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# Evolutions of metabolic parameters following switches of psychotropic drugs: a longitudinal cohort study.

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**Abstract**

**Background.** Several psychotropic drugs can induce weight gain and metabolic alterations. The authors compared metabolic evolutions of patients switching versus continuing psychotropic treatments with different risk profiles.

**Methods.** Patients either switched from a high- to a medium- (N=36) or low-risk drug (N=27), from a medium- to a low-risk drug (N=71), or to a same-risk drug (N=61). Controls kept using either a high- (N=35), medium- (N=155) or low-risk drug (N=47). The evolution over two years of weight and metabolic parameters was analyzed using linear mixed-effect models, also examining the influence of polygenic risk scores for BMI or BMI and psychiatric disorders.

**Study Results.** High-, medium- or low-risk controls gained on average 1.32%, 0.42% and 0.36% more weight per month than patients switching from or within these risk categories ($p<0.001$, $p<0.001$ and $p=0.003$, respectively). High-to-high or high-to-medium switches resulted in greater weight increase than switching to lower-risk categories (+0.77% and +0.39% respectively, $p<0.001$). No difference was found between switching medium-to-medium and medium-to-low ($p\approx1$). Switching high-to-low resulted in 10% weight loss after two years, with the greatest loss occurring the first six months after the switch. Compared with high-risk controls, lower total cholesterol (-0.27 mmol/l, $p=0.043$) in the high-to-low group, and lower glucose (-0.44 mmol/l, $p=0.032$) and systolic blood pressure (-5.50 mmHg, $p=0.034$) in the low-to-low group were found. Polygenic scores were not associated with weight changes in controls or after switching.

**Conclusions.** Psychotropic switches to a lower- or same-risk drug can attenuate weight gain, with only switching high-to-low resulting in weight loss.

**Keywords:** psychotropic switch, metabolic risk, weight gain.

## Introduction

Several psychotropic drugs can induce cardiometabolic diseases such as type II diabetes, dyslipidemia and/or obesity, contributing to the overall 10-year decrease in life expectancy among psychiatric patients[1]. Within six to twelve months of therapy, weight increases can reach up to 12% from baseline[2], and lipid and/or glucose dysregulation may also occur[3-5], with some psychotropic drugs leading to more metabolic alterations than others[6]. Among antipsychotics, clozapine and olanzapine show the highest risk for inducing metabolic alterations[6]. Quetiapine and risperidone follow as medium-risk drugs, while aripiprazole, amisulpride and lurasidone are classified as low-risk[6, 7]. Mood stabilizers such as valproate and lithium can also induce weight gain, with valproate leading to more weight increase[8], blood lipid and/or glucose impairments than lithium[9, 10]. Among antidepressants, mirtazapine was identified as one of the most likely to induce metabolic side effects[11], with weight gain over one year comparable to quetiapine and/or risperidone[7]. Along with psychotropic medication, risk factors for weight gain in the psychiatric population include female sex, young age and low baseline weight[12-14].

When non-pharmacological interventions (e.g., diet, physical exercise) are insufficient for losing weight, switching psychotropic drugs has been used as a strategy to attenuate and/or reverse metabolic adverse effects[7]. A six-week randomized open-label study[15] reported a weight loss of 2kg and 0.7kg among 173 and 112 patients switching from olanzapine or risperidone to aripiprazole, respectively, and similar results were reported in two open-label studies of 71 and 12 patients, respectively, reporting a weight loss of 1.3kg after 20 weeks and 2.25kg after ten weeks following a switch from olanzapine to risperidone or quetiapine, respectively[16, 17]. Weight loss of 2.9kg was also reported in a six-month open-label study

among 223 patients switching from risperidone to lurasidone[18]. On the other hand, another 12-week open label study did not find any significant changes in weight among 9 patients switching from risperidone to aripiprazole[19]. No weight changes when switching to a same-risk molecule (e.g., from quetiapine to risperidone[20]), and weight increases when switching for a higher-risk molecule have also been described[21]. A decrease in triglycerides of 32.7 mg/dl after switching from olanzapine, quetiapine or risperidone to aripiprazole was also reported for 109 patients in a 24-week randomized trial[22], along with an increase of 5.3 mg/dl of HDL cholesterol levels and a decrease of 11.7 mg/dl in total cholesterol levels among 61 patients switching from mixed antipsychotics to aripiprazole in a 26-week open-label study[23]. However, another 64-week open-label study did not find any differences in lipid levels among 79 patients switching from mixed antipsychotics to aripiprazole[24]. Changes in glucose levels were either not reported or not detected in the previously mentioned studies[22-24]. According to a meta-analysis, when compared with patients taking the same medication over the long term, only patients switching to aripiprazole lost weight and/or improved fasting glucose and/or triglyceride levels, while no glucose nor lipid level changes were detected after switching to amisulpride, paliperidone and/or risperidone, quetiapine, or lurasidone[21].

Most of the above-mentioned studies examined the metabolic consequences of switches over a period of up to six months only[15-20, 22, 23]. In addition, control groups continuing to use the previous psychotropic medication were either absent[15-17, 19, 20, 23, 24] or did not include switches to molecules presenting the same metabolic risk profile [18, 22].

Finally, because different classes of psychotropic drugs (antipsychotics, antidepressants, mood stabilizers) can be prescribed to treat different psychiatric disorders (e.g., antipsychotics for bipolar disorders[25] and/or general anxiety[26]), it is important to consider metabolic changes

after switching not only from one antipsychotic to another, but also from one class of psychotropic drugs to another, taking into account the class of risk for metabolic worsening.

In the present study, analyzing metabolic parameters before and after a switch and comparing them with a control group staying on the same medication, we evaluated whether switching psychotropic drugs for a lower- or same-risk molecule is a valid strategy for attenuating and/or reversing metabolic alterations in a large cohort of psychiatric patients in Switzerland.

## Methods

### Study design

Patients were selected from the Psymetab cohort started in 2007 at the Department of Psychiatry of Lausanne University Hospital, in collaboration with a private mental health care center (Les Toises). As previously described[27], upon signature of an informed consent, PsyMetab collects clinical and genetic data from patients taking psychotropic treatments known to induce metabolic alterations. The Ethics Committee of the Canton of Vaud also granted access to clinical data of patients followed at the Department of Psychiatry of Lausanne University Hospital from 2007 to 2015 (PsyClin) because of the non-interventional post hoc analysis design. Patients switching psychotropic drugs were included and compared to patients maintaining the same medication. High-risk drugs included clozapine, olanzapine and valproate; medium-risk drugs included levomepromazine, lithium, mirtazapine, quetiapine, risperidone/paliperidone and zuclopenthixol; and low-risk drugs included amisulpride, aripiprazole, brexpiprazole, flupenthixol, haloperidol and lurasidone. Patients either switched from a high-to-low, from a high-to-medium, from a medium-to-low risk drug, or for a molecule within the same risk category (see Figure 1 for proportions, and Supplementary Figure 1 for drug repartition). Switching was defined as starting a new medication within 30 days from the end of the previous one. If the previous psychotropic drug was quetiapine or aripiprazole, the gap between the two treatments had to be no longer than 14 and 60 days, respectively, due to the shorter and longer half-lives of the two drugs, respectively[28]. Duration of treatments (before and after switch) were available, and patients with treatment durations <21 days for both first and second treatments were excluded, along

with patients taking depot formulations during the first treatment. Controls were also classified as high-, medium- or low-control groups.

**Measurements**

Clinical data on age, sex, weight, height, diagnoses, lipids and/or glucose blood levels, and blood pressure were collected at the beginning of the treatment, after one and three months, and yearly. At two and six months, weight measurements were also scheduled. For hospitalized patients, supplementary observations of clinical data (e.g., weight, lipid values) collected during the stay were also available. Weight change was calculated as the percentage of change from baseline value (i.e., baseline weight at the beginning of the first treatment and/or at the beginning of the switch for the switch group).

**Statistical analysis**

Descriptive statistics comparing patients switching versus controls were performed using the Wilcoxon rank-sum test for continuous variables and the Pearson $\chi^2$ or Fisher exact test for categorical variables as appropriate. The evolution of weight and other metabolic parameters over time was analyzed using linear mixed-effect models. Since the evolution of each metabolic parameter is strongly correlated with follow-up duration and age, the models included equal follow-up and age ranges for controls and switch groups (e.g., for glucose observations available for 14-to-80-year-old controls and 15-to-80-year-old patients switching, only 15-to-80-year-old patients were included in the model). Linear mixed-effect models of weight change were adjusted by sex, age at baseline, baseline weight, medical environment (in- and outpatient) and by the interaction of both switch and control categories with time. Moreover, in order to compare switch groups versus their controls, and the different switches with one another, general linear hypothesis testing was used with contrast

matrices, corrected for multiple testing by the “holm” method. Furthermore, partial R square values indicated the share of variability explained by each covariate and variable importance using t-statistics were reported. Since observations after one year may have included only patients experiencing mild metabolic disturbances (i.e., patients with strong metabolic disturbances would have had their treatments changed), a quadratic model was applied including observations within one year to estimate the direction and the speed of weight changes over time. For glucose, total, HDL and LDL cholesterol, triglycerides and blood pressure, linear mixed-effect models over a two-year follow-up were also performed, adjusting by the switch and control categories, time, sex, age at baseline and baseline body mass index (BMI), and excluding patients taking somatic-related drugs (e.g., patients taking antidiabetic medication were excluded from models evaluating glucose). Models were also adjusted by fasting status for total, LDL and HDL cholesterol, while for glucose and triglycerides only fasting observations were included. Additional linear mixed-effect models on weight change were performed for genotyped patients adjusting separately for five polygenic risk scores (941 and 97 BMI-associated SNPs, 63 BMI- and schizophrenia-associated SNPs, 17 BMI- and bipolar disorder-associated SNPs and 32 BMI-and major depression-associated SNPs; see Supplementary Methods). Smoking status, psychotropic co-medications and the different diagnoses did not influence our outcomes (data not shown) and these covariates were therefore not included in the models. Stata 16.0 (StataCorp; College Station, Texas) and R environment for statistical computing version 4.0.2 were used for the analysis, and p values of ≤0.05 were considered statistically significant.

**Results**

Table 1 displays the clinical and demographic characteristics of the switch and control groups regardless of the risk categories. Patients who switched were younger ($p<0.001$), had shorter follow-up ($p<0.001$), were mostly inpatients ($p<0.001$) and diagnosed with psychotic disorders ($p<0.001$). Switch group BMI at baseline and between follow-ups did not differ from controls baseline BMI ($p=0.43$ and $p=0.10$, respectively).

For high-risk controls, a linear mixed-effect model (Table 2) showed a positive correlation between time and weight change with a +0.67% per month of treatment ($p<0.001$). Weight change was also negatively correlated with baseline weight (-0.10% for each additional Kg at baseline, $p<0.001$), and with age (-0.05% for each additional year, $p<0.001$). Inpatients gained less weight (mean -1.54%) than outpatients ($p<0.001$), and patients switching high-to-high gained less weight (mean -5.07%) than high-risk controls ($p=0.007$, data not shown). For patients switching high-to-medium and high-to-low (Table 2), weight changes of -0.04% and -0.43% for each additional month were found, respectively ($p<0.001$). Patients switching medium-to-low and medium-to-medium showed -0.41% and a -0.44% per month as compared to controls taking medium-risk drugs, respectively ($p<0.001$), whereas patients switching low-to-low drugs showed -0.36% compared to controls taking low risk drugs ($p<0.001$). Predicted values of weight change over time (Figure 2) showed weight loss only for patients switching high-to-low, with around 10% weight loss predicted after two years, which was the same amount of weight gain (+10%) predicted for high-risk controls over one year. Moreover, for patients switching high-to-low and their controls, the quadratic model (Supplementary Figure 2) predicted that the greatest weight decrease or increase, respectively, occurred during the first six months after the switch or treatment start, followed by a flattening of weight

evolution over time. Interestingly, switching high-to-medium or low-to-low led to a weight gain attenuation only after a moderate weight increase occurring during the first six months after the switch. On the other hand, patients switching medium-to-medium and medium-to-low experienced a moderate but constant weight increase over time. Since early weight gain (≥5% in one month) is a risk factor for further weight increase in the long-term[27], an additional analysis including this variable in the model and excluding baseline weight was performed, reporting similar results as in Table2 (data not shown). A sensitivity analysis also was performed excluding patients taking metformin (N=17)[29], this drug being also prescribed to attenuate psychotropic-induced weight gain, reporting similar results as in Table2 (data not shown).

Using general linear hypothesis testing (Table 3), high-, medium- or low-risk controls gained on average +1.32%, +0.42% and +0.36% more weight per month than patients switching from these categories ($p<0.001$, $p<0.001$ and $p=0.003$, respectively). Furthermore, switching high-to-high was associated with greater weight increase than switching from high-to lower-risk categories on average (+0.77% per month, $p<0.001$), and patients switching high-to-medium gained +0.39% more weight per month than patients switching high-to-low ($p<0.001$). No difference was found between switching medium-to-medium and switching medium-to-low ($p\approx1$).

Considering partial R square values (Supplementary Figure 3), 5.8% of variance was explained by baseline weight, followed by the interaction of time with both high-risk controls (3.4%) and patients switching high-to-low (3.3%). These last two co-variates also showed the highest levels of importance according to the t-statistics (Supplementary Figure 4).

Due to a significant interaction of age and sex with switch and/or control groups and time (data not shown), stratified models (data not shown) were created and linear hypotheses were tested (Supplementary Tables 1 and 2). Among young adults (≤25 years), only medium-risk controls gained significantly more weight per month when compared with patients switching from a medium-risk molecule (+0.89% per month, p<0.001). In addition, patients switching high-to-medium gained more weight per month than patients switching high-to-low (+1.31% per month, p<0.001). Concerning adults (>25 and <65 years), controls taking a medium-or low-risk molecule gained more weight than patients switching, +0.24% and +0.54% per month, respectively (p=0.029 and p<0.001, respectively), with no difference in weight change between the switch groups. On the other hand, old-age (≥65 years) controls taking low-risk drugs gained less weight per month than patients switching within this category (p<0.001), and switching within the medium-risk category resulted in greater weight increase than switching medium-to-low (+1.32% per month, p=0.003). Each control group among women gained more weight than the switch groups (p<0.001) whereas, among men, only medium-risk controls gained more weight per month than men switching from a medium-risk molecule (p<0.001). Moreover, switching within the high category was associated with greater weight increase per month than switching high-to-lower among women (+0.76%, p=0.001), as well as switching high-to-medium versus high-to-low (+0.46%, p=0.049), which was also found among men (+0.40%, p=0.006).

Polygenic risk scores for BMI or BMI and psychiatric disorders were not associated with weight changes in controls (N=241) or after a switch (N=93, Supplementary Table 3).

**Metabolic parameters**

No significant interaction between time and switch or control groups was found in linear mixed-effect models over a two-year follow-up on glucose, total, HDL, LDL cholesterol, triglycerides and systolic blood pressure, whereas a significant interaction for patients switching medium-to-medium was found on diastolic blood pressure, probably due to chance finding (-0.44 mmHg per month, p=0.029, data not shown). When compared with high-risk controls (Supplementary Table 4), a mean of -0.27 mmol/l (p=0.043) in total cholesterol for patients switching high-to-low (p=0.043) was found, as well as a mean -0.44 mmol/l (p=0.032) in glucose and -5.50 mmHg (p=0.034) in systolic blood pressure for patients switching low-to-low. No difference was found among the three control groups within each model.

**Discussion**

With a two-year naturalistic longitudinal study design, different weight patterns were found between controls continuing on the same psychotropic medication and patients switching for either a lower-risk or a same-risk molecule. Controls gained more weight per month than patients switching from their same risk category. This result is in line with a previous 24-week randomized trial including 215 patients, reporting -2.9kg for patients switching to aripiprazole when compared with patients continuing to use either olanzapine, risperidone or quetiapine[22]. However, those patients were randomized into switching or staying on the same medication with the outcome being the weight difference 24 weeks after switching, while in the present study switching was due to clinical needs (e.g., poor treatment response, excessive weight gain, etc.), and weight evolution before and after switching was modeled over two years. Moreover, since weight evolution is baseline-weight-dependent, percentages of weight change rather than absolute weight are more informative. In addition, to our knowledge, the present study is the first in which patients switching low-to-low were directly compared to low-risk controls, the latter group showing greater weight increase. In other words, switching to a drug in the same risk category could result in weight gain attenuation. This result is in agreement with a 12-week open-label observational study, with 19 patients switching from low-risk aripiprazole to low-risk ziprasidone, resulting in a mean loss of 3kg[30]. Given that higher weight gain is observed among antipsychotic-naïve patients[31], a progressive adaptation after each psychotropic therapy would partially explain why a same-risk switch could attenuate the weight increase of the previous psychotropic therapy, regardless of antipsychotic-naïve status.

To our knowledge, the present study is the first to compare weight change after switching from a high to a high-risk drug to both switching from a high-to-medium and low-risk drug, indicating that the first alternative leads to a greater weight change per month. Weight gain attenuation and weight loss were also reported for high-to-medium and high-to-low patients, respectively, when compared to high-risk controls. Similarly, a meta-analysis reported a mean weight increase of 2.8kg when switching to a high-risk drug (e.g., olanzapine or clozapine), no significant weight changes when switching to medium-risk drugs (e.g., to quetiapine and/or risperidone), and 2kg weight loss when switching to a low-risk drug (i.e., aripiprazole)[21]. On the other hand, our results did not show differences in the evolution of weight between patients switching medium-to-medium versus medium-to-low, probably because of the moderate difference in the metabolic risk between the two drug categories. Ultimately, our results show that only switching high-to-low resulted in weight loss, the amount of weight loss predicted after two years being the same amount gained by controls in half the time (i.e., one year). In addition, for patients switching high-to-low and their controls, the greatest weight decrease or increase, respectively, occurred during the first six months of treatment (switch or start). These results are in line with previous studies reporting a weight gain plateau after nine months[32] of olanzapine treatment and after one year[33] of a psychotropic treatment. Our results are also in line with another study reporting that the greatest weight loss is reached within six months among obese patients undergoing diet and anti-obesity pharmacological treatments[34]. To our knowledge, the present study is the first predicting that the greatest amount of weight loss is reached within the first six months after switching high-to-low.

Partial r-squared values highlighted the importance of accounting for baseline weight when considering weight evolutions, as this co-variate was the most explicative of our model variance. This is in agreement with other studies showing that a low baseline weight is a major

risk factor for important weight gain induced by psychotropic drugs[14, 35]. The second and third most explicative co-variates were weight evolutions over time of both high-controls and patients switching high-to-low, probably because the most important weight gain and loss, respectively, were found in these two groups.

Among both young adults and adults, no difference among high-risk controls and patients switching from a high-risk molecule was found, most probably because of the very low number of patients switching high-to-high (i.e., 2 young adults and 3 adults, data not shown). However, a difference in weight gain was found for patients switching high-to-medium versus high-to-low only among young adults. Since young age is a risk factor for psychotropic-induced weight gain[14], younger patients could be the age-category most benefitting from switching high-to-low. Interestingly, elderly patients switching low-to-low gained more weight than elderly controls staying on the same low-risk drugs, and elderly patients switching medium-to-medium also gained more weight per month than elderly patients switching medium-to-low, these results probably being explained by the lower sample size in the elderly group (i.e., 68 patients included) versus the others (i.e., 102 and 260 patients included in the young adult and adult groups, respectively). Of note, partial r-squared values indicated age as the fourth most explicative co-variate of our main model variance, underlying the need of further studies evaluating weight evolution among controls and patients switching in larger age-categorized sample sizes.

Concerning sex-stratified analysis, weight changes in women were similar to those found in the whole cohort. On the other hand, among men only medium-risk controls showed greater weight gain per month than patients switching from a medium-risk drug. A trend was, however, found of higher weight change among high-risk male controls versus patients

switching high-to-lower. Moreover, male patients switching high-to-medium gained more weight per month than patients switching high-to-low. Since female sex is a risk factor for psychotropic-induced weight gain, women could benefit more from switching drugs[36]. Moreover, similar results were found for young adults and men, probably because men were statistically younger than women (39 versus 46 years, $p<0.001$, data not shown), which would contribute to the different results between the sexes.

No differences in the evolution of blood glucose and/or lipid levels were found within control and switch groups. However, switching high-to-low resulted in lower concentrations of total cholesterol, in accordance with a previous 26-week open-label study reporting total cholesterol decrease after switching to aripiprazole[23]. On the other hand, our results are in contrast with a previous 24-week randomized trial reporting a decrease in triglycerides after switching to aripiprazole[22], and with a 26-week meta-analysis detecting fasting glucose and/or triglyceride improvements when switching to aripiprazole[21]. This discrepancy could be due to the shorter duration of treatment after a switch (i.e., median 20 weeks in the present study versus 24 and 26 weeks), to the risk defined before and after switching, and/or to the lower statistical power within each control and switch group (e.g., our 19 patients switching high-to-low with triglyceride levels versus 89 in the previously mentioned trial[22]).

Of note, polygenic risk scores for BMI or BMI and psychiatric disorders were not associated with weight changes either in controls or after a switch, probably due to the limited sample size and/or the limited effect sizes of genetic factors included in the scores and/or an overall limited influence of genetic factors. Further studies with greater sample sizes focusing on BMI and psychiatric-related polygenic risk scores are needed.

The present study has several limitations. Weight-impacting variables such as physical activity, diet, alcohol consumption and/or psychotropic-naïve status were unavailable. Adherence to treatment could not be ascertained, although for inpatients the record of daily-administered drugs was taken into account. Moreover, we could not account for the psychotropic dose, which could influence the weight change[37-39], nor for confounding factors such as age of onset for psychiatric illness and/or duration of total psychotropic treatment prior to the study entry and/or the initial weight before any psychotropic treatment. Concomitant prescription of all weight-impacting drugs could not be taken into account, but a sensitivity analysis excluding patients with metformin, a drug which could be prescribed to attenuate psychotropic-induced weight gain[29], was performed. An inclusion bias could be that controls may have stayed on their medication due to milder metabolic adverse effects than in patients who switched, the present results could therefore underestimate the effects of switching. On the other hand, patients switching due to excessive weight gain could have been advised to increase physical activity and/or be under diet supervision (i.e., first-line clinical approaches to reverse psychotropic-induced weight gain[7]), possibly leading to an over-estimation of our results. For the metabolic parameters, the duration of follow-up after switch was probably insufficient to detect differences among groups. Moreover, a limited sample size was available for certain switch categories (e.g., high-to-high), and for investigating the influence of polygenic risk scores. On the other hand, our study could benefit from real-world data, as it models for the first time weight changes of controls and patients switching from the same-risk drugs as the controls, and compares same-risk switches versus lower-risk ones.

**Conclusion**

Our results suggest that psychotropic switching to a lower or to a same-risk drug can attenuate psychotropic-induced weight gain, while only switching high-to-low resulted in weight loss occurring mainly during the first six month after the switch. Because of the slow effect of a switch on weight evolution, the cost benefit ratio of a psychotropic switch should be rapidly evaluated, in particular among patients experiencing early weight gain (i.e., ≥5% from baseline after one month[27]).

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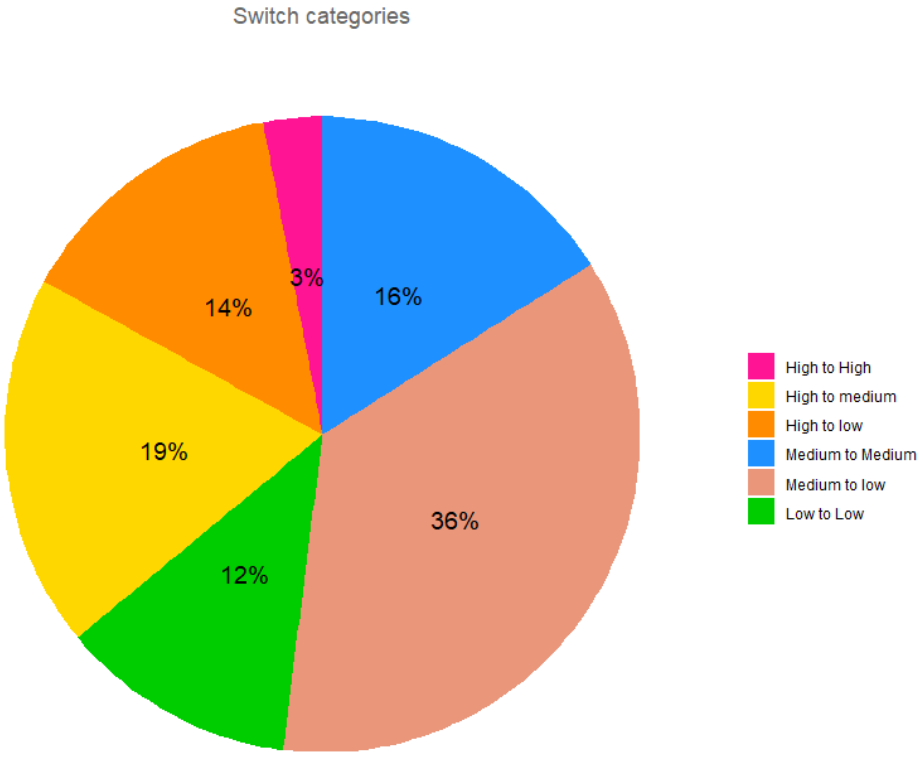
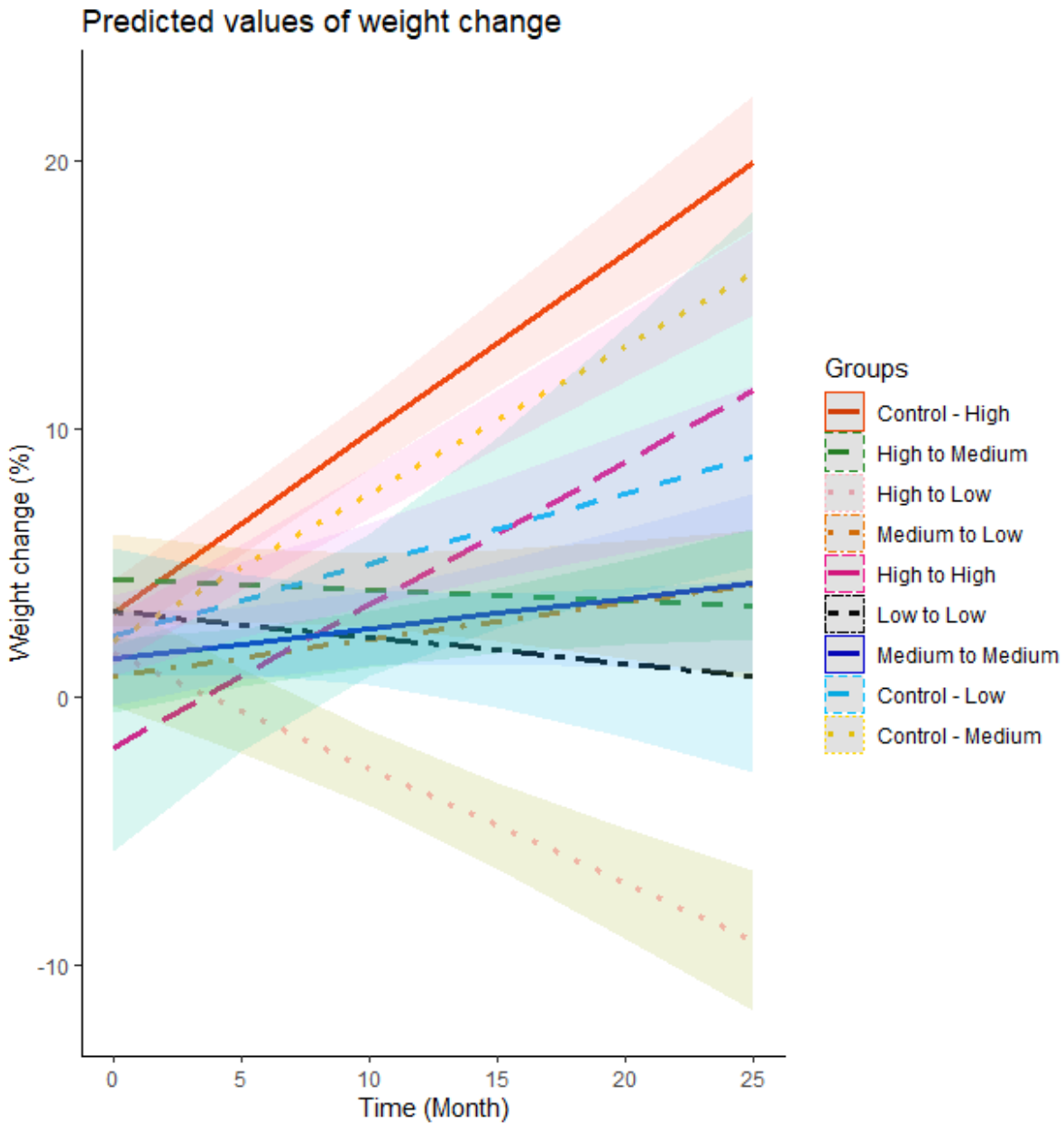
**Figure Legends**

**Figure 1.** Proportions of included patients in each switch category.




*Percentage of included patients in each switch category for the 195 patients switching psychotropic medication. High-risk drugs included clozapine, olanzapine and valproate; medium-risk drugs included levomepromazine, lithium, mirtazapine, quetiapine, risperidone/paliperidone and zuclopenthixol; and low-risk drugs included amisulpride, aripiprazole, brexpiprazole, flupenthixol, haloperidol and lurasidone.*

**Figure 2.** Predicted values of weight change in control patients and in the switch group




*Gradual weight loss is observed only in patients switching high-to-low, with a prediction of around 10% weight loss after two years, which is the same amount of weight gain in high-risk controls over one year. High-risk drugs included clozapine, olanzapine and valproate; medium-risk drugs included levomepromazine, lithium, mirtazapine, quetiapine, risperidone/paliperidone and zuclopenthixol; and low-risk drugs included amisulpride, aripiprazole, brexpiprazole, flupenthixol, haloperidol and lurasidone.*

Table 1: Descriptive statistics of switch and control groups.

| | Switch (N=195) | Control (N=237) | P-value | Total[a] (N=432) |
|---|---|---|---|---|
| **Age at baseline** (years) | 33 (23 - 50) | 44 (30 - 58) | **<0.001** | 39 (27 – 54) |
| **Sex** | | | 0.61 | |
| Men | 102 (52.3%) | 117 (49.4%) | | 219 (50.7%) |
| Women | 93 (47.7%) | 120 (50.6%) | | 213 (49.3%) |
| **Diagnoses**[b] | | | **<0.001** | |
| Psychotic disorders | 101 (51.8%) | 64 (27.0%) | | 165 (38.2%) |
| Depression | 29 (14.9%) | 42 (17.7%) | | 71 (16.4%) |
| Bipolar disorder | 20 (10.3%) | 45 (19.0%) | | 65 (15.0%) |
| Schizoaffective disorders | 26 (13.3%) | 13 (5.5%) | | 39 (9.0%) |
| Others | 10 (5.1%) | 23 (9.7%) | | 33 (7.6%) |
| Missing | 9 (4.6%) | 50 (21.1%) | | 59 (13.7%) |
| **Duration of 1st follow-up**[c] (days) | 92 (45 - 170) | 380 (360 - 430) | **<0.001** | 350 (100 - 390) |
| **Duration of 2nd follow-up**[c] (days) | 140 (61 - 340) | 380 (360 - 430) | **<0.001** | 360 (170 - 390) |
| **Total follow-up duration**[d] (days) | 290 (160 - 520) | 380 (360 - 430) | **<0.001** | 370 (290 - 460) |
| **BMI at baseline**[e] ($Kg/m^2$) | 23 (21 - 26) | 24 (21 - 27) | 0.43 | 23 (21 - 26) |
| Missing | 3 (1.5%) | 21 (8.9%) | | 24 (5.6%) |
| **BMI between follow-ups**[e] ($Kg/m^2$) | 24 (22 - 28) | 24 (21 - 27) | 0.10 | 24 (21 - 27) |
| Missing | 3 (1.5%) | 21 (8.9%) | | 24 (5.6%) |
| **Smoking** | | | 0.81 | |
| Yes | 95 (48.7%) | 95 (40.1%) | | 190 (44.0%) |
| No | 89 (45.6%) | 83 (35.0%) | | 172 (39.8%) |
| Missing | 11 (5.6%) | 59 (24.9%) | | 70 (16.2%) |
| **Psychotropic co-medication**[f] | | | 0.060 | |
| Yes | 50 (25.6%) | 42 (17.7%) | | 92 (21.3%) |
| No | 145 (74.4%) | 195 (82.3%) | | 340 (78.7%) |
| **Medical environment** | | | **<0.001** | |
| Inpatients | 134 (68.7%) | 30 (12.7%) | | 164 (38.0%) |
| Outpatients | 61 (31.3%) | 207 (87.3%) | | 268 (62.0%) |

*[a]Median with interquartile range and proportions are reported for continuous and categorical variables, respectively.*

*[b]ICD-10 classification: organic disorders, anxiety, personality disorder, intellectual disability, dementia and substance use disorder were classified together as "other."*

*[c]First (before switch) and second (after switch) follow-up duration is the same for controls.*

*[d]For the switch group, it refers to the sum of the two follow-ups durations (i.e., first and second).*

*[e]Controls have the same BMI at baseline and between follow-ups. For the switch group, BMI at baseline refers to the BMI at the beginning of the 1st follow-up, and BMI between follow-ups refers to the BMI at the moment of the switch.*

*[f]Psychotropic co-medication with potential for increasing weight: haloperidol, pipamperone, flupentixol, asenapine, amisulpride, aripiprazole, lurasidone, zuclopenthixol, levomepromazine,*

*risperidone/paliperidone, quetiapine, lithium, mirtazapine, valproate, olanzapine, and clozapine. Significant p-values are in bold.*

Table 2: Linear mixed-effect models of weight changes over a two-year follow-up.

| **Weight change over two-year follow-up[a]** | | | |
|---|---|---|---|
| Predictors | Estimates[b] | CI | p |
| Time [Control High][c] | 0.67 | 0.57 – 0.77 | **<0.001** |
| Control Medium * Time[d] | -0.12 | -0.24 – -0.00 | **0.045** |
| Control Low * Time[e] | -0.41 | -0.56 – -0.25 | **<0.001** |
| Switch High-to-Medium * Time | -0.71 | -0.87 – -0.55 | **<0.001** |
| Switch High-to-Low * Time | -1.10 | -1.26 – -0.94 | **<0.001** |
| Switch Medium-to-Low * Time | -0.53 | -0.68 – -0.39 | **<0.001** |
| Switch High-to-High * Time | -0.14 | -0.51 – 0.24 | 0.47 |
| Switch Medium-to-Medium * Time | -0.56 | -0.76 – -0.36 | **<0.001** |
| Switch Low-to-Low * Time | -0.77 | -0.98 – -0.55 | **<0.001** |
| N Patients | | 432 | |
| N Observations | | 5348 | |

*[a]Linear mixed-effect model adjusted by sex, age, medical environment and baseline weight.*
*[b]Estimates indicate mean weight change size per month.*
*[c]Reference group. Time is expressed in months. Weight change for patients switching from high-to-low risk is -0.43% (i.e., 0.67%-1.10%) for each additional month, whereas for patients switching from high-to-medium risk weight change is -0.04% (i.e., 0.67%-0.71%) for each additional month. No significant difference was found between controls taking high-risk drugs and patients switching within the high-risk category. Medium- and low-risk controls gained 0.55% (i.e. 0.67-0.12) and 0.26% (i.e. 0.67-0.41) in weight for each additional month.*
*[d]Switching medium-to-low and medium-to-medium showed -0.41% [(-0.53%) - (-0.12%)] and -0.44% [(-0.56%) – (-0.12%)] weight change compared to controls taking medium-risk drugs.*
*[e]Switching low-to-low drugs showed -0.36% [(-0.77%) – (-0.41%)] weight change compared to controls taking low-risk drugs.*
*Abbreviations: CI: confidence interval; p: p-value (significant values in bold). N: number*

Table 3: Test of linear hypotheses[a]

| Tested hypotheses[b,c,d] | Estimates[e] | p |
|---|---|---|
| Control High vs. average of Switch High-to-Low, -Medium and -High[b] | 1.32 | **<0.001** |
| Control Medium vs. average of Switch Medium-to-Low and -Medium[b] | 0.42 | **<0.001** |
| Control Low vs. Switch Low-to-Low[b] | 0.36 | **0.003** |
| Switch High-to-High vs average Switch High-to-Medium and -Low[c] | 0.77 | **<0.001** |
| Switch Medium-to-Medium vs. Switch Medium-to-Low[c] | -0.02 | ≈1 |
| Switch High-to-Medium vs. Switch High-to-Low[d] | 0.39 | **<0.001** |

*[a]Interactions of time with both switch and control categories shown in Table 2 tested using the matrix of contrasts.*
*[b]Hypothesis: after switch, weight change over time of controls equals weight change over time of patients switching from a molecule within the same risk category of controls.*
*[c]Hypothesis: after switch, mean weight change over time of patients switching within the same category of risk equals weight change over time of patients switching to a lower-risk molecule.*
*[d]Hypothesis: after switch, mean weight change over time of patients switching high-to-low equals weight change over time of patients switching high-to-medium.*
*[e]Controls taking high-risk drugs gained + 1.32% more weight for each additional month than patients switching from a high-risk drug. Moreover, patients switching high-to-high gained +0.77% more weight for each additional month than the other switch groups starting with a high-risk molecule, and patients switching high-to-medium gained +0.39% more weight for each additional month than patients switching high-to-low.*
*Abbreviations: p: p-value (significant values in bold)*

**Online Supplement**

**Supplementary Figure 1**: First and second psychotropic drug repartition in switching patients.

**Supplementary Figure 2:** Evolution of weight changes over time during the first year of treatment (start or switch of treatment).

**Supplementary Methods**: SNP selection and genotyping.

**Supplementary Figure 3**: Partial *r*-squared values of linear mixed-effect model of weight change for each of the first six covariates.

**Supplementary Figure 4**: Variable importance according to the t-statistics of linear mixed-effect model of weight change.

**Supplementary Table 1**: Test of linear hypothesis of linear mixed-effect models of weight change according to age categories.

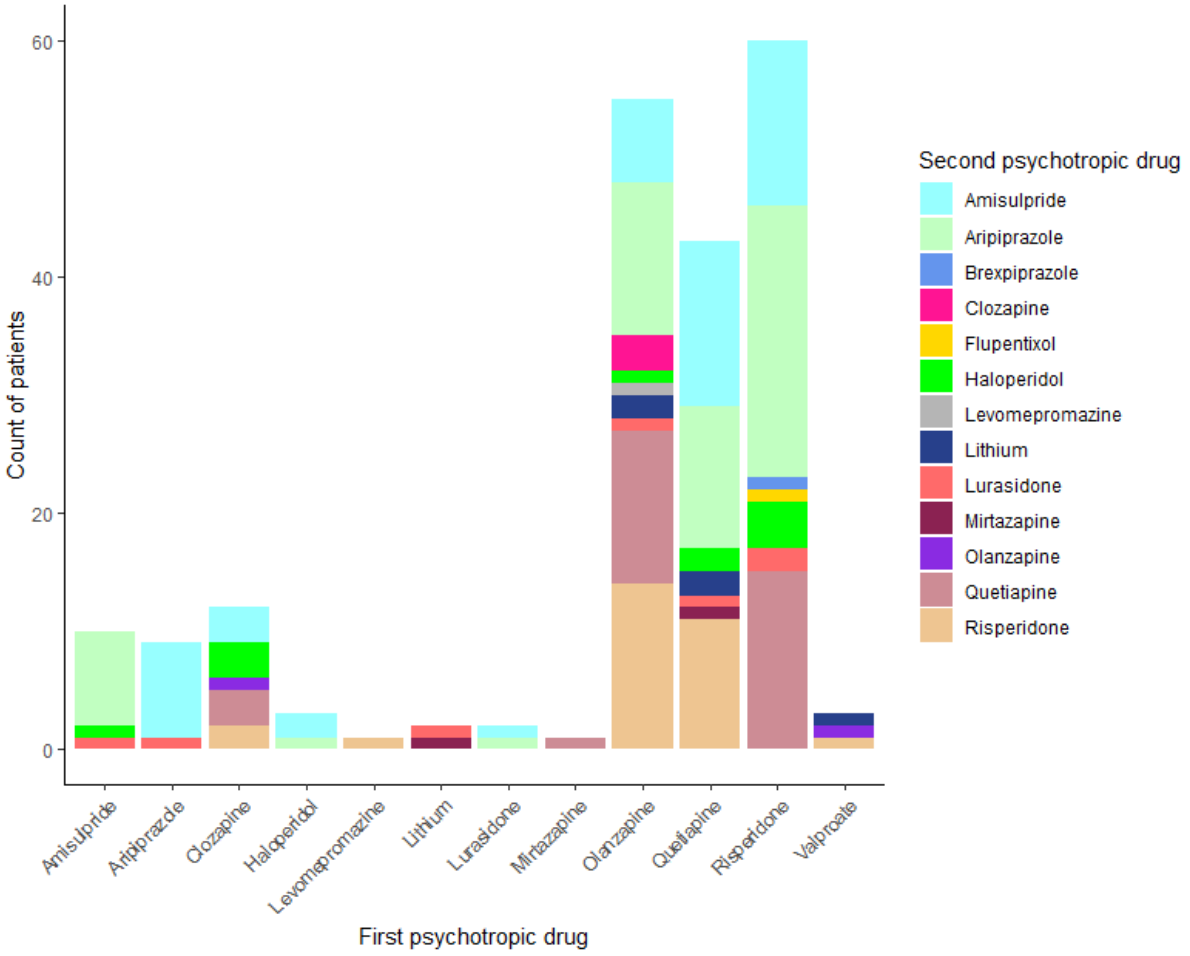
**Supplementary Table 2**: Test of linear hypothesis of linear mixed-effect models of weight change according to sex.

**Supplementary Table 3:** Linear mixed-effect models results for polygenic risk scores for BMI or BMI and psychiatric disorders.

**Supplementary Table 4**: Linear mixed-effect models of other metabolic outcomes.

**Supplementary References**

**Supplementary Figure 1.** First and second psychotropic drug repartition of patients switching drugs[a].



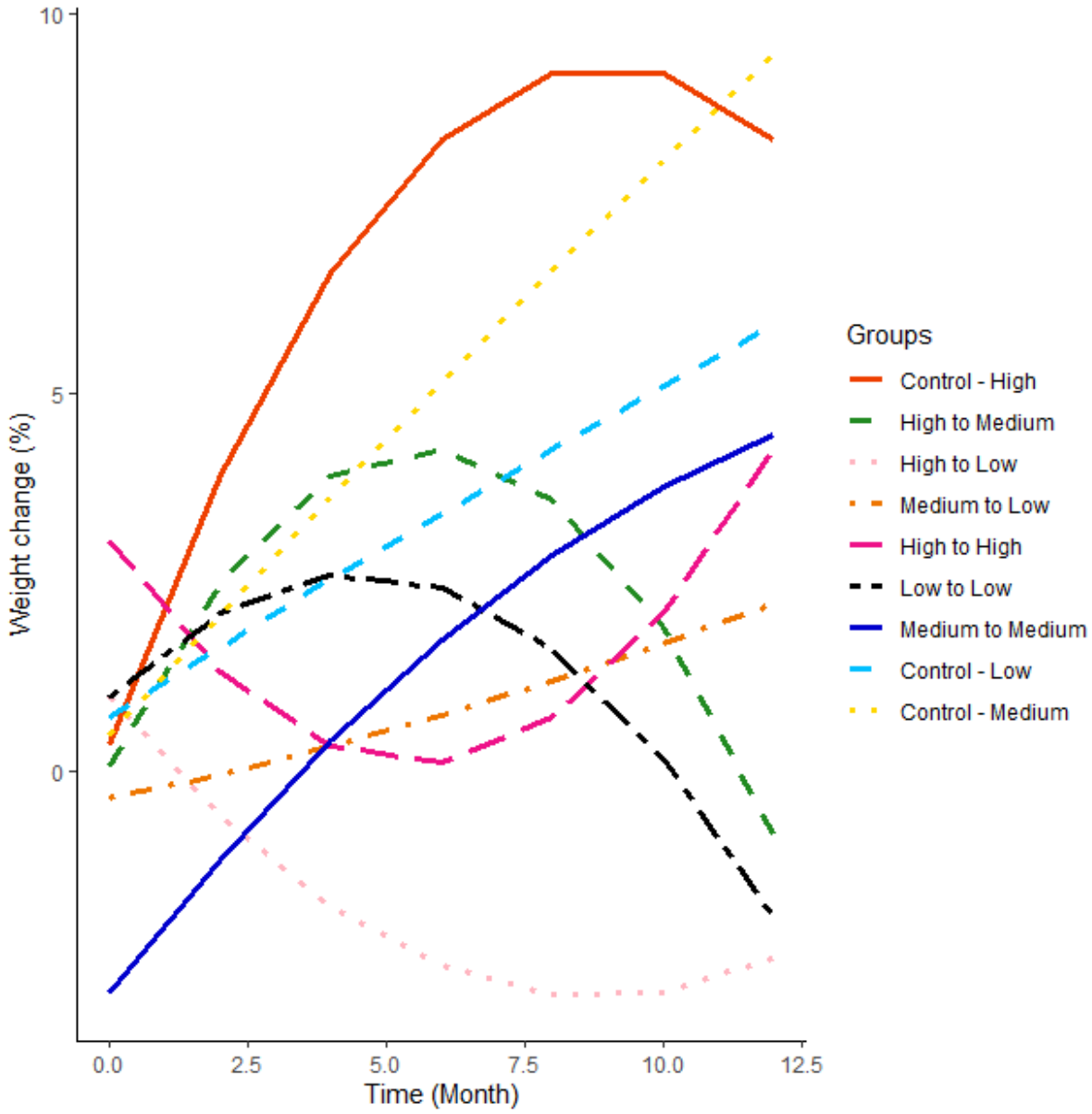

[a]*Patients taking paliperidone were classified with patients taking risperidone.*

**Supplementary Methods.**

SNP selection and genotyping. DNA was extracted from blood samples as described by the manufacturer's protocols using the Flexigene DNA kit and the QIAamp DNA Blood Mini QIAcube Kit (Qiagen AG, Switzerland). Genetic variants were determined by standard genotyping or imputation methods. DNA samples from all patients were genotyped using the Illumina Global Screening Array and processed on an iScan equipped platform (Illumina, San Diego, CA) at the iGE3 genomics platform of the University of Geneva (http://www.ige3.unige.ch/genomics-platform.php).

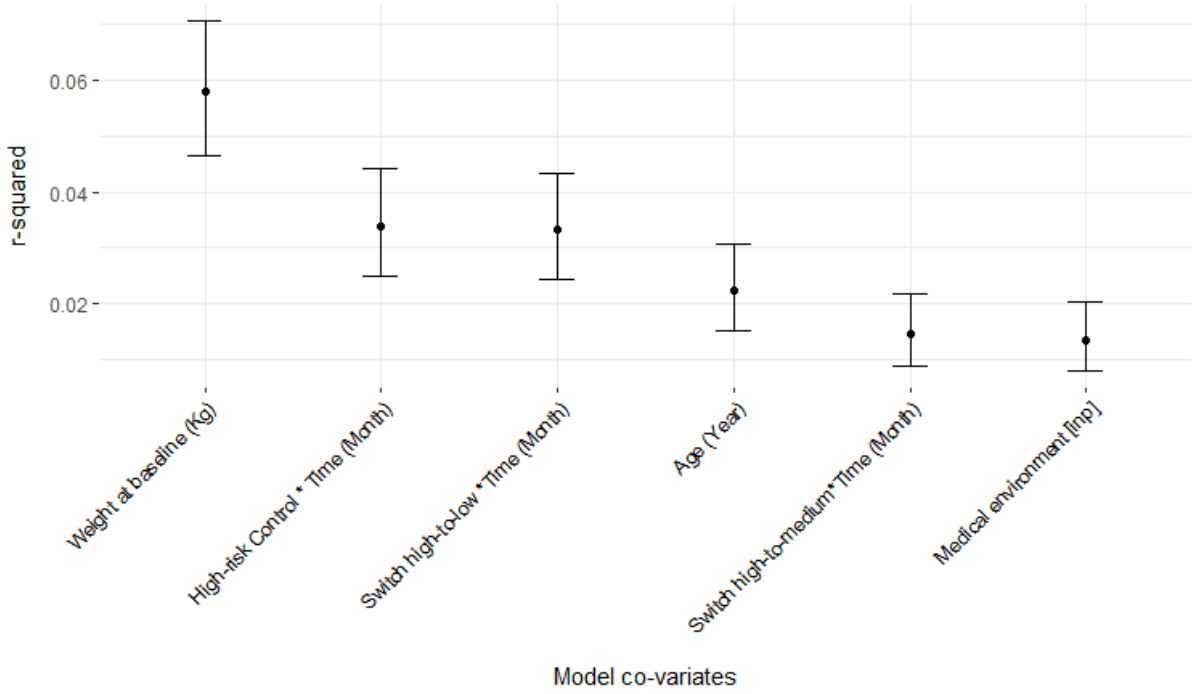
A total of 941 and 97 BMI-associated SNPs in the general population reaching genome-wide significance, 63 BMI and schizophrenia-associated, 17 BMI and bipolar disorder-associated and 32 BMI and major depression-associated SNPs at conjunctional false discovery rate less than 0.01 were combined into five distinct polygenic risk scores[1-3] , from which allele effects were used to assign weights to each variant for the calculation of genetic risk scores in the psychiatric samples. In the present study, genetic risk scores were constructed as a weighted sum of all SNPs. Each patient received for each SNP the coding value of 0, 1 or 2 according to the number of risk alleles. For instance, for a given SNP, a score of 1 was assigned for a carrier of one risk allele, whereas a value of 0 was attributed to non-carriers of this risk allele. Weighted GRSs were subsequently obtained by the summation of the BMI-associated risk alleles multiplied by their effect size reported for each SNP, assuming that each SNP contributes to the genetic risk score in an additive way. In order to facilitate results interpretation, wGRSs were then rescaled according to a calculation described elsewhere [4] . Of note, increasing the wGRS by one unit indicates one additional BMI-association risk allele [5] . All quality control (QC) and filtering steps were performed in PLINK [6] . Ancestry was determined using snpweights, a software for inferring genome-wide (GW) ancestry using SNP weights precomputed from large external reference panels[7] . Only individuals of European ancestry were considered in the present study.

**Supplementary Figure 2.** Evolution of weight changes over time during the first year of treatment (start or switch of treatment).



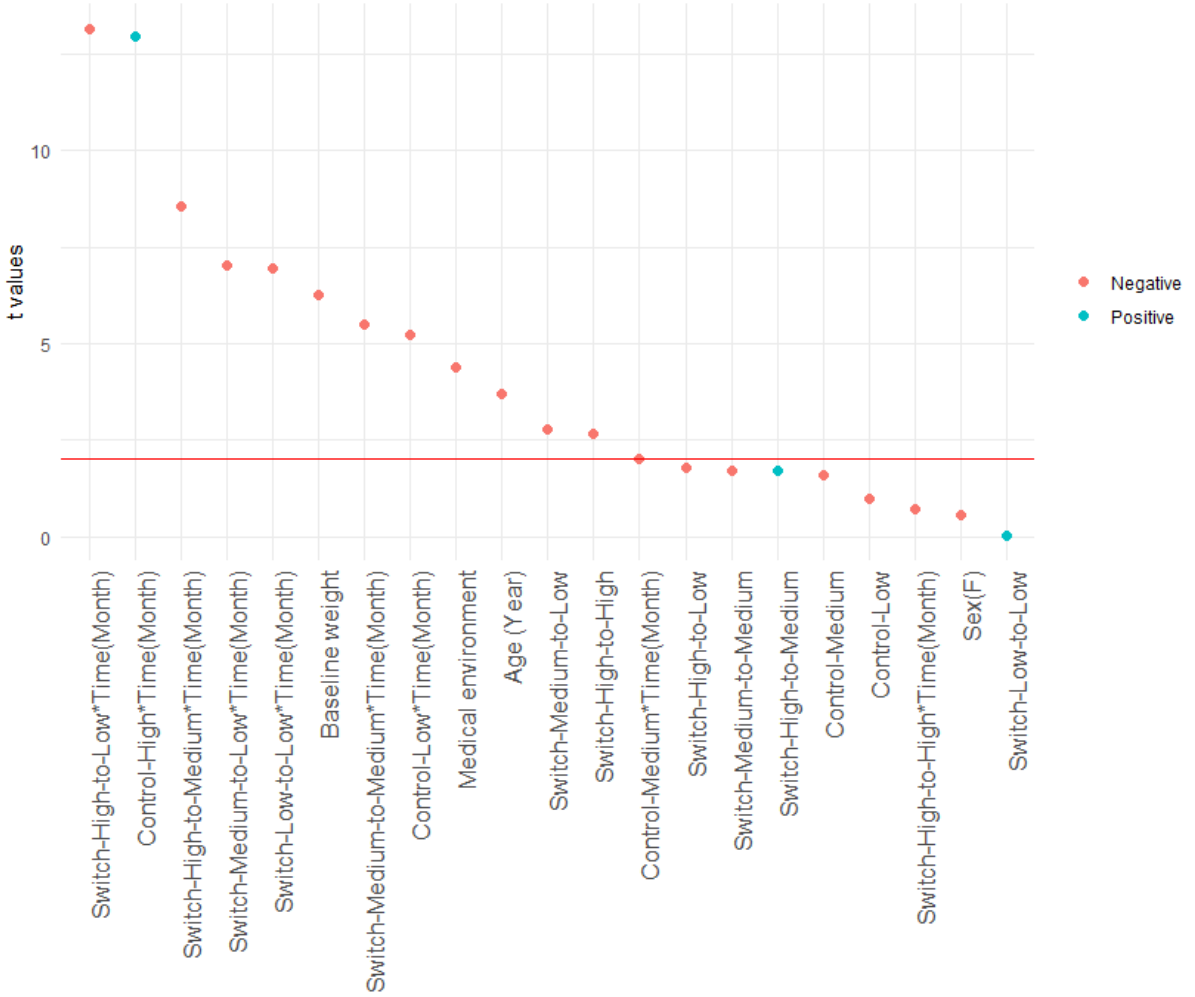

*Among patients switching high-to-low and their controls, the greatest loss or increase of weight, respectively, is observed during the first six months.*

**Supplementary Figure 3.** Partial *r*-squared values of linear mixed-effect model of weight change for the first six covariates.




*Partial r-squared values for the first six co-variates of linear mixed-effect model of weight change, adjusting by sex, age at baseline, baseline weight, medical environment and by the interaction of both switch and control categories with time.*
*Abbreviations: inp: inpatients*

**Supplementary Figure 4.** Importance of variables according to the t-statistics of linear mixed-effect model of weight change.




*T-statistic values and co-variates of linear mixed-effect model of weight change, adjusting by sex, age at baseline, baseline weight, medical environment and by the interaction of both switch and control categories with time. Dots over the red line including co-variate Control – Medium*Time(Month) indicate co-variates significantly associated with weight change.*

**Supplementary Table 1.** Test of linear hypothesis of linear mixed-effect models of weight change according to age categories.

| **Test of linear hypotheses**[a] | | | |
|---|---|---|---|
| **Young adults (≤25 years)** - Tested hypotheses[b,c,d] | **Estimates**[e] | **$p_{corrected}$** | **N total patients:** 102 **N total observations :**1305 |
| Control High vs. average Switch High-to-Low and -Medium/High[b] | 1.21 | 0.98 | |
| Control Medium vs. average Switch Medium-to-Low and -Medium[b] | 0.89 | **<0.001** | |
| Control Low vs. Switch Low-to-Low[b] | 0.41 | 0.60 | |
| Switch High-to-High vs. average Switch High-to-Medium and Low[c] | 1.83 | 0.46 | |
| Switch Medium-to-Medium vs. Switch Medium-to-Low[c] | -0.33 | 0.26 | |
| Switch High-to-Medium vs. Switch High-to-Low[d] | 1.31 | **<0.001** | |
| **Adults (>25 years & <65 years)** - Tested hypotheses[b,c,d] | **Estimates** | **$p_{corrected}$** | **N total patients:** 260 **N total observations:** 2903 |
| Control High vs. average Switch High-to-Low and Medium/High[b] | -0.64 | 0.99 | |
| Control Medium vs. average Switch Medium-to-Low and Medium[b] | 0.24 | **0.029** | |
| Control Low vs. Switch Low-to-Low[b] | 0.54 | **<0.001** | |
| Switch High-to-High vs. average Switch High-to-Medium and Low[c] | 0.44 | 0.14 | |
| Switch Medium-to-Medium vs. Switch Medium-to-Low[c] | 0.25 | 0.45 | |
| Switch High-to-Medium vs. Switch High-to-Low[d] | 0.21 | 0.72 | |
| **Elderly (≥65 years)** - Tested hypotheses[b,c,d,f] | **Estimates** | **$p_{corrected}$** | **N total patients:** 68 **N total observations:** 1107 |
| Control High vs. average Switch High-to-Low and -Medium/High[b] | 4.9 | 0.23 | |
| Control Medium vs. average Switch Medium-to-Low and -Medium[b] | -0.14 | 0.96 | |
| Control Low vs. Switch Low-to-Low[b] | -3.17 | **<0.001** | |
| Switch Medium-to-Medium vs. Switch Medium-to-Low[c] | 1.32 | **0.003** | |
| Switch High-to-Medium vs. Switch High-to-Low[d] | -0.99 | 0.99 | |

*[a]Interactions of time with both switch and control categories using the matrix of contrasts corrected for multiple testing. Median ages were 21, 42 and 76 years in the young adults, adults and elderly groups, respectively.*

*[b]Hypothesis: weight change over time of controls equals weight change over time of patients switching from a molecule within the same risk category of controls, after switch.*

*[c]Hypothesis: after switch, mean weight change over time of patients switching within the same category of risk equals weight change over time of patients switching to a lower-risk molecule.*

*[d]Hypothesis: after switch, mean weight change over time of patients switching high-to-low equals*

*weight change over time of patients switching high-to-medium.*
*[e]Young adult and adult controls taking medium risk drugs gained + 0.89% and +0.24 more weight for each additional month than patients switching from a medium-risk drug, respectively.*
*[f]No patients in the elderly category switched high-to-high.*
*Abbreviations: p: p-value (significant values in bold).*

**Supplementary Table 2.** Test of linear hypothesis of linear mixed-effect models of weight change according to sex.

| **Test of linear hypotheses**[a] | | | |
|---|---|---|---|
| **Men** - Tested hypotheses[b,c,d] | **Estimates**[e] | **$p_{corrected}$** | **N total patients:** 212 **N total observations :**2553 |
| Control High vs. average Switch High-to-Low and -Medium/High[b] | 1.03 | 0.091 | |
| Control Medium vs. average Switch Medium-to-Low and -Medium[b] | 0.45 | **<0.001** | |
| Control Low vs. Switch Low-to-Low[b] | -0.035 | 1 | |
| Switch High-to-High vs. average Switch High-to-Medium and -Low[c] | 1.62 | 0.65 | |
| Switch Medium-to-Medium vs. Switch Medium-to-Low[c] | -0.10 | 0.98 | |
| Switch High-to-Medium vs. Switch High-to-Low[d] | 0.40 | **0.006** | |
| **Women** - Tested hypotheses[b,c,d] | **Estimates** | **$p_{corrected}$** | **N total patients:** 212 **N total observations:** 2673 |
| Control High vs. average Switch High-to-Low and -Medium/High[b] | 1.40 | **<0.001** | |
| Control Medium vs. average Switch Medium-to-Low and -Medium[b] | 0.48 | **<0.001** | |
| Control Low vs. Switch Low-to-Low[b] | 0.92 | **<0.001** | |
| Switch High-to-High vs. average Switch High-to-Medium and -Low[c] | 0.76 | **0.001** | |
| Switch Medium-to-Medium vs. Switch Medium-to-Low[c] | -0.017 | 1 | |
| Switch High-to-Medium vs. Switch High-to-Low[d] | 0.46 | **0.049** | |

*[a]Interactions of time with both switch and control categories using the matrix of contrasts corrected for multiple testing.*
*[b]Hypothesis: weight change over time of controls equals weight change over time of patients switching from a molecule within the same risk category of controls, after switch.*
*[c]Hypothesis: after switch, mean weight change over time of patients switching within the same category of risk equals weight change over time of patients switching to a lower-risk molecule.*
*[d]Hypothesis: after switch, mean weight change over time of patients switching high-to-low equals weight change over time of patients switching high-to-medium.*
*[e]Among men, controls taking medium risk drugs gained + 0.45% more weight for each additional month than patients switching from a medium-risk drug, and patients switching high-to-medium gained 0.40% more weight per month than patients switching high-to-low.*
*Abbreviations: p: p-value (significant values in bold).*

**Supplementary Table 3.** Linear mixed-effect models results for polygenic risk scores for BMI or for BMI and psychiatric disorders**.**

| **Model 1[a] Polygenic risk score (BMI, general population[1])** | | | **Model 2[a,b] Polygenic risk score (BMI, general population[2])** | | | **Model 3 [a] Polygenic risk score (BMI and schizophrenia[3])** | | | **Model 4 [a] Polygenic risk score (BMI and bipolar disorder[3])** | | | **Model 5 [a] Polygenic risk score (BMI and major depression[3])** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| E | CI | p | E | CI | p | E | CI | p | E | CI | p | E | CI | p |
| -1.14 | -3.20 – 0.93 | 0.3 | -0.06 | -0.18 – 0.05 | 0.3 | 0.07 | -0.07 – 0.21 | 0.3 | 0.07 | -0.18 – 0.32 | 0.6 | 0.03 | -0.13 – 0.20 | 0.7 |
| $N_{patients}$: 241[c] $N_{observations}$: 3137 | | | | | | | | | | | | | | |
| -0.43 | -2.55 – 1.70 | 0.7 | -0.03 | -0.14 – 0.09 | 0.7 | 0.04 | -0.10 – 0.18 | 0.6 | 0.05 | -0.22 – 0.31 | 0.7 | -0.05 | -0.23 – 0.12 | 0.5 |
| $N_{patients}$: 241[d] $N_{observations}$: 2332 | | | | | | | | | | | | | | |
| -1.81 | -6.04 – 2.43 | 0.4 | -0.09 | -0.30 – 0.13 | 0.4 | 0.08 | -0.18 – 0.34 | 0.5 | 0.14 | -0.40 – 0.68 | 0.6 | 0.14 | -0.19 – 0.47 | 0.4 |
| $N_{patients}$: 93[e] $N_{observations}$: 801 | | | | | | | | | | | | | | |

*[1,2,3] See Supplementary References*

*[a]Models included only Psymetab genotyped participants of European ancestry.*

*[b]A sensitivity analysis was performed including a PRS constructed with the 10 SNPs most associated with BMI or with the highest beta from the GWAS study of Locke et al., with no difference in the results (data not shown).*

*[c]Linear mixed-effect model also adjusted by sex, age at baseline, medical environment, baseline weight, five principal components and by the interaction of both switch and control categories with time. Models included controls and switch patients (observations before and after the switch).*

*[d]Linear mixed-effect model also adjusted by sex, age at baseline, medical environment, baseline weight, five principal components and time. Models included switch patients (observations before the switch) and controls.*

*[e]Linear mixed-effect model also adjusted by sex, age at baseline, medical environment, weight at the moment of the switch, five principal components and time. Models included switch patients (observations after the switch).*

*Abbreviations: E: Estimates; CI: 95% confidence interval; p: p-value; N: number.*

**Supplementary Table 4.** Linear mixed-effect models of metabolic outcomes.

| | Glucose[c] | | Total cholesterol[d] | | LDL cholesterol[d] | | HDL cholesterol[d] | | Triglycerides[c] | | Systolic pressure | | Diastolic pressure[e] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Predictors [a,b] | E | p | E | p | E | P | E | p | E | p | E | p | E | p |
| Time (Month) | 0.01 | **0.047** | 0.02 | **0.001** | 0.01 | **0.005** | -0.00 | 0.098 | 0.02 | **0.001** | 0.04 | 0.51 | 0.21 | 0.12 |
| Control Medium | -0.11 | 0.30 | -0.08 | 0.55 | -0.08 | 0.52 | 0.00 | 0.92 | 0.02 | 0.87 | -1.31 | 0.43 | 0.78 | 0.57 |
| Control Low | -0.17 | 0.29 | -0.10 | 0.58 | -0.05 | 0.77 | 0.02 | 0.80 | -0.13 | 0.37 | -3.73 | 0.083 | -0.66 | 0.72 |
| High-to-Medium | 0.01 | 0.94 | -0.22 | 0.061 | -0.16 | 0.11 | 0.00 | 0.95 | -0.14 | 0.24 | -1.26 | 0.55 | 0.62 | 0.79 |
| High-to-Low | -0.10 | 0.51 | -0.27 | **0.043** | -0.13 | 0.28 | 0.02 | 0.76 | -0.25 | 0.080 | 1.81 | 0.37 | 1.76 | 0.52 |
| Medium-to-Low | -0.23 | 0.10 | -0.29 | 0.055 | -0.26 | 0.053 | -0.00 | 0.97 | -0.12 | 0.36 | 1.82 | 0.35 | 1.63 | 0.41 |
| High-to-High | 0.30 | 0.41 | -0.21 | 0.53 | -0.04 | 0.88 | -0.15 | 0.22 | -0.01 | 0.98 | -2.73 | 0.38 | -8.80 | 0.17 |
| Medium-to-Medium | -0.33 | 0.069 | 0.07 | 0.71 | 0.00 | 0.98 | 0.03 | 0.69 | 0.10 | 0.54 | -1.44 | 0.52 | 2.31 | 0.28 |
| Low-to-Low | -0.44 | **0.032** | -0.30 | 0.17 | -0.18 | 0.35 | 0.02 | 0.80 | -0.28 | 0.15 | -5.50 | **0.034** | -1.77 | 0.50 |
| N total patients | 329 | | 337 | | 333 | | 336 | | 331 | | 362 | | 362 | |
| N total observations | 822 | | 947 | | 906 | | 944 | | 879 | | 1996 | | 1996 | |

*[a]Linear mixed-effect model over two-year follow-up on glucose, total, LDL, HDL cholesterol, triglycerides, systolic and diastolic blood pressure adjusted by sex, age, baseline BMI and both switch and control groups. Glucose, total, LDL, HDL cholesterol and triglycerides are expressed in mmol/l. Blood pressure is expressed in mmHg.*

*[b]Reference group is High-risk control.*

*[c]Only fasting observation included.*

*[d]Adjusted by fasting status.*

*[e]Adjusted by both switch and control group interaction with time.*

*Abbreviations: N: number; E: estimates; p: p-value (significant values in bold).*

**Supplementary References**

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