979=TT} | 2 \text{ if rs12444979=TC} | 3 \text{ if rs12444979=CC}) \\ & + 1.645 * (1 \text{ if rs17587100=CC} | 2 \text{ if rs17587100=CA} | 3 \text{ if rs17587100=AA}) \\ & + 0.604 * (1 \text{ if rs2890652=CC} | 2 \text{ if rs2890652=CT} | 3 \text{ if rs2890652=TT}) \\ & + 0.536 * (1 \text{ if rs10968576=AA} | 2 \text{ if rs10968576=AG} | 3 \text{ if rs10968576=GG}) \\ & + 0.532 * (1 \text{ if rs10871777=AA} | 2 \text{ if rs10871777=AG} | 3 \text{ if rs10871777=GG}) \\ & + 0.505 * (1 \text{ if rs3817334=CC} | 2 \text{ if rs3817334=CT} | 3 \text{ if rs3817334=TT}) \\ & + 0.572 * (1 \text{ if rs1801131=GG} | 2 \text{ if rs1801131=GT} | 3 \text{ if rs1801131=TT}) \\ & + 0.8 * (1 \text{ if rs10150332=TT} | 2 \text{ if rs10150332=TC} | 3 \text{ if rs10150332=CC}) \\ & + 1.1 * (1 \text{ if rs2197423=GG} | 2 \text{ if rs2197423=GA} | 3 \text{ if rs2197423=AA}) \\ & + 0.477 * (1 \text{ if rs11041999=TT} | 2 \text{ if rs11041999=TC} | 3 \text{ if rs11041999=CC}) \\ & + 0.707 * (1 \text{ if rs543874=GG} | 2 \text{ if rs543874=GA} | 3 \text{ if rs543874=AA}) \\ & + 0.453 * (1 \text{ if rs7359397=TT} | 2 \text{ if rs7359397=TC} | 3 \text{ if rs7359397=CC}) \\ & + 0.779 * (1 \text{ if rs3810291=GG} | 2 \text{ if rs3810291=GA} | 3 \text{ if rs3810291=AA}) \\ & + 1.015 * (1 \text{ if rs6864049=AA} | 2 \text{ if rs6864049=AG} | 3 \text{ if rs6864049=GG})\end{aligned}$$

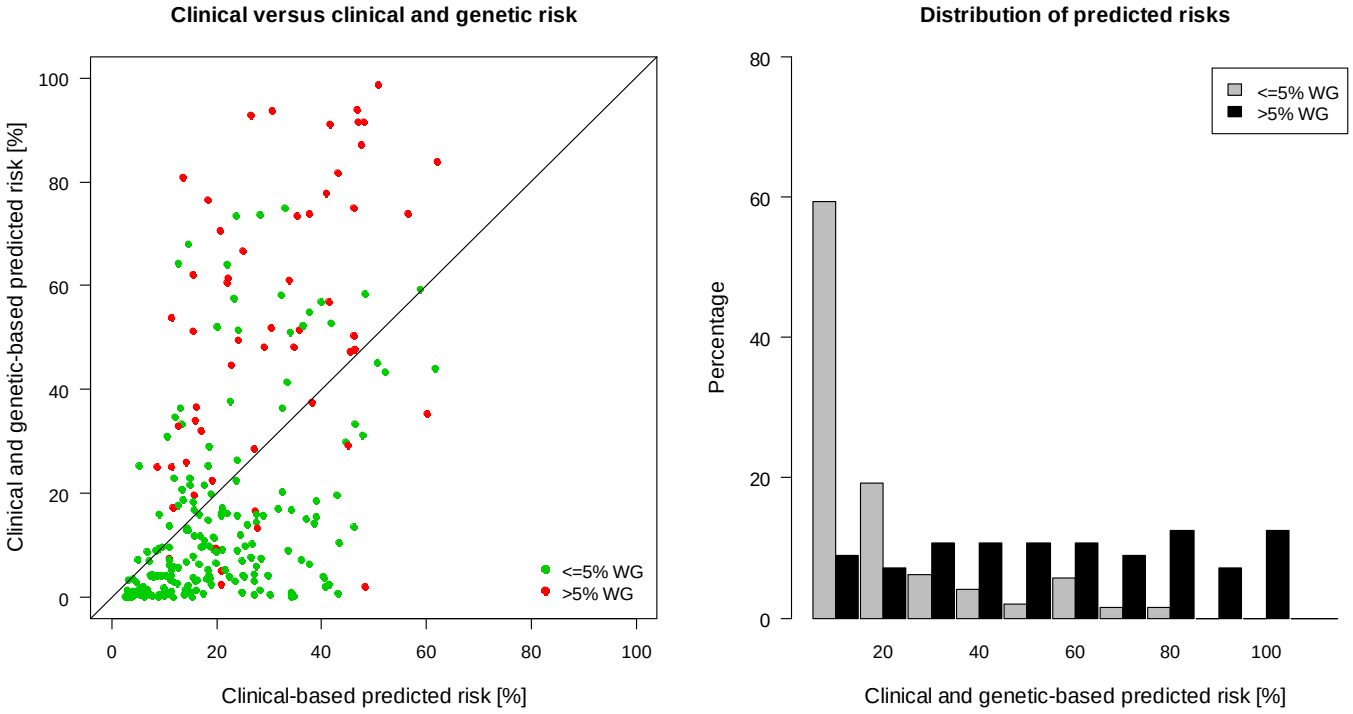


Figure 1: Left scatter plot indicates the predicted risk change between the model with only clinical variables and the model including both clinical and genetic variables. The dots upper the diagonal line indicates that adding genetic variables increases the predicted risk of >5% WG and the dots lower the diagonal line indicates a decrease of >5%WG predicted risk after adding genetic variables. The right bar plot represents the distribution of >5% WG and ≤5% WG cases according to the predicted risk.

Supplemental Digital Content 8: Demographic characteristics of the discovery and the replication cohort.

	All (n=280)	Discovery (n=248)	Replication(n=32)	P[a]
Age, median (IQR), years	44 (40)	46 (41)	33 (20)	**0.02**
Men, n/total n (%)	126/280 (45)	112/248 (45)	14/32 (44)	1
Smoking, n (%)	58/115 (50)	51/107 (48)	7/8 (88)	0.06
Illness duration, median (IQR), years	4 (10)	4 (10)	7 (8)	0.5
One month visit, median (IQR), days	31 (7)	31 (6)	32 (8)	0.08
One month weight gain, median (IQR), %	1.5 (5.8)	1.4 (5.8)	1.6 (4.7)	0.6
>5% weight gain after one month, n (%)	64/280 (23)	56/248 (23)	8/32 (25)	0.8
Metabolic traits prevalence at baseline, n/total n (%)				
BMI < 25 kg/m^2	179/280 (64)	159/248 (64)	20/32 (63)	0.8
BMI [25-30[, kg/m^2	64/280 (23)	55/248 (22)	9/32 (28)	0.5
BMI ≥ 30, kg/m^2	37/280 (13)	34/248 (14)	3/32 (9)	0.8
Waist circumference Men ≥ 94 cm , Women ≥ 80 cm	127/242 (52)	112/213 (53)	15/29 (52)	1
HDL-chol. Men ≤ 1.03 mmol/l, Women ≤ 1.29 mmol/l	37/156 (24)	36/151 (24)	1/5 (20)	1
Triglyceridemia ≥ 1.7 mmol/l or lipid lowering treatment	46/166 (28)	42/159 (26)	4/7 (57)	0.09
Fasting glucose ≥ 5.6 mmol/l or antidiabetic treatment	34/163 (21)	33/156 (21)	1/7 (14)	1
Blood pressure ≥ 130 / 85 mmHg or antihypertensive treatment	72/250 (29)	66/221 (30)	6/29 (21)	0.4
Metabolic syndrome[b]	27/142 (19)	26/127 (20)	1/15 (7)	0.3
Metabolic evolution at 3 months of treatment				
Month weight gain, median (IQR), %	3.8 (8.9)	3.7 (8.7)	5.8 (7.1)	0.3
Waist circumference, median (IQR), Δ cm	3 (9)	3 (9)	5 (8)	0.6
HDL-chol., median (IQR), Δ mmol/l	0 (0.3)	0 (0.3)	0.1 (0.2)	0.4
Triglyceridemia, median (IQR), Δ mmol/l	0.1 (0.7)	0.1 (0.7)	-0.1 (0.1)	0.4
Fasting glucose, median (IQR), Δ mmol/l	0 (0.8)	0 (0.8)	-0.4 (0.2)	0.2
Metabolic evolution at 12 months of treatment				
Month weight gain, median (IQR), %	6.6 (13.9)	6.6 (12.5)	6.4 (23.6)	0.9
Waist circumference, median (IQR), Δ cm	3 (9)	3 (9)	5 (8)	0.8
HDL-chol., median (IQR), Δ mmol/l	-0.1 (0.4)	-0.2 (0.4)	0.1 (0.2)	0.2
Triglyceridemia, median (IQR), Δ mmol/l	0 (0.7)	0.1 (0.8)	-0.1 (0.1)	0.5
Fasting glucose, median (IQR), Δ mmol/l	0.2 (0.8)	0.2 (0.8)	-0.4 (0.2)	0.1
Diagnosis, n/total n (%)				
Bipolar disorder	55/280 (20)	49/248 (20)	6/32 (19)	1
Depression	45/280 (16)	39/248 (16)	6/32 (19)	0.9
Organic disorders	24/280 (9)	23/248 (9)	1/32 (3)	0.4
Psychotic disorders	88/280 (31)	76/248 (31)	12/32 (38)	0.6
Schizoaffective disorder	22/280 (8)	18/248 (7)	4/32 (13)	0.5
Other	46/280 (16)	43/248 (17)	3/32 (9)	0.2
Medication, n/total n (%)				
Amisulpride	23/280 (8)	21/248 (8)	2/32 (6)	0.9
Aripiprazole	22/280 (8)	16/248 (6)	6/32 (19)	**0.03**
Clozapine	18/280 (6)	17/248 (7)	1/32 (3)	0.7
Lithium	24/280 (9)	18/248 (7)	6/32 (19)	**0.04**
Mirtazapine	16/280 (6)	15/248 (6)	1/32 (3)	0.8
Olanzapine	37/280 (13)	29/248 (12)	8/32 (25)	**0.05**
Quetiapine	32/280 (11)	31/248 (13)	1/32 (3)	0.2
Risperidone	105/280 (38)	98/248 (40)	7/32 (22)	**0.05**
Valproate	3/280 (1)	3/248 (1)	0/32 (0)	1
Polymedication[c]	132/280 (47)	119/248 (48)	13/32 (41)	0.5
Co-medicationpossibly inducing weight gain [d]	33/280 (12)	33/248 (13)	0/32 (0)	**0.03**

[a] p-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between both groups.

[b] 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 or treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l (IDF definition).

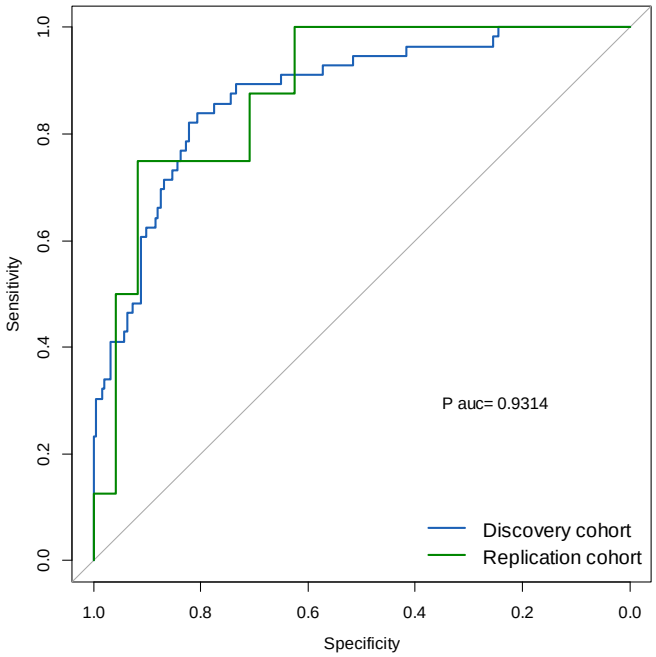
[C] Presence of more than one WG-inducing psychotropic drug (Amisulpride, Aripiprazole, Clozapine, Lithium, Mirtazapine, Olanzapine, Quetiapine, Risperidone, Valproate).

[d] Exhaustive list : Pioglitazone, Rosiglitazone, Cinnarizine, Levocetirizine, Chlormadinone, Desogestrel, Ethinylestradiol, Estradiol, Gestodene, Levonorgestrel, Medroxyprogesterone, Norelgestromin, Carbamazepine, Chlorprothixene, Clomipramine, Flupentixol, Mianserine, Pregabalin, Zuclopenthixol.

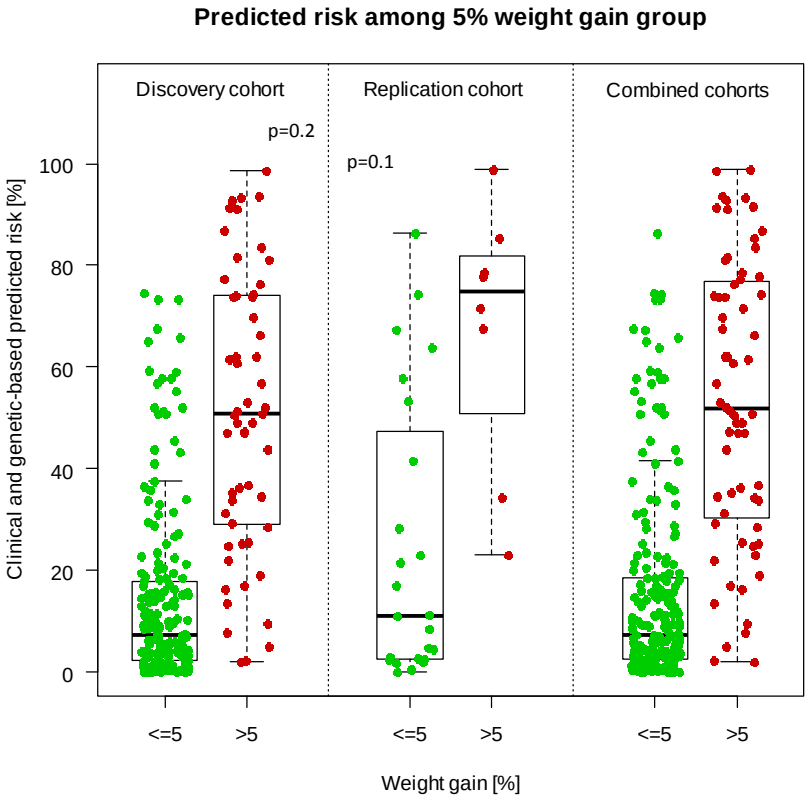
Supplemental Digital Content 9: 5% weight gain predicted on the replication cohort.

id	Baseline BMI	Age	Ilnessduation	Poly medication	Gender	Medication	Diagnostic	*rs17300539 (ADIPOQ)*	*rs10835187 (BDNF)*	*rs6277 (DRD2)*	*rs324420 (FAAH)*	*rs12444979 (GPRC5B, IQCK)*	*rs17587100 (INSIG2)*	*rs2890652 (LRP1B)*	*rs10968576 (LRRN6C)*	*rs10871777 (MC4R)*	*rs3817334 (MTCH2)*	*rs1801131 (MTHFR)*	*rs10150332 (NRXN3)*	*rs2197423 (PPARG)*	*rs11041999 (RPL27A, TUB)*	*rs543874 (SEC16B)*	*rs7359397 (SH2B1)*	*rs3810291 (TMEM160)*	*rs6864049 (ZNF608)*	>5% WG	Model prediction	Class
1	27.2	34	2	Yes	Female	Lithium	Other	0	1	1	1	0	0	0	0	0	2	2	0	1	1	1	1	0	2	No	negative	TN
2	21.5	29	7	Yes	Female	Lithium	Bipolar	0	1	1	1	1	1	1	0	1	1	0	0	0	1	0	0	0	0	No	negative	TN
3	27.5	56	9	Yes	Female	Mirtazapine	Other	0	0	2	1	0	1	0	1	2	1	1	0	0	0	0	1	1	0	No	negative	TN
4	20.7	18	4	No	Female	Risperidone	Depression	0	1	2	1	0	0	1	1	0	1	0	1	0	2	0	0	2	1	No	positive	FP
5	22.8	31	2	No	Female	Risperidone	Depression	0	2	1	1	0	0	0	0	0	0	1	2	0	2	0	0	0	0	Yes	positive	TP
6	24.2	45	9	No	Male	Aripiprazole	Psychotic	1	0	0	1	0	0	0	1	0	2	2	0	0	0	1	2	1	1	No	positive	FP
7	29.4	37	4	Yes	Male	Aripiprazole	Schizoaffective	0	1	1	1	0	0	0	1	0	2	1	0	0	0	0	0	1	2	No	positive	FP
8	18.4	28	10	No	Female	Olanzapine	Psychotic	0	1	2	0	0	1	1	0	0	1	2	0	0	1	0	1	2	2	Yes	positive	TP
9	29.0	45	6	Yes	Female	Lithium	Depression	0	0	0	0	0	0	1	0	0	0	1	0	0	1	0	0	1	1	No	positive	FP
10	41.7	50	7	No	Female	Risperidone	Depression	1	1	0	1	0	0	0	2	1	1	1	0	0	2	1	1	1	2	No	negative	TN
11	20.4	20	1	No	Male	Olanzapine	Psychotic	0	1	1	0	0	0	1	0	0	1	0	0	1	1	0	0	1	1	Yes	positive	TP
12	15.6	33	7	No	Female	Olanzapine	Psychotic	0	1	1	1	1	0	1	0	0	0	1	0	0	1	1	0	0	1	Yes	positive	TP
13	17.9	51	16	Yes	Female	Lithium	Depression	0	1	1	0	0	0	0	1	1	0	0	0	1	0	0	0	1	2	No	negative	TN
14	20.6	22	4	No	Female	Risperidone	Bipolar	0	0	1	0	0	0	0	1	1	2	2	1	0	1	0	1	0	1	No	negative	TN
15	32.9	25	15	No	Male	Aripiprazole	Psychotic	0	1	2	0	0	0	0	2	1	1	0	0	0	1	1	2	1	1	No	negative	TN
16	26.3	30	8	No	Male	Amisulpride	Psychotic	0	1	2	1	0	0	0	2	1	1	0	0	0	2	0	1	0	1	No	negative	TN
17	23.3	20	1	Yes	Female	Aripiprazole	Psychotic	0	0	1	0	0	0	1	0	1	1	1	0	0	1	1	0	0	2	No	positive	FP
18	24.3	61	4	No	Male	Olanzapine	Bipolar	0	2	1	0	0	0	0	0	0	2	1	0	1	1	0	1	2	1	No	negative	TN
19	25.1	75	9	No	Male	Olanzapine	Depression	0	0	1	0	0	0	1	0	0	0	0	0	1	1	1	1	1	1	No	positive	FP
20	21.4	40	1	No	Male	Olanzapine	Psychotic	0	0	2	0	0	0	0	0	0	1	1	0	0	1	0	0	1	0	No	negative	TN
21	23.1	33	0	Yes	Female	Olanzapine	Psychotic	0	0	1	0	0	0	0	0	1	1	0	2	1	1	1	1	1	1	No	negative	TN
22	24.3	84	0	No	Female	Risperidone	Organic	0	2	0	1	0	0	0	0	1	2	0	0	0	1	1	1	0	0	No	negative	TN
23	19.1	55	24	No	Female	Olanzapine	Bipolar	0	1	1	0	0	1	0	1	0	0	1	0	1	1	0	0	0	1	No	negative	TN
24	34.2	33	23	Yes	Female	Amisulpride	Schizoaffective	0	1	0	0	2	0	0	0	0	2	1	1	0	2	1	0	0	0	No	positive	FP
25	21.4	28	10	Yes	Male	Quetiapine	Psychotic	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	2	0	No	negative	TN
26	23.4	23	0	No	Male	Aripiprazole	Psychotic	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	1	2	1	No	positive	FP
27	22.6	38	1	No	Male	Risperidone	Bipolar	0	1	1	1	0	0	1	0	0	1	0	0	0	1	1	0	2	1	No	positive	FP
28	20.8	24	0	No	Female	Risperidone	Psychotic	0	0	1	0	1	0	0	1	0	0	2	1	0	1	2	1	2	0	Yes	positive	TP
29	24.5	44	18	Yes	Female	Clozapine	Schizoaffective	0	1	0	0	0	0	0	0	1	1	0	0	0	1	1	0	2	1	Yes	positive	TP
30	27.2	23	13	Yes	Male	Lithium	Schizoaffective	0	2	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	1	Yes	positive	TP
31	29.6	35	18	Yes	Male	Lithium	Bipolar	0	2	2	0	0	0	1	0	1	1	0	0	1	1	0	1	0	1	No	negative	TN
32	28.0	20	9	No	Male	Aripiprazole	Psychotic	1	1	1	2	0	0	1	0	0	0	0	0	0	1	0	0	0	2	Yes	positive	TP

Abbreviations: TN=True negative; TP=True positive; FN=False negative; FP=False positive.



Supplemental Digital Content 10: Comparison between discovery and replication ROC curves of the clinical and genetic-based model.



Supplemental Digital Content 11: Comparison of predicted risk between patients having ≤5% WG and >5% WG in the 2 cohorts and combined.

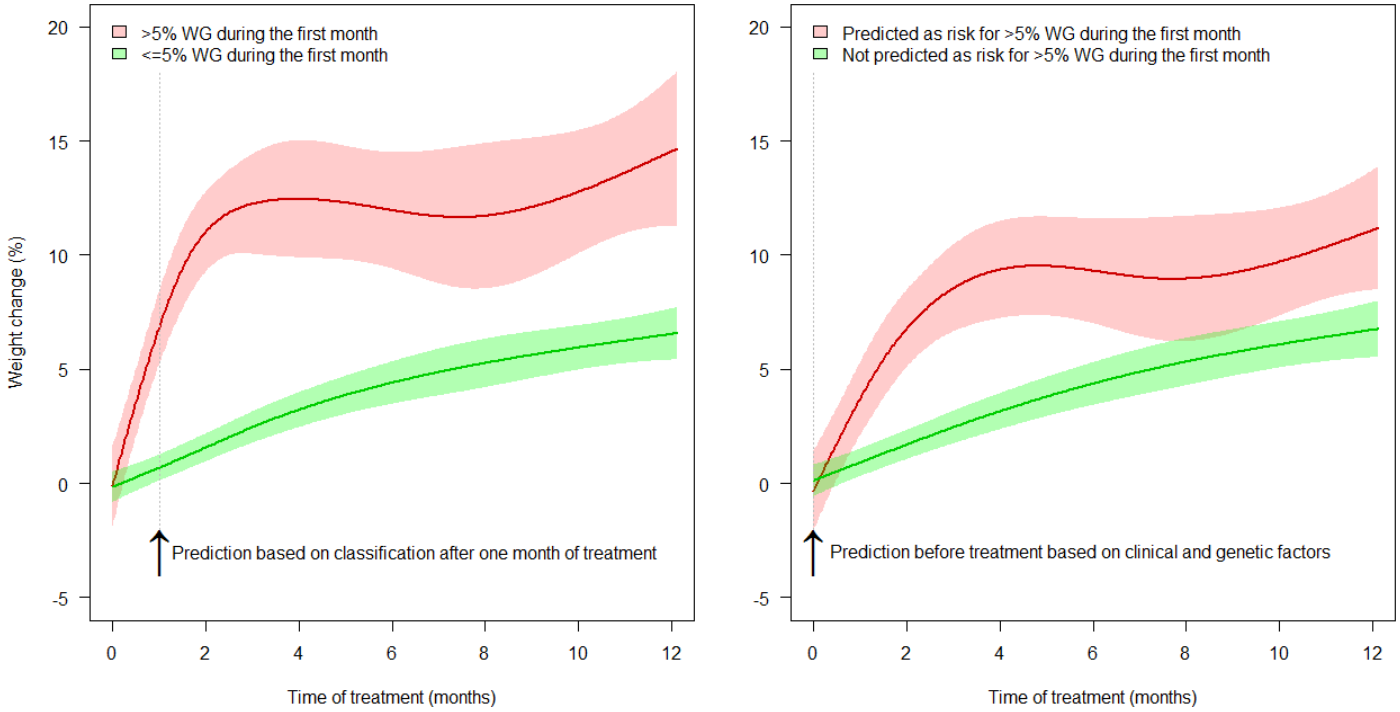
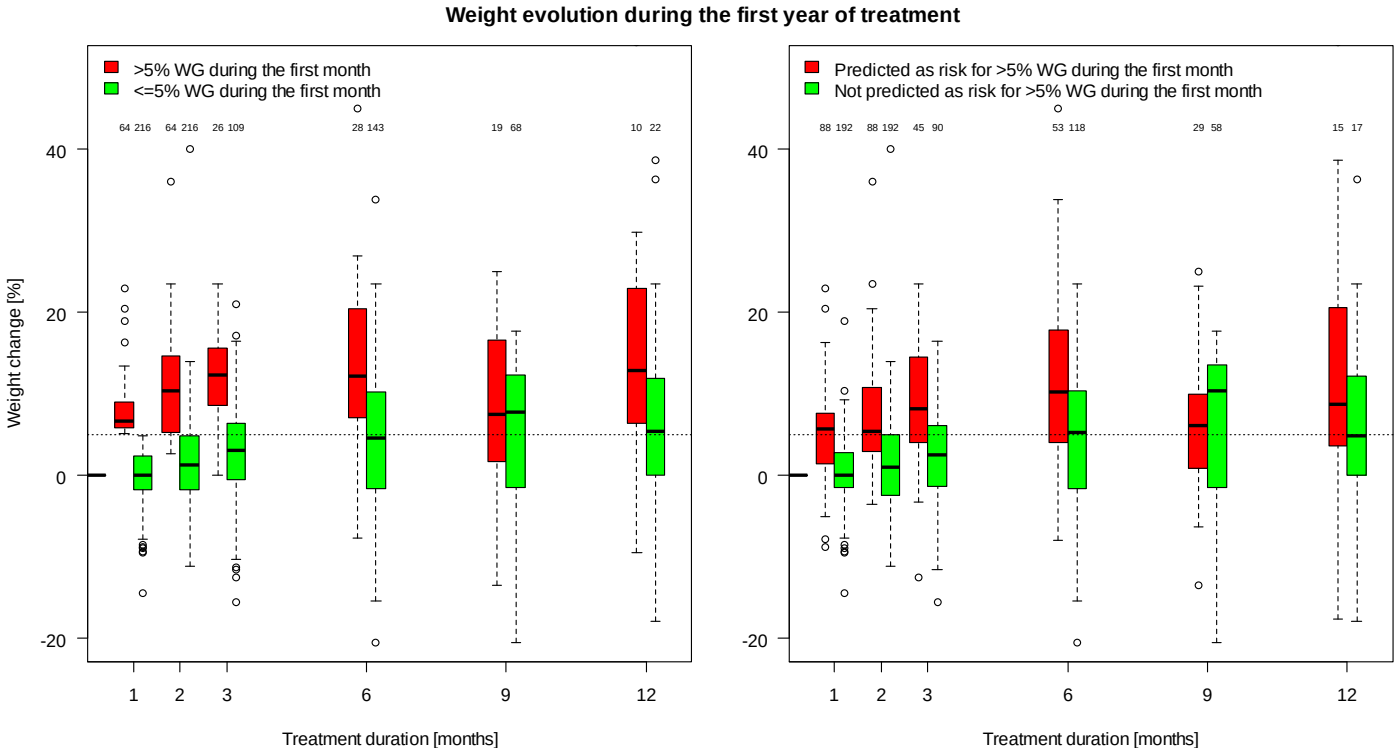


Figure 2: Generalized additive mixed model prediction of weight over one year. The left plot represents weight changes in patients having >5%WG (red) or ≤5%WG (green) after one month following the introduction of weight gain-inducing psychotropic drugs. The right plot represent the prediction before treatment of 5%WG in patients after one month based on clinical and genetic data >5%WG (red) or ≤5%WG (green). CI_{95} is represented by the shaded area.



Supplemental Digital Content 12: The left boxplot represents the evolution of patients having >5% WG and ≤5% WG at one month over the first year of treatment. The right boxplot describes the evolution of the patients predicted before treatment to have >5% WG or ≤5% WG at one month over the first year of treatment based on clinical and genetic data. The black dotted line corresponds to 5% WG.

Supplemental Digital Content 13: Linear mixed effect model fitted on weight change (%) over one year.

	Difference of weight change (%) between ≤5%WG and >5%WG over one year (95%IC)	P
Prediction based on weight changes observed after one month :	7.8 % (6.8% to 8.9%)	<0.0001
Prediction before treatment, based on clinical and genetic data:	4.4% (3.4% to 5.3%)	<0.0001

[a]Results were obtained by fitting a linear mixed model controlling for age, sex, time, baseline BMI .