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Published in final edited form as:

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

Authors: Vandenberghe F, Saigí-Morgui N, Delacrétaz A, Quteineh L, Crettol S, Ansermot N, Gholam-Rezaee M, von Gunten A, Conus P, Eap CB

Journal: Pharmacogenetics and genomics

Year: 2016 Dec

Volume: 26

Issue: 12

Pages: 547-557

DOI: 10.1097/FPC.0000000000000249

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

Frederik Vandenberghe, PharmD, PhD⁽¹⁾; Núria Saigí-Morgui, PharmD, PhD⁽¹⁾; Aurélie Delacrétaz, MSc⁽¹⁾; Lina Quteineh, MD, PhD⁽¹⁾; Séverine Crettol, PharmD, PhD⁽¹⁾; Nicolas Ansermot, PharmD, PhD⁽¹⁾; Mehdi Gholam-Rezaee, PhD⁽²⁾; Armin von Gunten, MPhil, MD⁽³⁾; Philippe Conus, MD⁽⁴⁾; Chin B. Eap, PhD^(1,5).

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

^C For correspondence: Prof CB. Eap

Hospital of Cery, 1008 Prilly – Lausanne, Switzerland

Tel 00 41 21 314 26 04

Fax: 00 41 21 314 24 44

Email: chin.eap@chuv.ch

Key words: weight gain, genetic risk prediction, atypical antipsychotics, mood stabilizers, mirtazapine, weight monitoring.

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 ($AUC_{\text{final}}:0.92$, $AUC_{\text{clinical}}:0.75$, $p<0.0001$). Predicted accuracy increased by 17% with genetic markers ($\text{Accuracy}_{\text{final}}:87\%$), 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 $\leq 5\%$ WG ($p\leq 0.0001$).

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

INTRODUCTION

Overweight and obesity are major public health problems of the current decade, with a prevalence of obesity (body mass index (BMI) $\geq 30 \text{ kg/m}^2$) in the general population ranging from 20% to 23% in Europe (1) and reaching 35% in the US (2). In the psychiatric population, an even higher prevalence of obesity is reported, reaching 49% and 55% for bipolar and schizophrenic patients, respectively (3). In line with obesity-related problems, the psychiatric population have a quadrupled and doubled incidence of type 2 diabetes mellitus (T2DM) and hypertension, respectively, 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 D₂ receptor* or *histamine H₁ 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 $\leq 5\%$ 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 (95th) of accuracy (percentage of correctly classified cases among all subjects), specificity (percentage of correctly predicted patients with $\leq 5\%$ WG among all patients with $\leq 5\%$ 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 $\leq 5\%$ WG among patients who were predicted a $\leq 5\%$ 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 95th 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 $\leq 5\%$ 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 method is based on the inverse of the difference between the accuracy of the model including both clinical and genetic data and the accuracy of the model including clinical data only.

All tests were two sided and p-values ≤ 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 overweighted ($25\text{-}30\text{kg/m}^2$) and 14% were obese ($\geq 30\text{kg/m}^2$). 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 $\leq 5\%$ 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 $< 25\text{kg/m}^2$ were less frequent in the $\leq 5\%$ WG than in the >5% WG patients (60% vs 79%, $p=0.01$). Abdominal obesity and hypo HDL-cholesterolemia were more prevalent in the $\leq 5\%$ 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 $\leq 5\%$ WG and >5% WG patients were observed between baseline and 3 months (median (IQR) $\Delta\text{mmol/l}$ triglycerides: 0.1 (0.6) vs 0.3 (1.1), $p=0.04$; $\Delta\text{mmol/l}$ HDL-cholesterol: 0 (0.3) vs -0.1 (0.2), $p=0.03$) and as well as between baseline and 12 months ($\Delta\text{mmol/l}$ triglycerides: -0.1 (0.5) vs 1.3 (3), $p\leq 0.001$; $\Delta\text{mmol/l}$ 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 ($AUC_{\text{clinical}}(95^{\text{th}}) = 0.75(0.68-0.82)$, $AUC_{\text{clinical/GWAS}}(95^{\text{th}}) = 0.88(0.82-0.93)$, $p_{\text{AUC}} = 0.0002$). Likelihood ratio test between the two models indicated that adding genetic data improved the goodness of fit ($p_{\text{LRT}} < 0.001$), 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 ($\text{Accuracy}_{\text{clinical}}(95^{\text{th}})=70(54-83)$, $\text{Accuracy}_{\text{clinical}/\text{GWAS}}(95^{\text{th}})=83(72-90)$).

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 ($\text{AUC}_{\text{clinical}}(95^{\text{th}})=0.75(0.68-0.82)$, $\text{AUC}_{\text{clinical}/\text{candidate gene}}(95^{\text{th}})=0.85(0.79-0.91)$, $p_{\text{AUC}}=0.01$). Likelihood ratio test confirms that the model containing genetic and clinical data should be preferred to the model including only clinical variables ($p_{\text{LRT}}<0.001$). 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 ($\text{AUC}_{\text{clinical}}:0.75$; $\text{AUC}_{\text{final}}:0.92$; $p_{\text{AUC}}<0.001$) as well as the goodness of fit compared to the model containing only clinical data ($p_{\text{LRT}}<0.001$). 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 $\leq 5\%$ WG (green dots) whereas 10 patients with >5% WG and 147 patients with $\leq 5\%$ WG have a

decrease of their predicted risk after inclusion of genetic data. Distribution of predicted risk (figure1, right), indicates that 80% of $\leq 5\%$ 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, $AUC_{\text{replication}}=0.9$; $p_{AUC}=0.9$). Accuracy, specificity, sensitivity, NPV and PPV layed outside of the 95th interval (Table 3) which may be explained, in part, by the small size of the replication cohort. There was no difference as to the predicted risk between the two cohorts when comparing patients with $\leq 5\%$ 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 $\leq 5\%$ WG (green line; linear mixed model controlled by several confounders: $\beta=7.8\%$; $p_{\text{adjusted}} < 0.0001$; see Table, Supplemental Digital Content 13).

Patients predicted before treatment to have $>5\%$ or $\leq 5\%$ 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 ($\beta=4.4\%$; $p_{\text{adjusted}} < 0.0001$; 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 in two meta-analyses investigating obesity and T2DM (38, 39). The *FAAH rs324420* SNP is located in the fatty acid amide hydrolase locus, and the present result is in agreement with a study investigating PIWG (40). 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.

Funding:

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

Previous results presentation:

Previously presented in part at the 168th annual meeting of the American Psychiatric Association, May 16–20, 2015, Toronto, Canada.

Previously presented in part at the 12th World Congress of Biological Psychiatry, June 14–18, 2015, Athens, Greece.

Acknowledgement:

The authors are grateful to all participating psychiatrists and medical staff who were involved in the metabolic monitoring program.

Author disclosure information:

CBE received research support from Takeda and The Roche Transplantation Research Foundation in the past 3 years.

CBE received honoraria for conferences or teaching CME courses from Advisis, Astra Zeneca, Lundbeck, MSD, Otsuka; Sandoz, Servier and Vifor-Pharma in the past 3 years. A von Gunten received honoraria for a conference and a workshop, not related to this study, organized by Vifor and Bayer Schering within the previous 3 years. All other authors declare no conflict of interest in relation to the content of the paper.

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.

Study concept and design: CB. Eap

Acquisition of data: F. Vandenberghe, N. Saigí-Morgui, A. Delacrétaz, A. von Gunten, P. Conus

Analysis and interpretation: F. Vandenberghe, M. Gholam-Rezaee

Drafting of the manuscript: F. Vandenberghe

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

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

Obtained funding: CB. Eap, P Conus

Administrative, technical, or material support: S. Crettol, N. Ansermot, A. von Gunten, P.

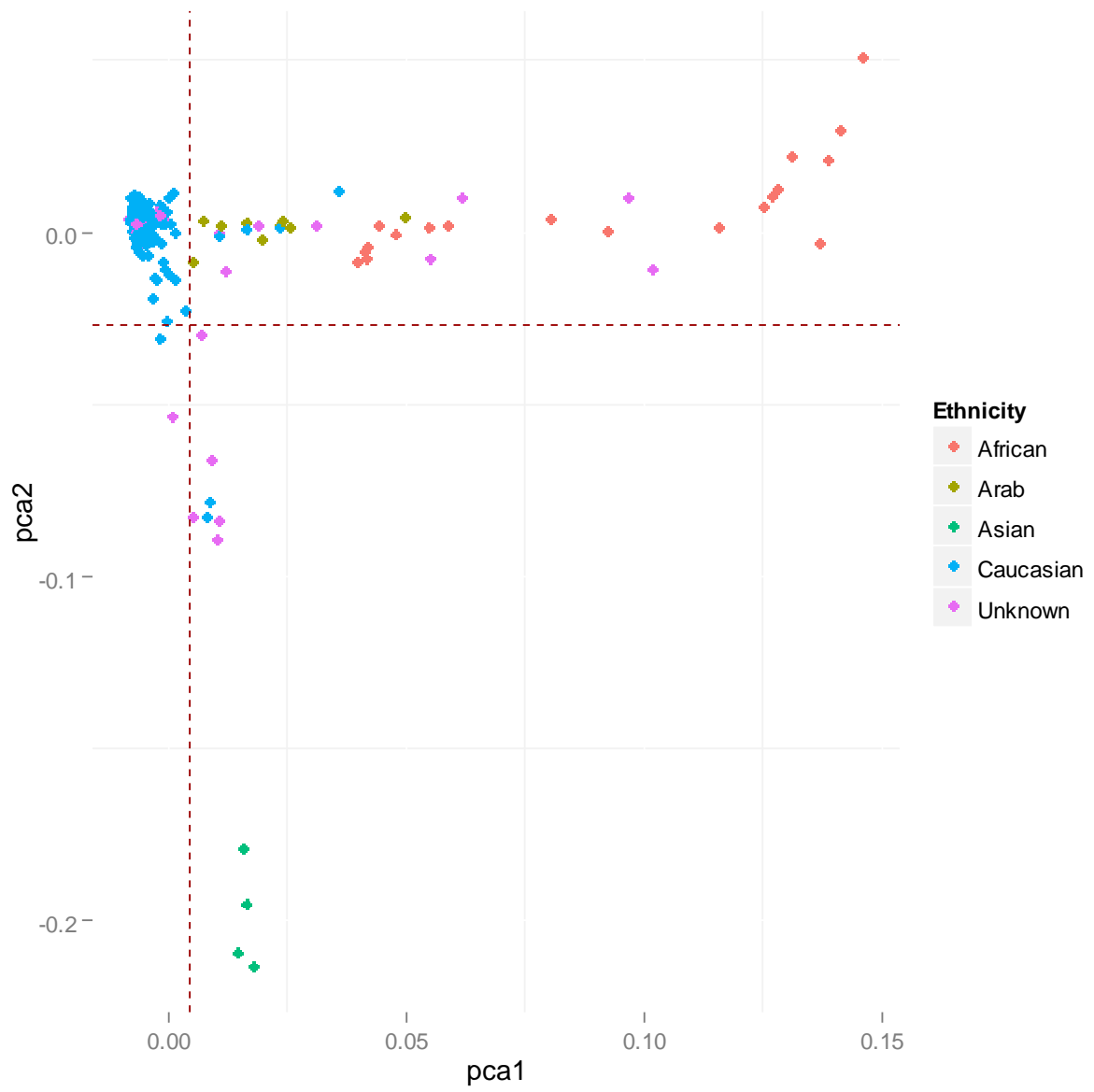
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REFERENCES

1. World Health Organization. 2015 [cited 2015 April]; Available from: www.euro.who.int.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity among adults: United States, 2011-2012. NCHS data brief. 2013(131):1-8. Epub 2013/10/25.
3. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry*. 2009;24(6):412-24.
4. Goff DC, Cather C, Evins AE, Henderson DC, Freudenrich O, Copeland PM, et al. Medical Morbidity and mortality in schizophrenia: guidelines for psychiatrists. *J Clin Psychiatry*. 2005;66(2):183-94.
5. Allison DB, Mentore JL, Heo M, Chandler LP, Capelleri JC, Infante MC, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *American Journal of Psychiatry*. 1999;156:1686-96.
6. Laimer M, Kramer-Reinstadler K, Rauchenzauner M, Lechner-Schoner T, Strauss R, Engl J, et al. Effect of mirtazapine treatment on body composition and metabolism. *Journal of Clinical Psychiatry*. 2006;67(3):421-4. Epub 2006/05/03.
7. Russell JM, Mackell JA. Bodyweight gain associated with atypical antipsychotics: epidemiology and therapeutic implications. *CNS drugs*. 2001;15(7):537-51.
8. Choong E, Bondolfi G, Etter M, Jermann F, Aubry JM, Bartolomei J, et al. Psychotropic drug induced weight gain and other metabolic complications in a Swiss Psychiatric population. *Journal of psychiatric research*. 2012;46:540-48. Epub 2012/02/10.
9. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *Jama: Journal of the American Medical Association*. 2009;302(16):1765-73.
10. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42(11):937-48.
11. Gebhardt S, Theisen FM, Haberhausen M, Heinzl-Gutenbrunner M, Wehmeier PM, Krieg JC, et al. Body weight gain induced by atypical antipsychotics: an extension of the monozygotic twin and sib pair study. *Journal of Clinical Pharmacy and Therapeutics*. 2010;35(2):207-11. Epub 2010/05/12.
12. Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Muller DJ. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Mol Psychiatry*. 2012;17(3):242-66. Epub 2011/09/07.
13. Li A, Meyre D. Challenges in reproducibility of genetic association studies: lessons learned from the obesity field. *Int J Obes (Lond)*. 2013;37(4):559-67.
14. Choong E, Quteineh L, Cardinaux JR, Gholam-Rezaee M, Vandenberghe F, Dobrinas M, et al. Influence of CRT1 polymorphisms on body mass index and fat mass in psychiatric patients and in the general adult population. *JAMA psychiatry (Chicago, Ill)*. 2013;70(10):1011-9. Epub 2013/08/09.
15. Quteineh L, Vandenberghe F, Saigi Morgui N, Delacretaz A, Choong E, Gholam-Rezaee M, et al. Impact of HSD11B1 polymorphisms on BMI and components of the metabolic syndrome in patients receiving psychotropic treatments. *Pharmacogenetics and genomics*. 2015;25(5):246-58.

16. Saigi Morgui N, Vandenberghe F, Delacrétaz A, Quteineh L, Choong E, Gholam-Rezaee M, et al. Association of PCK1 with Body Mass Index and Other Metabolic Features in patients with psychotropic treatments. *J Clin Psychopharmacol*. 2015;35(5):544-52.
17. Delacrétaz A, Preisig M, Vandenberghe F, Saigi Morgui N, Quteineh L, Choong E, et al. Influence of MCHR2 and MCHR2-AS1 genetic polymorphisms on body mass index in psychiatric patients and in subjects from the general population with present or past atypical depression. *PLoS ONE*. 2015;10(10): e0139155.
18. Hoffmann VP, Case M, Stauffer VL, Jacobson JG, Conley RR. Predictive value of early changes in triglycerides and weight for longer-term changes in metabolic measures during olanzapine, ziprasidone or aripiprazole treatment for schizophrenia and schizoaffective disorder post hoc analyses of 3 randomized, controlled clinical trials. *Journal of clinical psychopharmacology*. 2010;30(6):656-60. Epub 2010/11/26.
19. Lipkovich I, Citrome L, Perlis R, Deberdt W, Houston JP, Ahl J, et al. Early predictors of substantial weight gain in bipolar patients treated with olanzapine. *Journal of clinical psychopharmacology*. 2006;26(3):316-20. Epub 2006/05/17.
20. Lipkovich I, Jacobson JG, Hardy TA, Hoffmann VP. Early evaluation of patient risk for substantial weight gain during olanzapine treatment for schizophrenia, schizophreniform, or schizoaffective disorder. *BMC psychiatry*. 2008;8:78. Epub 2008/09/17.
21. Vandenberghe F, Gholam-Rezaee M, Saigi-Morgui N, Delacrétaz A, Choong E, Solida-Tozzi A, et al. Importance of early weight gain changes to predict long term weight gain during psychotropic drug treatment. *The Journal of Clinical Psychiatry*. 2015;76(11):e1417-23. Epub 2015/12/10.
22. Choong E, Solida A, Lechaire C, Conus P, Eap CB. Suivi du syndrome métabolique induit par les antipsychotiques atypiques: recommandations et perspectives pharmacogénétiques. *Rev Med Suisse*. 2008;4(171):1994-9.
23. Hiemke C, Baumann P, Bergemann N, Conca A, Dietmaier O, Egberts K, et al. AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011. *Pharmacopsychiatry*. 2011;44(6):195-235.
24. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *American journal of human genetics*. 2011;88(1):76-82. Epub 2010/12/21.
25. Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet*. 2010;42(7):579-89. Epub 2010/06/29.
26. Venables WN, Ripley BD. *Modern Applied statistics with S*: Springer; 2002.
27. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, et al. pROC: display and analyze ROC curves. 1.7.3 ed2014.
28. Janssens AC, Moonesinghe R, Yang Q, Steyerberg EW, van Duijn CM, Khoury MJ. The impact of genotype frequencies on the clinical validity of genomic profiling for predicting common chronic diseases. *Genet Med*. 2007;9(8):528-35.
29. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology*. 1983;148(3):839-43.
30. Pinheiro J, Bates D, DebRoy S, Sarkar D, Team RC. *nlme: linear and nonlinear mixed effects models*. 2013.
31. Pinheiro JC, Bates DM. *Mixed-Effects Models in S and S-PLUS*: Springer; 2000.
32. Davison AC, Hinkley DV. *Bootstrap Methods and their Application*. Cambridge, New York: Cambridge University Press; 1997. 1-592 p.
33. International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med*. 2009;360(8):753-64.

34. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nature reviews Endocrinology*. 2012;8(2):114-26.
35. De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: A systematic review of randomized, placebo controlled trials and guidelines for clinical practice. *Eur Psychiatry*. 2011;26(3):144-58. Epub 2011/02/08.
36. Grarup N, Sandholt CH, Hansen T, Pedersen O. Genetic susceptibility to type 2 diabetes and obesity: from genome-wide association studies to rare variants and beyond. *Diabetologia*. 2014;57(8):1528-41. Epub 2014/05/27.
37. Hivert MF, Manning AK, McAteer JB, Florez JC, Dupuis J, Fox CS, et al. Common variants in the adiponectin gene (ADIPOQ) associated with plasma adiponectin levels, type 2 diabetes, and diabetes-related quantitative traits: the Framingham Offspring Study. *Diabetes*. 2008;57(12):3353-9.
38. Han LY, Wu QH, Jiao ML, Hao YH, Liang LB, Gao LJ, et al. Associations between single-nucleotide polymorphisms (+45T>G, +276G>T, -11377C>G, -11391G>A) of adiponectin gene and type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetologia*. 2011;54(9):2303-14.
39. Lu JF, Zhou Y, Huang GH, Jiang HX, Hu BL, Qin SY. Association of ADIPOQ polymorphisms with obesity risk: A meta-analysis. *Hum Immunol*. 2014;75(10):1062-8.
40. Monteleone P, Milano W, Petrella C, Canestrelli B, Maj M. Endocannabinoid Pro129Thr FAAH functional polymorphism but not 1359G/A CNR1 polymorphism is associated with antipsychotic-induced weight gain. *J Clin Psychopharmacol*. 2010;30(4):441-5. Epub 2010/07/16.
41. Ando T, Tamura N, Mera T, Morita C, Takei M, Nakamoto C, et al. Association of the c.385C>A (p.Pro129Thr) polymorphism of the fatty acid amide hydrolase gene with anorexia nervosa in the Japanese population. *Molecular genetics & genomic medicine*. 2014;2(4):313-8.
42. Monteleone P, Bifulco M, Maina G, Tortorella A, Gazzero P, Proto MC, et al. Investigation of CNR1 and FAAH endocannabinoid gene polymorphisms in bipolar disorder and major depression. *Pharmacol Res*. 2010;61(5):400-4.
43. Albayrak O, Putter C, Volckmar AL, Cichon S, Hoffmann P, Nothen MM, et al. Common obesity risk alleles in childhood attention-deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2013;162B(4):295-305.



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	Voight et al. 2010(1)	rs9368222	G A	46	45	0.327		
rs10440833	CDKAL1			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			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			Speliotes et al. 2010(2)	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, HMGR	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	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		

^aProxies ($R^2 > 0.75$) were selected when the SNP of interest was not available in the CardiometaboChip.

^bLeft allele corresponds to the ancestral allele.

^cMAF from the 1000 Genome Project Phase 1.

^dCorrespond to the analyzed proxy if used.

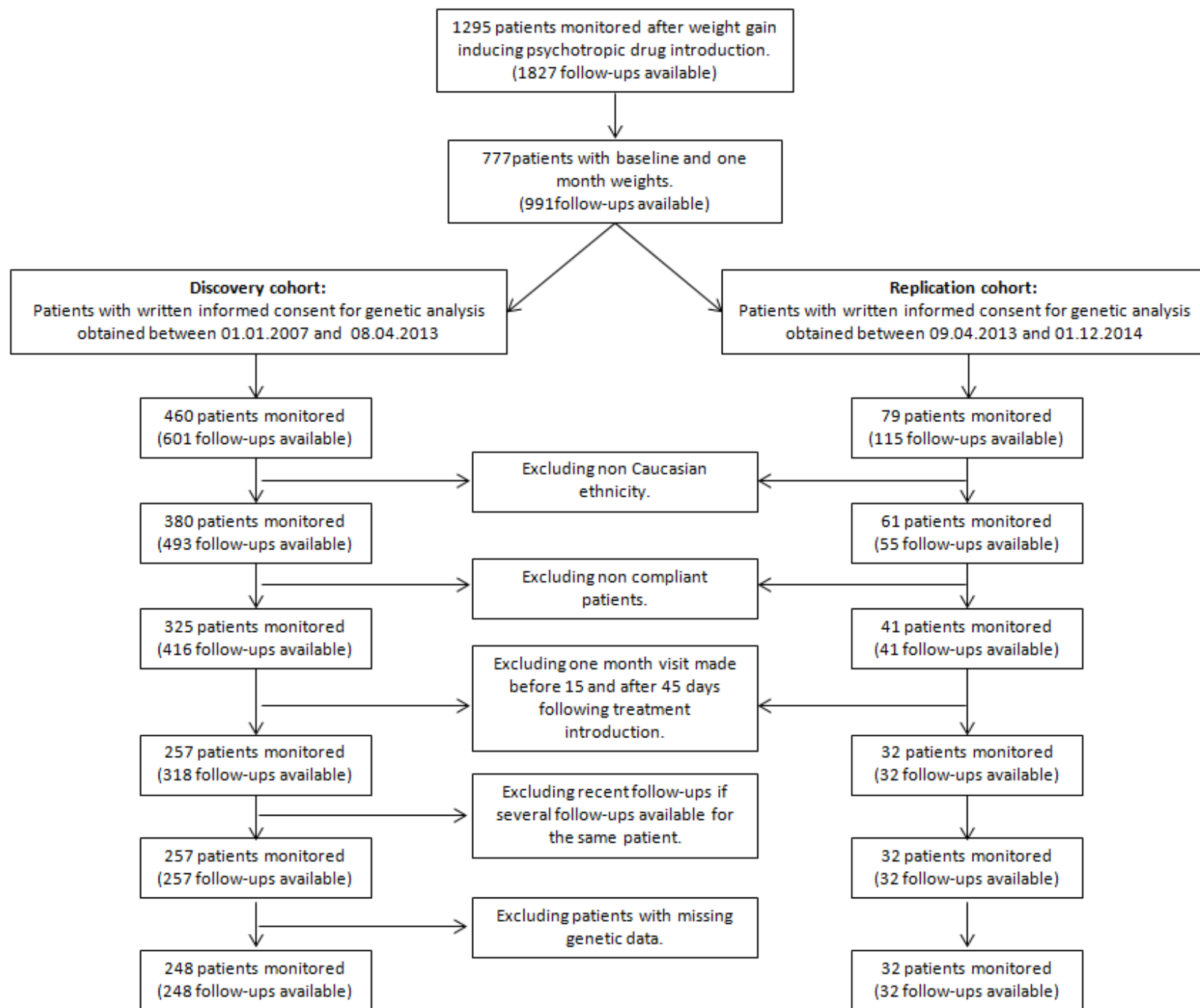
^eP-values in bold when SNPs deviate from Hardy-Weinberg equilibrium.

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

References:

1. Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nat Genet.* 2010;42(7):579-89.
2. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet.* 2010;42(11):937-48.
3. Kuzman MR, Medved V, Bozina N, Hotujac L, Sain I, Bilusic H. The influence of 5-HT(2C) and MDR1 genetic polymorphisms on antipsychotic-induced weight gain in female schizophrenic patients. *Psychiatry Res.* 2008;160(3):308-15.
4. Jassim G, Ferno J, Theisen FM, Haberhausen M, Christoforou A, Havik B, et al. Association study of energy homeostasis genes and antipsychotic-induced weight gain in patients with schizophrenia. *Pharmacopsychiatry.* 2011;44(1):15-20.
5. Ujike H, Nomura A, Morita Y, Morio A, Okahisa Y, Kotaka T, et al. Multiple genetic factors in olanzapine-induced weight gain in schizophrenia patients: a cohort study. *J Clin Psychiatry.* 2008;69(9):1416-22.
6. Houston JP, Kohler J, Bishop JR, Ellingrod VL, Ostbye KM, Zhao F, et al. Pharmacogenomic associations with weight gain in olanzapine treatment of patients without schizophrenia. *J Clin Psychiatry.* 2012;73(8):1077-86.
7. Müller DJ, Zai CC, Sicard M, Remington E, Souza RP, Tiwari AK, et al. Systematic analysis of dopamine receptor genes (DRD1-DRD5) in antipsychotic-induced weight gain. *The pharmacogenomics journal.* 2012;12(2):156-64.
8. Tsai A, Liou YJ, Hong CJ, Wu CL, Tsai SJ, Bai YM. Association study of brain-derived neurotrophic factor gene polymorphisms and body weight change in schizophrenic patients under long-term atypical antipsychotic treatment. *Neuromolecular medicine.* 2011;13(4):328-33.
9. Zai GC, Zai CC, Chowdhury NI, Tiwari AK, Souza RP, Lieberman JA, et al. The role of brain-derived neurotrophic factor (BDNF) gene variants in antipsychotic response and antipsychotic-induced weight gain. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012;39(1):96-101.
10. Lane HY, Liu YC, Huang CL, Chang YC, Wu PL, Lu CT, et al. Risperidone-related weight gain - Genetic and nongenetic predictors. *Journal of clinical psychopharmacology.* 2006;26(2):128-34.
11. Tiwari AK, Zai CC, Likhodi O, Lisker A, Singh D, Souza RP, et al. A common polymorphism in the cannabinoid receptor 1 (CNR1) gene is associated with antipsychotic-induced weight gain in Schizophrenia. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2010;35(6):1315-24.
12. Monteleone P, Milano W, Petrella C, Canestrelli B, Maj M. Endocannabinoid Pro129Thr FAAH functional polymorphism but not 1359G/A CNR1 polymorphism is associated with antipsychotic-induced weight gain. *J Clin Psychopharmacol.* 2010;30(4):441-5.
13. Godlewska BR, Olajosy-Hilkesberger L, Ciwoniuk M, Olajosy M, Marmurowska-Michalowska H, Limon J, et al. Olanzapine-induced weight gain is associated with the -759C/T and -697G/C polymorphisms of the HTR2C gene. *The pharmacogenomics journal.* 2009;9(4):234-41.
14. Le Hellard S, Theisen FM, Haberhausen M, Raeder MB, Ferno J, Gebhardt S, et al. Association between the insulin-induced gene 2 (INSIG2) and weight gain in a German sample of antipsychotic-treated schizophrenic patients: perturbation of SREBP-controlled lipogenesis in drug-related metabolic adverse effects? *Mol Psychiatry.* 2009;14(3):308-17.
15. Srivastava V, Deshpande SN, Nimgaonkar VL, Lerer B, Thelma B. Genetic correlates of olanzapine-induced weight gain in schizophrenia subjects from north India: role of metabolic pathway genes. *Pharmacogenomics.* 2008;9(8):1055-68.
16. Brandl EJ, Frydrychowicz C, Tiwari AK, Lett TA, Kitzrow W, Buttner S, et al. Association study of polymorphisms in leptin and leptin receptor genes with antipsychotic-induced body weight gain. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012;38(2):134-41.

17. Ellingrod VL, Bishop JR, Moline J, Lin YC, Miller dD. Leptin and leptin receptor gene polymorphisms and increases in body mass index (BMI) from olanzapine treatment in persons with schizophrenia. *Psychopharmacology Bulletin*. 2007;40(1):57-62.
18. Czerwensky F, Leucht S, Steimer W. Association of the common MC4R rs17782313 polymorphism with antipsychotic-related weight gain. *J Clin Psychopharmacol*. 2013;33(1):74-9.
19. Malhotra AK, Correll CU, Chowdhury NI, Muller DJ, Gregersen PK, Lee AT, et al. Association Between Common Variants Near the Melanocortin 4 Receptor Gene and Severe Antipsychotic Drug-Induced Weight Gain. *Archives of general psychiatry*. 2012;69(9):904-12.
20. Kao AC, Rojnic Kuzman M, Tiwari AK, Zivkovic MV, Chowdhury NI, Medved V, et al. Methylenetetrahydrofolate reductase gene variants and antipsychotic-induced weight gain and metabolic disturbances. *J Psychiatr Res*. 2014;54:36-42.
21. Tiwari AK, Brandl EJ, Weber C, Likhodi O, Zai CC, Hahn MK, et al. Association of a functional polymorphism in neuropeptide Y with antipsychotic-induced weight gain in schizophrenia patients. *J Clin Psychopharmacol*. 2013;33(1):11-7.
22. Hu X, Zhang J, Jin C, Mi W, Wang F, Ma W, et al. Association study of NRXN3 polymorphisms with schizophrenia and risperidone-induced bodyweight gain in Chinese Han population. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;43:197-202.
23. Chowdhury NI, Souza RP, Tiwari AK, Brandl EJ, Sicard M, Meltzer HY, et al. Investigation of melanocortin system gene variants in antipsychotic-induced weight gain. *World J Biol Psychiatry*. 2014;15(3):251-8.
24. Herken H, Erdal M, Aydin N, Sengul C, Karadag F, Barlas O, et al. The association of olanzapine-induced weight gain with peroxisome proliferator-activated receptor-gamma2 Pro12Ala polymorphism in patients with schizophrenia. *DNA Cell Biol*. 2009;28(10):515-9.
25. Souza RP, Tiwari AK, Chowdhury NI, Ceddia RB, Lieberman JA, Meltzer HY, et al. Association study between variants of AMP-activated protein kinase catalytic and regulatory subunit genes with antipsychotic-induced weight gain. *Journal of psychiatric research*. 2012;46(4):462-8.



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
Illness 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)			
<i>CHCHD9</i> , rs4295736(G)	1.104 (0.8)	3 (0.8-20.4)	0.2
<i>ZBED3</i> , rs4457053(G)	0.376 (0.262)	1.5 (0.9-2.4)	0.2
<i>IRS1</i> , rs7578326(A)	0.376 (0.263)	1.5 (0.9-2.5)	0.2
<i>TCF7L2</i> , rs7903146(T)	0.444 (0.251)	1.6 (1-2.6)	0.08

Table 3: Predictive statistics

Logistic model	TN (%)	TP (%)	FN (%)	FP (%)	Accuracy % (95 th) ^a	SP % (95 th) ^a	SE % (95 th) ^a	NPV % (95 th) ^a	PPV % (95 th) ^a	AUC (95 th) ^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)			
<i>FANCL</i> , rs887912 (T)	0.491 (0.282)	1.6 (0.9-2.9)	0.08
<i>GPRC5B</i> , <i>IQCK</i> rs12444979 (T)	1.095 (0.385)	3 (1.4-6.5)	0.004
<i>LRP1B</i> , rs2890652 (C)	0.573 (0.325)	1.8 (0.9-3.4)	0.08
<i>LRRN6C</i> , rs10968576 (A)	0.485 (0.326)	1.6 (0.9-3.2)	0.1
<i>MTCH2</i> , <i>NDUFS3</i> , <i>CUGBP1</i> rs3817334 (C)	0.459 (0.294)	1.6 (0.9-2.9)	0.1
<i>MTIF3</i> , <i>GTF3A</i> rs4771122 (G)	0.534 (0.314)	1.7 (0.9-3.2)	0.09
<i>NRXN3</i> , rs10150332 (T)	0.621 (0.384)	1.9 (0.9-4.2)	0.1
<i>RPL27A</i> , <i>TUB</i> rs11041999 (T)	0.402 (0.274)	1.5 (0.9-2.6)	0.1
<i>SEC16B</i> , rs543874 (G)	0.713 (0.361)	2 (1-4.2)	0.05
<i>SH2B1</i> , <i>APOB48R</i> , <i>SULT1A2</i> , <i>AC138894.2</i> , <i>ATXN2L</i> , <i>TUFM</i> , rs7359397 (T)	0.445 (0.294)	1.6 (0.9-2.8)	0.1
<i>TMEM160</i> , <i>ZC3H4</i> rs3810291 (G)	0.589 (0.283)	1.8 (1-3.2)	0.04
<i>ZNF608</i> , 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)			
<i>ADIPOQ</i> , rs17300539 (G)	1.364 (0.503)	3.9 (1.6-11.5)	0.007
<i>BDNF</i> , rs10835187 (C)	0.402 (0.267)	1.5 (0.9-2.5)	0.1
<i>DRD2</i> , rs6277 (G)	0.559 (0.271)	1.7 (1-3)	0.04
<i>FAAH</i> , rs324420 (A)	0.709 (0.333)	2 (1.1-3.9)	0.03
<i>INSIG2</i> , rs17587100 (C)	1.591 (0.713)	4.9 (1.4-24.3)	0.03
<i>LEPR</i> , rs1137101 (A)	0.408 (0.266)	1.5 (0.9-2.5)	0.1
<i>MC4R</i> , rs10871777 (A)	0.524 (0.31)	1.7 (0.9-3.2)	0.09
<i>MTHFR</i> , rs1801131 (G)	0.57 (0.281)	1.8 (1-3.1)	0.04
<i>PPARG</i> , rs2197423 (G)	0.811 (0.444)	2.3 (1-5.6)	0.07

Supplemental Digital Content 7: Final model equation.

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

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

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

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

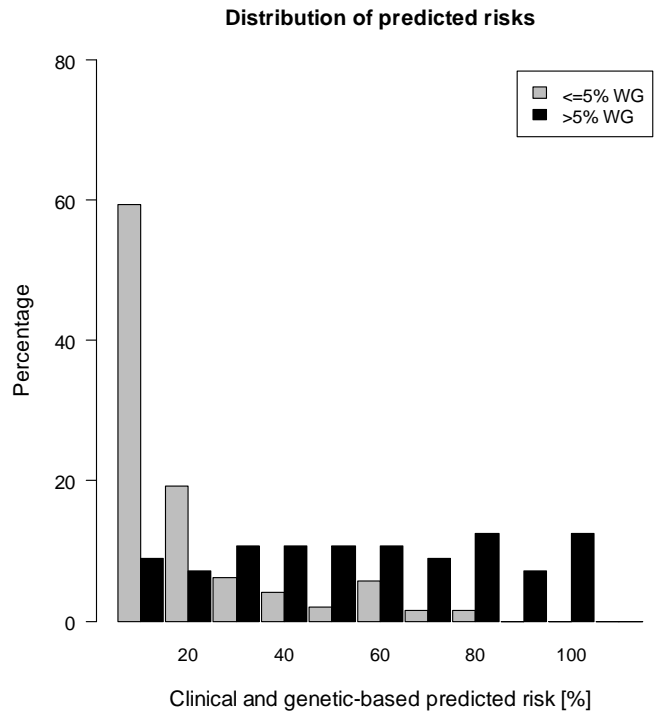
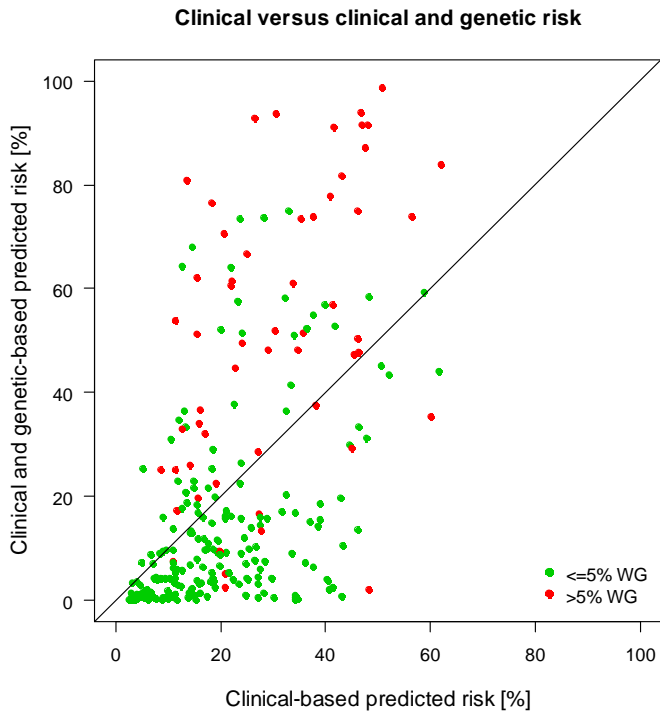


Figure 1: Left scatter plot indicates the predicted risk change between the model with only clinical variables and the model including both clinical and genetic variables. The dots upper the diagonal line indicates that adding genetic variables increases the predicted risk of $> 5\%$ WG and the dots 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 $\leq 5\%$ 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
Schizo affective 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-medication possibly 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).

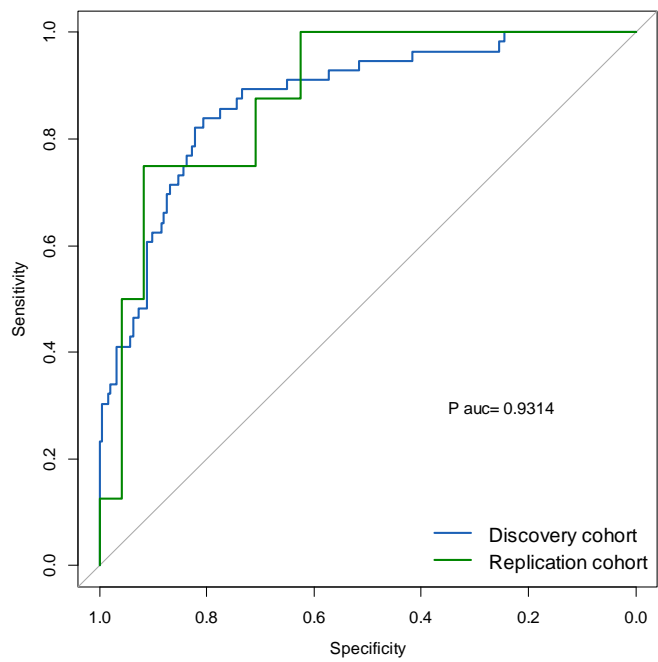
^c Presence of more than one WG-inducing psychotropic drug (Amisulpride, Aripiprazole, Clozapine, Lithium, Mirtazapine, Olanzapine, Quetiapine, Risperidone, Valproate).

^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.

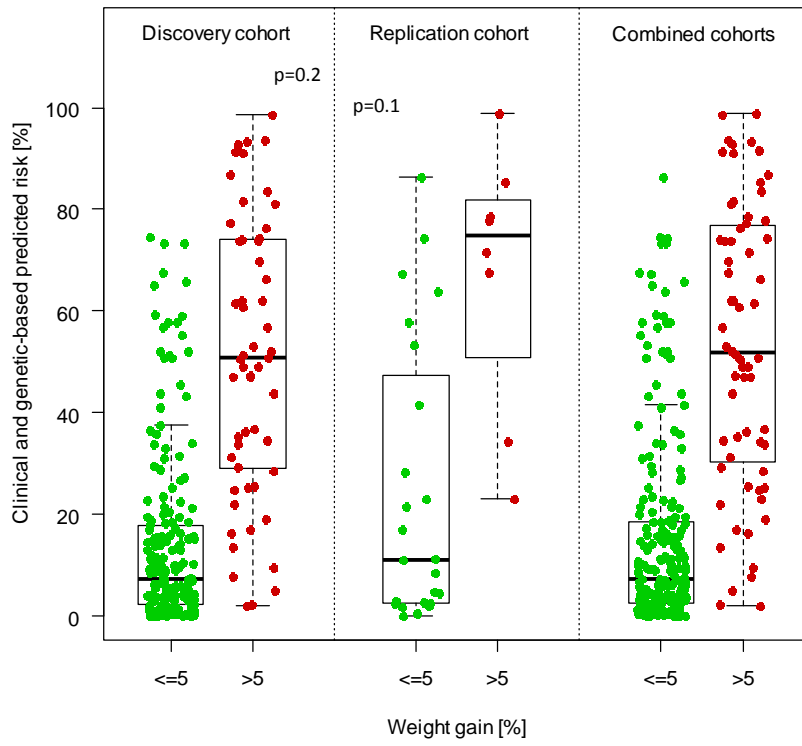
id	Baseline		Illnessduration	Poly medication	Gender	Medication	Diagnostic	rs17300539	rs10835187	rs6277	rs324420	rs12444979	rs17587100	rs2890652	rs10968576	rs10871777	rs3817334	rs1801131	rs10150332	rs2197423	rs11041999	rs543874	rs7359397	rs3810291	rs6864049	>5% WG	Model prediction	Class
	BMI	Age						(ADIPOQ)	(BDNF)	(DRD2)	(FAAH)	(GPCR5B, IQCK)	(INSIG2)	(LRP1B)	(LRRN6C)	(MC4R)	(MTHFR)	(NRXN3)	(PPARG)	(RPL27A, TUB)	(SEC16B)	(SH2B1)	(TMEM160)	(ZNF608)				
1	27.2	34	2	Yes	Female	Lithium	Other	0	1	1	1	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	0	1	1	0	0	0	1	0	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	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.

Predicted risk among 5% weight gain group



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

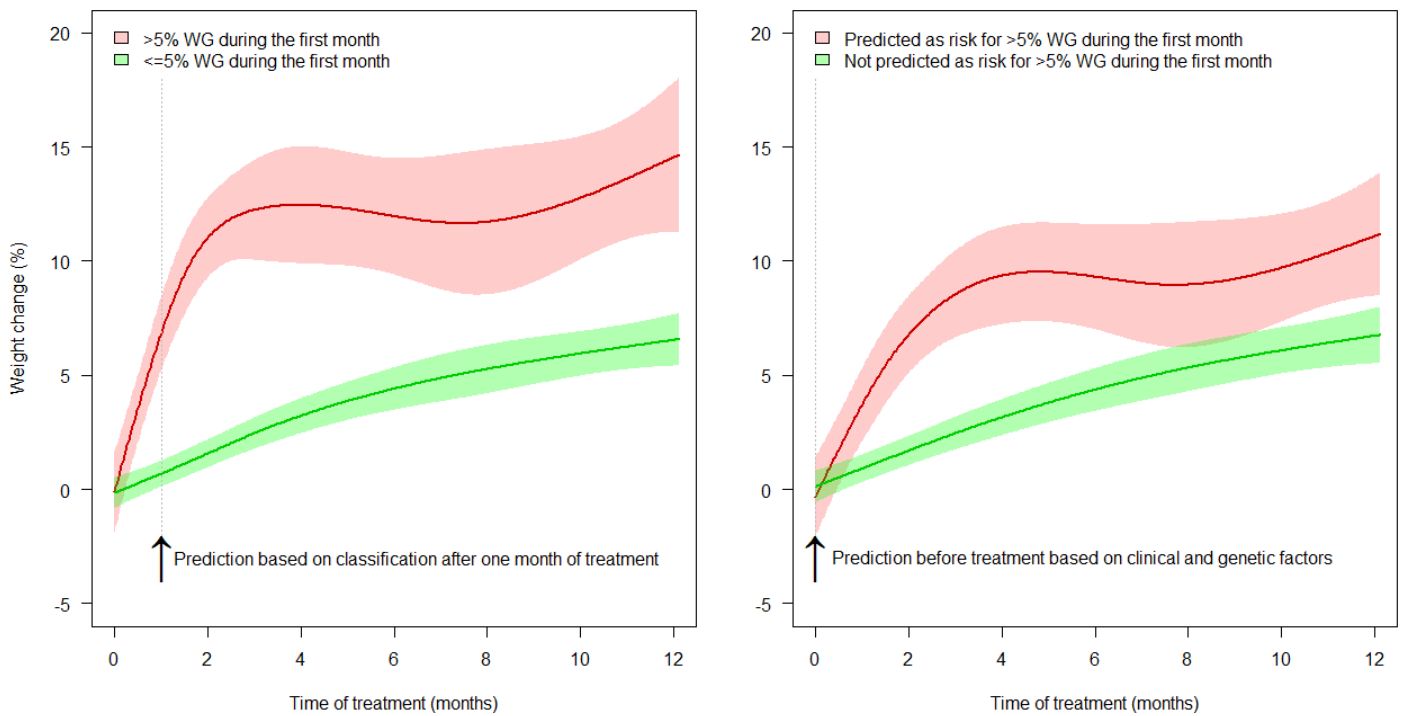
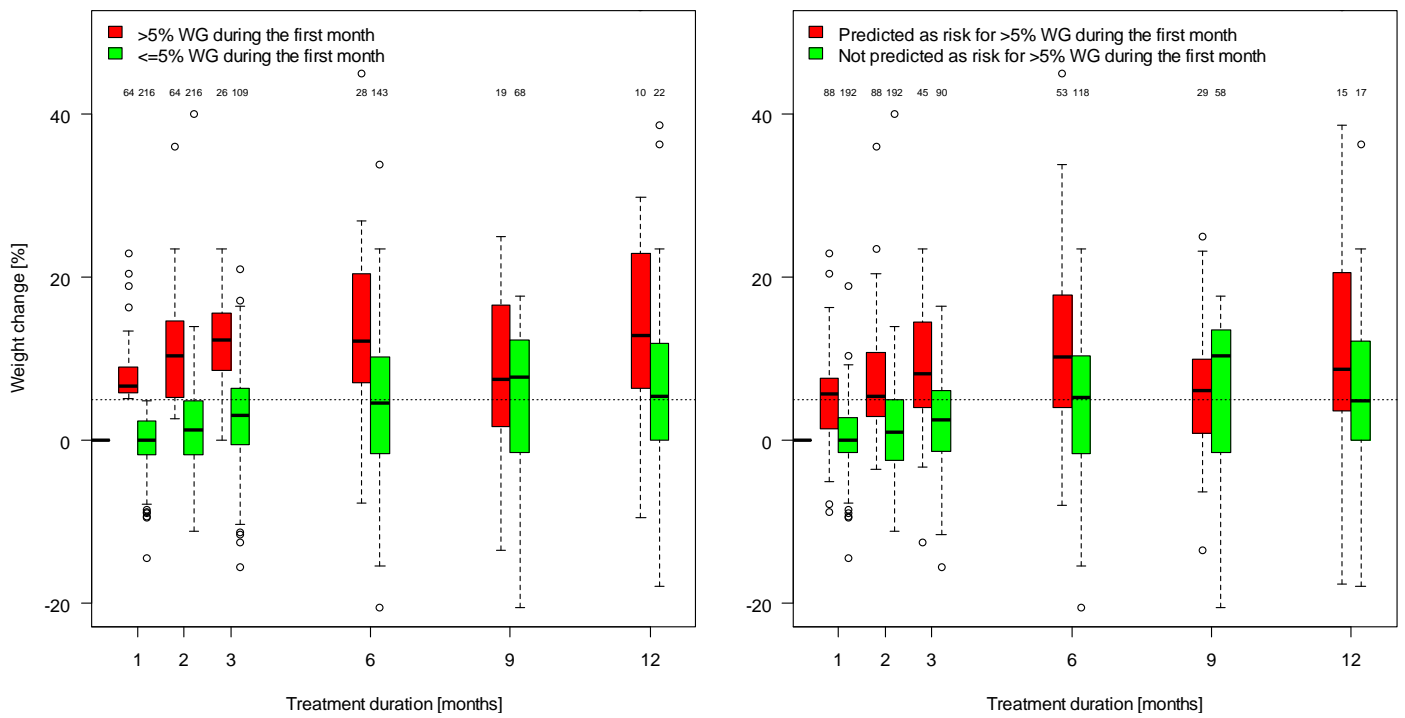


Figure 2: Generalized additive mixed model prediction of weight over one year. The left plot represents weight changes in patients having >5%WG (red) or ≤5%WG (green) after one month following the introduction of weight gain-inducing psychotropic drugs. The right plot represent the prediction before treatment of 5%WG in patients after one month based on clinical and genetic data >5%WG (red) or ≤5%WG (green). CI₉₅ is represented by the shaded area.

Weight evolution during the first year of treatment



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 $\leq 5\%WG$ 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

^aResults were obtained by fitting a linear mixed model controlling for age, sex, time, baseline BMI .