See commentary by Tohen

Importance of Early Weight Changes to Predict Long-Term Weight Gain During Psychotropic Drug Treatment

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ABSTRACT

Background: Psychotropic drugs can induce substantial weight gain, particularly during the first 6 months of treatment. The authors aimed to determine the potential predictive power of an early weight gain after the introduction of weight gain–inducing psychotropic drugs on long-term weight gain.

Method: Data were obtained from a 1-year longitudinal study ongoing since 2007 including 351 psychiatric (*ICD-10*) patients, with metabolic parameters monitored (baseline and/or 1, 3, 6, 9, 12 months) and with compliance ascertained. International Diabetes Federation and World Health Organization definitions were used to define metabolic syndrome and obesity, respectively.

Results: Prevalences of metabolic syndrome and obesity were 22% and 17%, respectively, at baseline and 32% and 24% after 1 year. Receiver operating characteristic analyses indicated that an early weight gain > 5% after a period of 1 month is the best predictor for important long-term weight gain (≥ 15% after 3 months: sensitivity, 67%; specificity, 88%; ≥ 20% after 12 months: sensitivity, 47%; specificity, 89%). This analysis identified most patients (97% for 3 months, 93% for 12 months) who had weight gain ≤ 5% after 1 month as continuing to have a moderate weight gain after 3 and 12 months. Its predictive power was confirmed by fitting a longitudinal multivariate model (difference between groups in 1 year of 6.4% weight increase as compared to baseline, $P = .0001$).

Conclusion: Following prescription of weight gain–inducing psychotropic drugs, a 5% threshold for weight gain after 1 month should raise clinician concerns about weight-controlling strategies.

J Clin Psychiatry 2015;76(11):e1417–e1423
dx.doi.org/10.4088/JCP.14m09358

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A high prevalence of obesity (body mass index [BMI] ≥ 30 kg/m^2, World Health Organization definition) is reported in psychiatric populations, reaching 49% and 55% of bipolar and schizophrenic patients, respectively.[1] Obesity can lead to several metabolic complications, such as hypertension, lipid profile perturbation, or both, contributing to the reported 20-year shorter life expectancy in psychiatric patients as compared to the general population.[2] Several factors contribute to the high prevalence of metabolic disorders in psychiatry, such as the illness itself as well as lifestyle factors. In addition, antipsychotics (most atypicals but also some typicals), mood stabilizers (eg, valproate and lithium), and some antidepressants (eg, mirtazapine) can induce important weight gain.[3,4]

Several factors have been shown to be associated with drug-induced weight gain, including female gender, low baseline BMI, young age, or nonwhite ethnicities.[5] A high interindividual variability of drug-induced weight gain is observed, explained in part by genetic variability (eg, in H_1 receptor, M_3 receptor, or *CRTC1* gene),[6,7] underlining the importance of monitoring metabolic parameters.

The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes guideline[8] considers that a weight gain > 5% during treatment should be a sign to reconsider the treatment. However, no notion of time was defined, so that a weight gain of 5% after 1 month may be inappropriately compared to a comparable weight gain after 1 year of treatment. A joint statement of the European Psychiatric Association, the European Association for the Study of Diabetes, and the European Society of Cardiology defines a weight gain of 7% after 6 weeks of treatment as a clinically significant weight gain.[1] This 7% threshold was chosen for its clinical significance and not for its predictive value for an important weight gain during long-term treatment. To our knowledge, 3 studies have investigated the predictive values of an early weight gain. The first two studies[9,10] found that a 2-kg increase after 1 month was a good predictor for a 10-kg increase after 6 months in patients treated for schizophrenia with olanzapine, ziprasidone, and aripiprazole. The third study[11] in bipolar patients treated with olanzapine found that a 2-kg weight gain after 3 weeks will predict a 7% increase after 30 weeks of treatment. Notably, the above-mentioned studies were post hoc analyses of clinical trials examining the effects of specific drugs, with restrictions on the number of drugs that could be prescribed, conditions that are not comparable to usual clinical practice. In addition, nonobservance of the pharmacologic treatment is poor, particularly during long-term treatment.[12] In the above-mentioned studies, compliance was assessed by patient self-declaration,[13–15] which can be overestimated. Finally, the longest study duration was of 30 weeks, with no long-term data (1 year).

Clinical Points

- Psychotropic drug–induced weight gain is associated with high morbidity and mortality.
- Rapid detection of high risk patients is of major clinical significance.
- Weight gain of more than 5% after 1 month of treatment was found to be a good predictor for important long-term weight gain.

Because of the high mortality and morbidity associated with obesity, early detection of patients who have a higher risk of developing an important weight gain during psychotropic treatment is of major clinical relevance. In the present study, we sought to determine, in a cohort of psychiatric patients with compliance ascertained by therapeutic drug monitoring, how weight change during short-term treatment (1 month) could predict intermediate (3 months) and long-term (1 year) weight evolution during treatment with psychotropic drugs known to potentially induce important weight gain. Self-reported increase of appetite and modification of physical activity during the first month after drug introduction were also examined as possible weight gain predictors.

METHOD

Study Design

A longitudinal observational study has been ongoing since 2007 in the Department of Psychiatry of the Lausanne University Hospital in which inpatients starting a pharmacologic treatment with clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, lithium, valproate, and/or mirtazapine are included. Baseline clinical data were obtained during hospitalization, and follow-up data (1, 3, 6, 9, and/or 12 months) were obtained in the hospital or in outpatient centers during a medical examination based on the department guideline for metabolic follow-up performed on a routine basis.[16] When a treatment was stopped for more than 2 weeks, or if a drug was replaced by another drug on the list, the follow-up was restarted from baseline. In case of the introduction of a second studied drug, the follow-up was restarted and the last introduced drug considered as the main treatment (for more information, see eMethods 1). If 2 or more follow-ups were available for the same patient, only the longest one was included in the analysis (Supplementary eFigure 1). Diagnoses were based on the *ICD-10* classification (F00–F09, organic disorder; F20.0–F24.9 and F28–F29, psychotic disorders; F25.0–F25.9, schizoaffective disorder; F30.0–F31.9, bipolar disorder; F32.0–F33.9, depression; F10–F19, drug addiction). Anxiety, personality disorder, and mental retardation were classified together as "others." Compliance was evaluated by therapeutic drug monitoring (more information in eMethods 2). The study was approved by the ethics committee of the Lausanne University Hospital. Because of the noninterventional post hoc analysis study design, no informed consent was requested.

Exploratory Statistics

Mean values were presented with their respective standard error (SE), and significance threshold was fixed at $P < .05$.

To assess the predictive value of an early weight gain during the first month of treatment on long-term weight gain (3 and 12 months), sensitivity, specificity, positive predictive value, and negative predictive value were calculated using the *pROC* R package.[17] Sensitivity was defined as the percentage of correctly predicted high-risk patients among all truly long-term high-risk patients. Specificity was defined as the percentage of patients predicted as low-risk patients among all truly low-risk patients. Positive predictive value indicates the percentage of patients with an important long-term weight gain and who were classified as having a high early weight gain. Negative predictive value indicates the percentage of patients who did not have an important long-term weight gain and were classified as having a low early weight gain.

Thresholds for early weight gain were examined in 1% increments (from 2% to 8%) to find the best predictors for long-term weight gain as defined by a minimal weight gain of 10%, 15%, or 20% at 3 and 12 months of treatment (more information in eMethods 3). The same analysis was made to predict the effect of activity and appetite increase on long-term weight gain.

Confirmatory Analysis

A linear mixed-effect model was fitted on the weight gain percentage after separating patients into 2 groups based on their initial weight gain after 1 month of treatment, physical activity, and appetite increase (eMethods 4).

RESULTS

Demographics

Three hundred fifty-one patients were included (selection criteria in Supplementary eFigure 1). Male subjects (47%) were significantly younger (mean [SE] = 39 [1.6] years) than female subjects (51 [1.6] years, $P < .001$), which probably explains the lower prevalence of obesity in men (9%) than in women (23%, $P = .003$) (Supplementary eTable 1). No significant differences in other demographic variables were found between genders. Psychotic disorders (F20.0–F24.9 and F28–F29) were the most frequent diagnosis (41%), and quetiapine was the most frequently prescribed psychotropic drug (32%) (Table 1). Data were available for 313 subjects at 3 months and for 154 subjects at 12 months.

Metabolic Parameters

Twenty-one percent of patients were overweight (BMI = 25–30 kg/m^2) and 17% were obese (BMI ≥ 30 kg/m^2) at baseline (Supplementary eTable 2). In patients with 1-year follow-up, prevalence of patients with normal weight (BMI < 25 kg/m^2) decreased from 61% to 49% ($P = .007$)

Table 1. Overall Demographic Parameters and Comparisons Between Early and Nonearly Weight Gainers

Demographic	All (N = 351)	First Month Weight Gain ≤ 5% (n = 288)	First Month Weight Gain > 5% (n = 63)	P[a]
Age, mean (SE), y	46 (1.2)	46 (1.3)	43 (2.6)	.4
Men, n/total (%)	164/351 (47)	131/288 (45)	33/63 (52)	.3
Follow-up duration, mean (SE), d	237 (8.18)	240 (8.59)	223 (23.22)	.1
Illness duration, mean (SE), y	8 (0.6)	8 (0.7)	8 (1.2)	.6
Smoking, n/total (%)	76/351 (22)	64/288 (22)	12/63 (19)	.7
Diagnosis, n/total (%)				
Bipolar disorder	59/351 (17)	51/288 (18)	8/63 (13)	.5
Depression	61/351 (17)	49/288 (17)	12/63 (19)	.7
Organic disorders	27/351 (8)	24/288 (8)	3/63 (5)	.4
Psychotic disorders	143/351 (41)	113/288 (39)	30/63 (48)	.3
Schizoaffective disorder	26/351 (7)	22/288 (8)	4/63 (6)	.9
Other	30/351 (9)	26/288 (9)	4/63 (6)	.6
Not available	5/351 (1)	3/288 (1)	2/63 (3)	.2
Medication, n/total (%)				
Amisulpride	36/351 (10)	29/288 (10)	7/63 (11)	.8
Aripiprazole	30/351 (9)	27/288 (9)	3/63 (5)	.3
Clozapine	24/351 (7)	22/288 (8)	2/63 (3)	.3
Lithium	19/351 (5)	15/288 (5)	4/63 (6)	.8
Mirtazapine	11/351 (3)	9/288 (3)	2/63 (3)	.9
Olanzapine	44/351 (13)	29/288 (10)	15/63 (24)	**.006**
Quetiapine	112/351 (32)	95/288 (33)	17/63 (27)	.4
Risperidone	64/351 (18)	53/288 (18)	11/63 (17)	.9
Valproate	10/351 (3)	8/288 (3)	2/63 (3)	.7
Prevalence of metabolic syndrome IDF, n/total (%)[b]				
Baseline	35/161 (22)	34/139 (25)	1/22 (5)	.06
After 1-y treatment	32/100 (32)	21/79 (27)	11/21 (52)	**.04**
Prevalence of overweight status (BMI = 25–30 kg/m^2), n/total (%)				
Baseline	62/294 (21)	21/237 (22)	11/57 (19)	.8
1 Year	36/135 (27)	29/114 (25)	7/21 (33)	.4
Prevalence of obesity (BMI ≥ 30 kg/m^2), n/total (%)				
Baseline	49/294 (17)	46/237 (19)	3/57 (5)	**.009**
1 Year	33/135 (24)	28/114 (25)	5/21 (24)	1

[a] *P* values were calculated using Wilcoxon rank sum tests for continuous variables and Fisher exact tests for categorical variables between both groups. Values in bold are significant.

[b] Metabolic syndrome was present if patients had central obesity (men, ≥ 94 cm; women, ≥ 80 cm) and at least 2 other following factors: triglycerides ≥ 1.7 mmol/L or lipid-lowering treatment; glucose ≥ 5.6 mmol/L or type 2 diabetes treatment; blood pressure ≥ 130/85 mm Hg or treatment for hypertension; and high-density lipoprotein cholesterol (men, ≤ 1.03 mmol/L; women, ≤ 1.29 mmol/L).

Abbreviations: BMI = body mass index, IDF = International Diabetes Foundation, SE = standard error.

(Table 2). Mean BMI increase after 1 year of treatment was dependent on age, being 2.7 kg/m^2 in young patients (aged ≤ 25 years), 2.2 kg/m^2 in young adults (aged 25–45 years), 1.8 kg/m^2 in adult patients (aged 45–65 years), and 1 kg/m^2 in elderly patients (aged > 65 years) (Supplementary eTable 3). Prevalence of metabolic syndrome (MetS [International Diabetes Federation definition]) was 22% at baseline and 32% after 1 year (Supplementary eTable 2). In patients with baseline and 1-year data, a trend for an increased prevalence during treatment was observed (from 9% to 23%, *P* = .07) (Table 2). Other metabolic traits, including their evolutions during treatment, are described in eResults 1.

Short-Term Weight Gain as Predictors of Long-Term Weight Gain

The best early weight gain predictor (highest area under the curve [AUC] values, integrating both sensitivity and specificity of the predictor) was found to be a weight gain of more than 5% (Figure 1) after 1 month of treatment (mean [SE] = 31 [0.4] days) for predicting a weight gain of 15% or more after 3 months of treatment (mean [SE] = 102 [2] days). This threshold had a sensitivity of 67%, specificity of 88%, positive predictive value of 29%, and negative predictive value of 97%. Prevalence of a 15% weight gain after 3 months was 7.5%. The 5% threshold was also found to be the best predictor for a weight gain of 20% or more after 1 year of treatment (mean [SE] = 393 [7] days; sensitivity, 47%; specificity, 89%; positive predictive value, 30%; negative predictive value, 93% [Supplementary eTable 4]). A weight gain > 20% was observed in 10% of patients after 1 year. Patients who had a weight gain > 5% at 1 month and who did not reach a 15% weight gain at 3 months (false positives) had still a higher weight gain than patients with ≤ 5% weight gain (8.1% vs 2.4%, *P* = .000005). However, the difference was not significant anymore after 1 year (6.1% vs 3.9%, *P* = .2). In young adults and adults combined (age, 25–65 years), this threshold was also found to be the best predictor for a 20% weight gain after 3 months (sensitivity, 100%; specificity, 82%; positive predictive value, 7%; negative predictive value, 100%) and after 12 months (sensitivity, 55%; specificity, 83%; positive predictive value, 30%; negative predictive value, 93%) (Supplementary eTable 5). Due to an insufficient number of observations, no specific threshold could be calculated in young (aged ≤ 25 years) and elderly (aged > 65 years) subjects or in different diagnostic and medication groups.

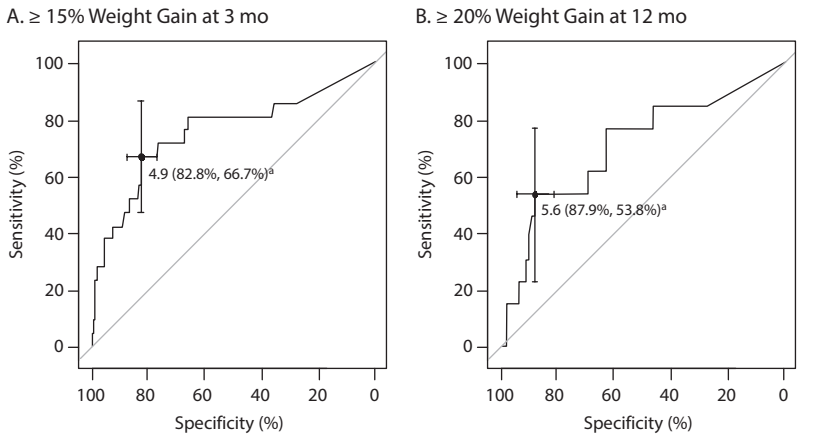
Using the 5% threshold, 18% of patients had a > 5% weight gain after 1 month. By integrating the 5% threshold in a generalized additive mixed model (Figure 2), patients with an early weight gain > 5% had a strong and fast increase of weight gain during the first 3 months of treatment, with a much slower increase thereafter (Supplementary eFigure 2). On the other hand, patients with an early weight gain ≤ 5% had a slower but steady 1-year weight gain. No differences of age, gender, follow-up duration, illness duration, or diagnosis were observed between the 2 groups. Medication was similar between the 2 groups except for olanzapine, which was present in 24% and 10% of the patients gaining more weight versus those gaining less than 5%, respectively (*P* = .006) (Table 1). When considering MetS traits at baseline, only BMI was significantly different between both groups (*P* = .001), being lower in the > 5% group. After 1 year, mean (SE) BMI increases of 1.2 (0.3) kg/m^2 and 3.1 (0.8) kg/m^2 were observed in the low and high weight–gain group, respectively (*P* = .01) (Supplementary eTable 6). A stronger decrease of high-density lipoprotein (HDL) cholesterol (β = −0.3 mmol/L,

Table 2. Evolution of Metabolic Parameters and Syndrome at Baseline, 3 Months, and 1 Year (only patients with 1-year follow-up included)

Variable	Baseline	3 mo	*P*[a]	1 y	*P*[a]
Prevalence of normal weight, overweight, and obesity, n/total (%)					
Normal weight (BMI < 25 kg/m^2)	71/116 (61)	60/116 (52)	**.01**	57/116 (49)	**.007**
Overweight (BMI = 25–30 kg/m^2)	25/116 (22)	32/116 (28)	.2	33/116 (28)	.2
Obese (BMI ≥ 30 kg/m^2)	20/116 (17)	24/116 (21)	.2	26/116 (22)	.07
Prevalence of abdominal obesity, n/total (%)					
Waist circumference ≥ 94 cm (men), ≥ 80 cm (women)[b]	42/86 (49)	53/86 (62)	**.02**	53/86 (62)	**.02**
Waist circumference ≥ 102 cm (men), ≥ 88 cm (women)[c,d]	25/86 (29)	28/86 (33)	.50	35/86 (41)	**.02**
Prevalence of HDL hypocholesterolemia, n/total (%)					
HDL cholesterol ≤ 1.03 mmol/L (men), ≤ 1.29 mmol/L (women)	18/61 (30)	16/61 (26)	.8	17/61 (28)	1.00
Prevalence of hypertriglyceridemia, n/total (%)					
Triglyceridemia ≥ 1.7 mmol/L or lipid-lowering treatment	13/63 (21)	20/63 (32)	.1	25/63 (40)	**.006**
Prevalence of hyperglycemia, n/total (%)					
Fasting glucose ≥ 5.6 mmol/L or antidiabetic treatment[b,d]	10/61 (16)	16/61 (26)	.1	23/61 (38)	**.002**
Fasting glucose ≥ 6.1 mmol/L or antidiabetic treatment[c]	7/61 (11)	5/61 (8)	.6	9/61 (15)	.7
Prevalence of hypertension, n/total (%)					
Blood pressure ≥ 130/85 mm Hg or antihypertensive treatment	14/80 (18)	15/80 (19)	1	16/80 (20)	.8
Prevalence of metabolic syndrome, n/total (%)					
ATP III[e]	3/35 (9)	1/35 (3)	.6	6/35 (17)	.2
Adapted ATP III[f]	3/35 (9)	2/35 (6)	1	6/35 (17)	.2
IDF[g]	3/35 (9)	6/35 (17)	.5	8/35 (23)	.07

[a]*P* values were calculated using McNemar tests between baseline versus 3 months and baseline versus 12 months. Values in bold are significant.
[b]According to IDF definition.
[c]According to National Cholesterol Education Program's ATP III[18] definition.
[d]According to adapted ATP III definition.
[e]Metabolic syndrome is present if at least 3 of the following criteria are present: central obesity (men, ≥ 102 cm; women, ≥ 88 cm); triglycerides ≥ 1.7 mmol/L or lipid-lowering treatment; glucose ≥ 6.1 mmol/L or type 2 diabetes treatment; blood pressure ≥ 130/85 mm Hg or treatment for hypertension; and HDL cholesterol (men, ≤ 1.03 mmol/L; women, ≤ 1.29 mmol/L).
[f]Same as ATP III definition but the following: glucose ≥ 5.6 mmol/L or type 2 diabetes treatment.
[g]Metabolic syndrome was present if patients had central obesity (men, ≥ 94 cm; women, ≥ 80 cm) and at least 2 other following factors: triglycerides ≥ 1.7 mmol/L or lipid-lowering treatment; glucose ≥ 5.6 mmol/L or type 2 diabetes treatment; blood pressure ≥ 130/85 mm Hg or treatment for hypertension; and HDL cholesterol (men, ≤ 1.03 mmol/L; women, ≤ 1.29 mmol/L).
Abbreviations: ATP III = Adult Treatment Panel III, BMI = body mass index, HDL = high-density lipoprotein, IDF = International Diabetes Foundation.

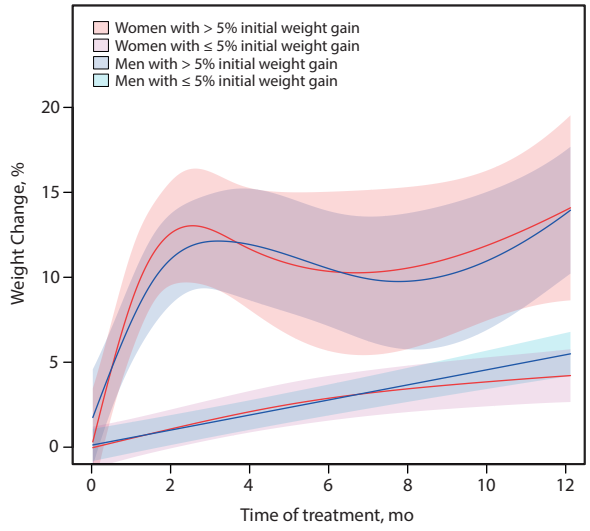
Figure 1. Receiver Operating Characteristic (ROC) Curves Indicating the Best Early Weight Gain Threshold to Predict a Weight Gain ≥ 15% After 3 Months and ≥ 20% After 1 Year of Treatment



[a]The number on the right side of the cross represents the best weight gain threshold after 1 month of treatment; specificity and sensitivity, respectively, are enclosed within the parentheses.

$P_{adjusted} < .0001$) and increase of triglyceride (β = 1.5 mmol/L, $P_{adjusted} < .0001$) were also observed in the > 5% group by using a linear model controlled by several confounders (Table 3). In the final linear mixed model with an early weight gain > 5% as predictor, it was confirmed that this threshold was a significant predictor of long-term weight gain over 1 year of treatment (difference between groups in 1 year [β] of 6.4% weight gain as compared to baseline, $P_{adjusted} = .0001$). This predictor was also found significant for a stronger long-term weight gain in young patients (aged ≤ 25 years) (β = 8.7%, $P_{adjusted} < .0001$), young adults (aged 25–45 years) (β = 7.3%, $P_{adjusted} = .0001$), adults (aged 45–65 years) (β = 7.4%, $P_{adjusted} = .005$), and elderly patients (aged > 65 years) (β = 13.6%, $P_{adjusted} < .01$). This predictor

Figure 2. Generalized Additive Mixed Model Prediction of Weight Over a 1-Year Period in Psychiatric Patients Having a > 5% Weight Increase Versus ≤ 5% After 1 Month Following the Introduction of Weight Gain–Inducing Psychotropic Drugs[a]



[a]Shaded area represents 95% CI. Men and women are represented by blue and red lines, respectively.

Table 3. Linear Model Comparing 1-Year Change of Metabolic Parameters Between Early and Nonearly Weight Gainers[a]

Parameter	Difference Between ≤ 5% and > 5% Weight Gain Group, Adjusted Mean (95% CI)	*P*[b]
Waist circumference, cm	1.7 (−4.8 to 8.2)	.6
Glucose, mmol/L	0.7 (−0.2 to 1.5)	.1
HDL cholesterol, mmol/L	−0.3 (−0.5 to −0.2)	**<.0001**
Triglycerides, mmol/L	1.5 (0.8 to 2.2)	**<.0001**

[a]Results were obtained by fitting a linear model controlling for age, sex, time, baseline body mass index, and current psychotropic drug.
[b]Values in bold are significant.
Abbreviation: HDL = high-density lipoprotein.

was also found significant in patients with psychotic or schizoaffective disorder (β = 7.0%, $P_{adjusted} < .0001$), bipolar disorder or depression (β = 9.1%, $P_{adjusted} = .0006$), and in the other diagnoses (β = 11.6%, $P_{adjusted} < .01$). Significant results were also observed in patients treated with amisulpride or aripiprazole (β = 6.6%, $P_{adjusted} = .003$); mirtazapine, lithium, quetiapine, or risperidone (β = 8.4%, $P_{adjusted} < .0001$); and finally with clozapine, olanzapine, or valproate (β = 7.4%, $P_{adjusted} < 0.0001$) (Supplementary eTable 7).

Effect of Changes in Appetite and Physical Activity During Treatment

Calculations were also made to assess the predictive power value of moderate or high (≥ 30 min/d) physical activity and of an appetite increase during the first month of treatment on long-term weight gain (Supplementary eTables 8 and 9). The AUC value indicated no predictive power for either parameter (AUC ≈ 50).

DISCUSSION

Confirming previous studies in psychiatric patients,[19,20] our study found a high prevalence of overweight status or obesity (39%) in the present cohort at baseline, which even increased after 1 year of treatment (50%). Notably, a higher (68%) prevalence of overweight status or obesity was measured in another Swiss cohort,[20] which is probably explained by the longer treatment duration in the latter cohort (median = 2.3 years vs mean = 0.65 years). The increase of mean BMI after 1 year of treatment was dependent on age (decreasing with increasing age), which is in agreement with previous studies showing that being of young age is a risk factor for a stronger increase in BMI.[21] Although weight gain in elderly patients is subject to controversial results,[22,23] in the present study a moderate mean gain of 1 BMI unit was observed after 1 year in this age group, which is in agreement with the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATI-AD) study[23] conclusion supporting the importance of metabolic monitoring also in elderly patients. Because of the small cohort size after stratification by the type of drugs prescribed, the frequent polymedication, and the previous history of past medications, it was not possible to differentiate the effects of each psychotropic drug separately.

An early weight gain of more than 5% was found to be the best predictor for a weight gain of ≥ 15% after 3 months and of ≥ 20% after 1 year. Of note, AUC values have also been calculated for the previously published threshold of 2 kg after 1 month.[9–11] Similar results to the present analysis in terms of AUC values were found (data not shown). Because an absolute threshold expressed in kilograms does not take into account the large variability of baseline weight, a relative threshold expressed in percentage as presented in this study appears to be more relevant. The high negative predictive value indicates that this measure will correctly predict the future status of most patients (97% for 3 months, 93% for 12 months) who had a weight gain less than or equal to 5% after 1 month as continuing to have a moderate weight gain after 3 and 12 months, respectively. Over 1 year, these patients had a mean BMI increase of 1.2 kg/m^2, which is significantly lower than the 3.1-kg/m^2 increase observed in the high early weight–gain group. The low positive predictive value indicates that 71% and 70% of patients with an early weight gain > 5% will not reach the 15% and 20% threshold at 3 and 12 months. Although weight gain in this false-positive group at 3 months is still significantly higher than in the low weight–gain group, the difference was no longer significant at 12 months, indicating the necessity of long-term weight monitoring also in the group with low initial weight gain. Monitoring of metabolic parameters is performed in our department with advice to take into account significant changes of parameters by different means (discussion with the patients, diet and physical activity counseling, drug evaluation and changes). Because

such possible interventions were not collected in this post hoc noninterventional study, it is not known if they could have contributed to part of the false-positive results.

These predictive parameters are in agreement and complete previous results obtained from clinical trials.[9,10,24] Female gender, young age, low baseline BMI, and low triglyceride levels were proposed to predict antipsychotic-induced weight gain.[3,20,25,26] In the present study, only BMI was found to be significantly different between both groups, being lower in the early weight-gain group at baseline. However, triglyceride values increased and HDL cholesterol values decreased with higher amplitude over 1 year, showing that these parameters are worsening faster in the early high weight–gain group, paralleling the faster increase of BMIs.

The threshold of more than 5% in the early phase of the treatment remained significant ($\beta = 6.4\%$, $P_{adjusted} = .0001$), even after adjusting for several confounders. These results indicate the robustness of this predictor and should motivate clinicians to monitor early weight changes more thoroughly for all patients and not only patients with known risk factors (ie, young patients, drug naive, and other factors). Although not formally demonstrated in the present study, the threshold of more than 5% weight gain after 1 month of treatment may also be used to detect some patients who could reach this threshold in a shorter period of time. Thus, very rapid and important weight gain should be evaluated by the treating physician and nurses independently of the usual time schedules for weight monitoring.

No significant influence of prescribed antipsychotics was found in the confirmatory analysis. This is in agreement with a previous study showing that an early weight gain of 2 kg is a good predictor for more weight gain during 24- to 28-week treatment with olanzapine and aripiprazole, 2 drugs with important differences in their potential to induce weight gain.[9] These results suggest that, independently of the prescribed drugs (ie, atypical antipsychotics, mood stabilizers such as lithium or valproate, or sedative antidepressants such as mirtazapine), the 5% threshold should be used when monitoring weight gain during treatment.

To our knowledge, only 1 study[27] previously investigated the role of appetite on long-term weight change, concluding that early weight gain was found to be a better predictor for further weight gain than appetite increase, which is in agreement with the present study. In addition, medium or high physical activity was also a poor predictor. However, the present results do not preclude the use of health promotion intervention, including physical activity or behavioral interventions that have shown some effect in psychiatric populations.[28]

Several limitations of the present study have to be mentioned. First, the majority of patients were not drug naive, and the observed weight gain was probably also the result of past treatments. However, such patients constitute the majority of psychiatric populations, which therefore might even strengthen the clinical validity of the present finding. Second, the follow-up period lasted only 1 year, but previous studies,[29,30] as well as the present study, show that following drug introduction, most of the weight gain occurs during this period. Third, due to an insufficient number of observations, we could not determine an early weight–gain threshold specifically in young and elderly patients. However, the 5% threshold was significantly associated with important weight gain in these 2 age classes. Finally, the results concerning activity and appetite change have to be interpreted with caution because the evaluation was self-reported, used a nonvalidated scale, and may be not sensitive enough.

A strength of the present study is its longitudinal design with weight monitoring at regular time points during 1 year when patients started a weight-inducing psychotropic drug or switched the treatment. In addition, the use of therapeutic drug monitoring allowed us to assess the compliance of the patients, which is an important issue in psychiatric treatment.

In conclusion, this work underlines the importance of weight monitoring at the introduction and after a switch of antipsychotic drugs, mood stabilizers, or sedative antidepressants for all patients, independently of their gender, age, initial body weight, previous treatments, or illness duration. A weight gain of more than 5% during the first month of treatment should be used by the clinician as one of the early warning signs to consider those patients as being at higher risk of important weight gain during long-term treatment. A particular emphasis should be put on such patients by using all available strategies (ie, behavioral interventions or even replacing the causative weight gain–inducing drug if clinically possible, after a careful evaluation of the risk-benefit ratio of a drug switch), considering the major impact weight gain and its consequences have on quality of life and general health of patients.

Submitted: July 3, 2014; accepted November 11, 2014.

Drug names: aripiprazole (Abilify and others), clozapine (Clozaril, FazaClo, and others), lithium (Lithobid and others), mirtazapine (Remeron and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

Author contributions: Drs Vandenberghe and Gholam-Rezaee contributed equally to the work. Dr Eap had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design was provided by Dr Eap. Acquisition of data was provided by Drs Vandenberghe, Saigí-Morgui, Choong, Solida-Tozzi, Kolly, Gallo, Thonney, Hedjal, Ambresin, von Gunten, and Conus and Ms Delacrétaz. Analysis and interpretation was provided by Drs Vandenberghe and Gholam-Rezaee. Drafting of the manuscript was provided by Drs Vandenberghe and Gholam-Rezaee. Critical revision of the manuscript for important intellectual content was provided by all authors. Statistical analysis was provided by Drs Gholam-Rezaee and Vandenberghe. Drs Eap and Conus obtained funding for the study. Administrative, technical, or material support was provided by Drs von Gunten, Ambresin, and Conus.

Potential conflicts of interest: **Dr Eap** received research support from Takeda and from the Roche Organ Transplantation Research Foundation (#152358701) in the previous 3 years. He received honoraria for conferences or teaching CME courses from Advisis, AstraZeneca, Essex Chemie, Lundbeck, Merck Sharp & Dohme, Sandoz, Servier, and Vifor-Pharma in the previous 3 years. **Dr von Gunten** received honoraria for a conference or a workshop participation from Vifor, Bayer Schering, and Schwabe in the previous 3 years. **Drs Vanderberghe**, **Gholam-Rezaee**, **Saigí-Morgui**, **Choong**, **Solida-Tozzi**, **Kolly**, **Thonney**, **Gallo**, **Hedjal**, **Ambresin**, and **Conus** and **Ms Delacrétaz** declare no conflict of interest in relation to the content of the article.

Funding/support: This work has been funded in part by the Swiss National Research Foundation (CBE and PC: 320030-120686 and 324730-144064).

Role of the sponsor: The funding sources had no role in the writing of the manuscript or in the decision to submit it for publication.

Previous presentation: Previously presented in part at the 22nd Annual European Congress of Psychiatry; March 1–4, 2014; Munich, Germany ▪ 168th Annual Meeting of the American Psychiatric Association; May 16–20, 2015; Toronto, Canada.

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

Additional information: The original dataset is in possession of Dr Eap.

Supplementary material: See accompanying pages, which includes eTable 10 about comedication possibly inducing weight gain and additional eReferences.

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Supplementary material follows this article.

THE JOURNAL OF
CLINICAL PSYCHIATRY
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Supplementary Material

Article Title: Importance of Early Weight Changes to Predict Long-Term Weight Gain During Psychotropic Drug Treatment

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DOI Number: 10.4088/JCP.14m09358

List of Supplementary Material for the article

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CLINICAL PSYCHIATRY
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Supplementary data

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eTable 10: Co-medication possibly inducing weight gain[1, 2].

eFigure 1: Flow chart for selection of patients.

eFigure 2: Weight changes at 1 month (mean(se) 31(0.4) days), 2 months (mean(se) 64(1.8) days), 3 months (mean(se) 102(2) days), 6 months (mean(se) 189(2.3) days), 9 months (mean(se) 278(3.7) days) and one year (mean(se) 393(7.1) days). Red and blue box plots represent the patient's observation with a first month weight gain of more than 5% and less or equal to 5%, respectively. Dotted black line represents no weight change; red dotted line represents 5% weight increase.

eMethods 1: Study design and subject selection.

Patients with missing weight at baseline or at one month were excluded from analysis (eFigure 1). If two or more studied drugs (clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, lithium, valproate and/or mirtazapine) were prescribed concomitantly, the latest introduced compound was considered as the main treatment and the other drugs were pooled with co-medication possibly inducing weight gain (eTable 10). Medications could be changed by the treating physician according to the response to treatment and side-effects with no influence of the inclusion of patients in the study (non-interventional study).Weight was measured in the morning in fasting conditions by using professional medical scales. No retrospective or self-estimated patient data was used. Appetite assessment was based on a five item scale (self evaluation): low, moderate, medium, high and very high appetite. Physical activity, which was defined as walking, climbing stairs or specific sport activity, was based on daily physical activity duration (self evaluation): <30 min, 30-60 min, >60 min. For statistical tests on long term weight gain, appetite increase was defined as an elevation of appetite between baseline and the first month of treatment (eg. low to moderate, moderate to high). In addition, physical activity was defined by the daily activity duration at one month treatment (less vs equal or more than 30 minutes).

eMethods 2: Determinations of clinical chemistry parameters and drug plasma concentrations.

Metabolic syndrome (MetS) prevalence was assessed according to the Adult Treatment Panel III (ATP III) [3], the adapted definition (ATP III-A) [4] and the International Diabetes Federation (IDF) [5] which has different cut-offs for waist circumference (WC) depending on the ethnicities (e.g. for the 95% of our patients who are Caucasian, Sub-Saharan Africans, Eastern Mediterranean and Middle East populations, WC of 90 cm for men and 80 cm for women are used for the definition of metabolic syndrome. This same cut-off was used for the 5% other patients who were Asians (n=2) or of unknown ethnic group (n=17)). Blood samples were drawn in the morning in fasting conditions (blood samples drawn after 10H00 AM were excluded from analysis) to measure clinical chemistry parameters and drug plasma concentrations. Plasma drug concentrations were quantified at one, three and 12 months in trough conditions (in the morning before the next drug intake). Liquid chromatography/mass spectrometry methods were used for measuring aripiprazole, clozapine, or olanzapine plasma levels as previously described[6], and also for risperidone, OH-risperidone, quetiapine or amisulpride (Eap et al., unpublished data, available on request). Mirtazapine was measured by gas-chromatography-nitrogen detector (Eap et al., unpublished data, available on request), valproate by fluorescence polarization immunoassay (Cobas integra 400 plus Roche®, Roche Diagnostic, Rotkreuz, Switzerland) and lithium by ion selective electrode (EasyLyte Na/K/Cl/Li, Medica®, Chatel St-Denis, Switzerland). All methods are used on a routine basis in our accredited laboratory (ISO 15189 and 17025), with external quality controls (LGC Standards Proficiency Testing (Teddington, United Kingdom); Arvecon (Walldorf, Germany; Quality Control Centre Switzerland (Chêne-Bourg, Switzerland)). Patients were considered compliant when drug plasma concentrations were higher than 10 % of the lower value of the recommended therapeutic range [7]. For this purpose, for all substances except risperidone, the concentration of the prescribed drug was used, while for risperidone, the sum of risperidone and of its metabolite 9-OH risperidone was used. Drug plasma concentration at month one and three, and at month one and 12 were evaluated for follow ups shorter or equal to 12 months, respectively. Reports of non-compliance as observed by the medical or nursing staff were also taken into account. Patients who were considered non-compliant at any of the time periods of observations were excluded from analysis.

Patients' blood pressures were measured once after five minutes rest in a sitting position.

eMethods 3: Exploratory analysis.

Marginal analyses were done using Wilcoxon rank-sum (*W+*) and Kruskal-Wallis tests (*KW*) for comparing continuous traits. Fisher's exact tests (*FET*) were used to compare categorical variables and McNemar tests (*MN*) were used to compare the prevalence of outrange metabolic parameters between baseline, three and 12 months. Thresholds for early WG were examined by 1% increments (ranging from 2% to 8%) to find the best predictors for long term WG as defined by a minimal WG of 10%, 15% or 20% at 3 and 12 months of treatment. These analyses allowed to assess the best relation between SN and SP to find an acceptable threshold for short and long term WG. To explore the adequacy of linear evolution of BMI along time, a Generalized Additive Mixed Model (GAMM) was also fitted to the same data. The response variable in this model corresponded to the ratio of the weight at each time point divided by the weight at baseline, which represents the weight gain at that time point. Observations made at two, three, six, nine and 12 months (analyzed as a continuous variable) were used to fit the model, while observations made at baseline and/or at the first month were used to construct the grouping variable. The effect of time on weight gain was not considered as linear but was better represented by a smooth semi-parametric curve (with cubic regression spline basis). GAMMs were fitted separately for each sub-group to give the possibility of capturing the weight-gain trend without restraint at each sub-group (otherwise, a parallel trend in time would have been imposed on all sub-groups). These models were not adjusted for multiple comparisons, covariates or cofactors as they were used only to explore the data and the adequacy of the final model.

eMethods 4: Confirmatory Analysis.

The "nlme" package of R[8] was used to fit a linear mixed effect model adjusted for age (at baseline), gender, BMI (at baseline), psychotropic drugs, presence of co-medication possibly inducing weight gain, triglycerides, glucose and HDL concentrations. The fitted linear mixed effect model[9] had a random effect at the subject level. To be more robust in inferences, a bootstrap analysis[10] was used to evaluate the uncertainty of estimated parameters (evaluated uncertainties are more conservative, but more reliable if there are violations from model assumptions, as normality assumption for residuals). Results were based on 10000 bootstrap replicates at the subject level (subjects were considered to be independently recruited) and increasing the number of bootstraps did not influence substantially the uncertainty of estimated parameters.

eResults 1: Metabolic parameters.

Abdominal obesity (M≥94cm, F≥80cm) was observed in 54% of patients at baseline, and increased from 49% to 62% after one year (p=0.02, table 2) in patients with one year follow-up. This prevalence increased significantly with age (from 30% to 66% at baseline, p=0.001 and from 45% to 76% at one year, p=0.004) (eTable 3).Hypo HDL-cholesterolemia (M≤1.03mmol/l; F≤1.29mmol/l)) was observed in 31% of patients at baseline with no evolution during treatment. Prevalence at baseline was higher in women except in elderly patients (young, p=0.02; young adults, p=0.03: adults, p=0.01). Baseline hypertriglyceridemia (≥1.7mmol/l or presence of lipid lowering drug) was observed in 28% of the patients at baseline. In patients with baseline and one year data, hypertriglyceridemia increased from 21% to 40% after one year (p=0.006). Hypertriglyceridemia increased along the four age categories from 8% to 36% at baseline (p=0.01) (eTable 3). Hyperglycemia or diabetes (≥5.6mmol/l or antidiabetic medication) was observed in 25% of patients at baseline. In patients with baseline and one year data, hyperglycemia increased from 16% to 38% (p=0.002). No gender differences were observed at baseline and after one year, however hyperglycemia was significantly increased with increasing age (p=0.003). No gender differences in the prevalence of hypertension (130/85mmHg or antihypertensive medication) were observed, with an unchanged prevalence during treatment. However, as expected, hypertension was found to increase significantly with increasing age both at baseline and after one year (p=0.001). Prevalence of metabolic syndrome (MetS, IDF definition) was 22% at baseline. In patients with baseline and one year data, a trend for an increased prevalence during treatment was observed (from 9% to 23%, p=0.07). In agreement with other parameters, MetS increases with increasing age (6% to 44%, p=0.001) at baseline, however no significant age related increase was observed after one year.

eTable 1: Baseline demographics stratified by gender.

Characteristics	Total (351)	Men (164)	Women (187)	P [a]
Age, mean (se), years	46 (1.2)	39 (1.6)	51 (1.6)	**<0.001**
BMI				
Mean (se), kg/m^2	24.4 (0.3)	24.1 (0.3)	24.7 (0.5)	0.7
Overweight [25-30[kg/m^2, n/total n (%)	62/294 (21%)	35/130 (27%)	27/164 (16%)	**0.03**
Obese ≥ 30 kg/m^2, n/total n (%)	49/294 (17%)	12/130 (9%)	37/164 (23%)	**0.003**
Smoking, n/total n (%)	76/137 (55%)	42/67 (63%)	34/70 (49%)	0.9
Illness duration, mean (se), years	8.0 (0.6)	6.7 (0.8)	9 (1)	0.4
Follow up duration, mean (se), days	237.2 (8.2)	253.8 (12.9)	222.7 (10.3)	0.1
Month 1, mean (se), days	31 (0.4)	31 (0.6)	32 (0.5)	0.3
Month 3, mean (se), days	102 (2)	100 (1.8)	103 (3.6)	0.9
Month 12, mean (se), days	393 (7.1)	404 (12.8)	381 (5.8)	0.2
Medication, n/total n (%)				
Amisulpride	36/351 (10%)	20/164 (12%)	16/187 (9%)	0.3
Aripiprazole	30/351 (9%)	14/164 (9%)	16/187 (9%)	0.9
Clozapine	24/351 (7%)	12/164 (7%)	12/187 (6%)	0.8
Lithium	19/351 (5%)	10/164 (6%)	9/187 (5%)	0.6
Mirtazapine	11/351 (3%)	5/164 (3%)	6/187 (3%)	0.9
Olanzapine	44/351 (13%)	19/164 (12%)	25/187 (13%)	0.6
Quetiapine	112/351 (32%)	48/164 (29%)	64/187 (34%)	0.4
Risperidone	64/351 (18%)	32/164 (20%)	32/187 (17%)	0.6
Valproate	10/351 (3%)	3/164 (2%)	7/187 (4%)	0.3
More than one AP, n/total n (%)	110/351 (31%)	50/164 (30%)	60/187 (32%)	0.8
AP and mirtazapine, n/total n (%)	16/351 (5%)	8/164 (5%)	8/187 (4%)	0.8
AP and MS, n/total n (%)	47/351 (13%)	19/164 (12%)	28/187 (15%)	0.4
Co-mediation possibly causing weight gain, n/total n (%)	46/255 (18%)	19/106 (18%)	27/149 (18%)	0.9

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

Abbreviations :AP = Atypical antipsychotics; MS = lithium, valproic acid.

eTable 2: Metabolic parameters and syndrome at baseline, 3 months and one year.

	Baseline	3 Months	P[a]	One year	P[b]
Prevalence of normal weight, overweight and obesity, n/total n (%)					
Normal weight: BMI < 25 kg/m2	183 /294 (62%)	132 /241 (55%)	**0.0005**	66 /135 (49%)	**0.01**
Overweight: BMI [25-30[kg/m^2	62/294 (21%)	63/241 (26%)	0.05	36/135 (27%)	0.32
Obese: BMI ≥ 30 kg/m^2	49/294 (17%)	46/241 (19%)	0.4	33/135 (24%)	**0.03**
Prevalence of abdominal obesity, n/total n (%)					
Waist circumference Men ≥ 94 cm , Women ≥ 80 cm[(c)]	162/300 (54%)	142/231 (61%)	**0.0004**	89/135 (66%)	**0.01**
Waist circumference Men ≥ 102 cm, Women ≥ 88 cm[(d,e)]	99/300 (33%)	87/231 (38%)	**0.01**	58/135 (43%)	**0.03**
Prevalence of hypocholesterolemia, n/total n (%)					
HDL-chol. Men ≤ 1.03 mmol/l, Women ≤ 1.29 mmol/l	61/194 (31%)	56/198 (28%)	0.8	35/122 (29%)	1.00
Prevalence of hypertriglyceridemia, n/total n (%)					
Triglyceridemia ≥ 1.7 mmol/l or lipid lowering treatment	56/201 (28%)	70/207 (34%)	**0.03**	42/123 (34%)	**0.01**
Prevalence of hyperglycemia, n/total n (%)					
Fasting glucose ≥ 5.6 mmol/l or antidiabetic treatment[(e,c)]	50/204 (25%)	55/202 (27%)	0.7	53/122 (43%)	**0.0001**
Fasting glucose ≥ 6.1 mmol/l or antidiabetic treatment[(d)]	25/204 (12%)	22/202 (11%)	1	22/122 (18%)	0.15
Prevalence of hypertension, n/total n (%)					
Blood pressure ≥ 130 / 85 mmHg or antihypertensive treatment	58/305 (19%)	41/229 (18%)	1	27/134 (20%)	0.50
Prevalence of metabolic syndrome, n/total n (%)					
ATP-III[f]	24/161 (15%)	23/154 (15%)	1	23/100 (23%)	0.22
ATP-III-A[g]	30/161 (19%)	27/154 (18%)	1	28/100 (28%)	0.22
IDF[h]	35/161 (22%)	33/154 (21%)	0.5	32/100 (32%)	**0.04**

[a] p-value were calculated using McNemar tests between baseline and 3 months.
[b] p-value were calculated using McNemar tests between baseline and 12 months.
[c] According to IDF definition.
[d] According to ATP-III definition.
[e] According to ATP-III-A definition.
[f] Metabolic syndrome is present if at least 3 criterias are present: central obesity (M ≥ 102 cm , F ≥ 88 cm); triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 6.1 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85mmHg or treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.
[g] Same as [e] but: glucose ≥ 5.6 mmol/l or type 2 diabetes treatment.
[h] Metabolic syndrome is present if: presence of central obesity (M ≥ 94 cm, F ≥ 80 cm) and at least two other following factors: triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 5.6 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85 mmHg of treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.

eTable 3: Demographic and clinical parameters stratified for age and gender at baseline and 12 months of treatment.

Baseline, (age range)	**Young (age ≤ 25)**				**Young adult (age :]25-45])**				**Adult (age :]45-65])**				**Elderly (age : > 65)**				**Overal p[a]**
Gender, (total n)	**All (72)**	**Men (47)**	**Women (25)**	**P[b]**	**All (114)**	**Men (62)**	**Women (52)**	**P[b]**	**All (78)**	**Men (30)**	**Women (48)**	**P[b]**	**All (87)**	**Men (25)**	**Women (62)**	**P[b]**	
BMI																	
Mean (se), kg/m^2	22.9 (0.5)	23.7 (0.6)	21.3 (1.0)	**0.002**	25.3 (0.6)	24.4 (0.5)	26.3 (1.0)	0.4	25.6 (0.8)	24.4 (0.9)	26.3 (1.1)	0.6	23.8 (0.6)	24 (1.0)	23.7 (0.7)	0.8	**0.01**
Overweight [25-30[kg/m^2, n/total n (%)	9/67 (13%)	8/45 (18%)	1/22 (5%)	0.3	21/89 (24%)	13/44 (30%)	8/45 (18%)	0.2	15/61 (25%)	7/21 (33%)	8/40 (20%)	0.3	17/77 (22%)	7/20 (35%)	10/57 (18%)	0.1	0.4
Obese ≥ 30 kg/m^2, n/total n (%)	7/67 (10%)	5/45 (11%)	2/22 (9%)	0.9	17/89 (19%)	3/44 (7%)	14/45 (31%)	**0.006**	13/61 (21%)	2/21 (10%)	11/40 (28%)	0.2	12/77 (16%)	2/20 (10%)	10/57 (18%)	0.7	0.4
Waist circumference																	
Mean (se), cm	83 (1)	87 (2)	78 (2)	**0.01**	91 (1)	90 (1)	92 (2)	0.8	91 (2)	96 (2)	89 (3)	**0.02**	90 (2)	93 (2)	89 (2)	0.1	**0.0004**
M ≥ 94cm , F ≥ 80cm[(c)], n/total n (%)	19/64 (30%)	10/41 (24%)	9/23 (39%)	0.3	49/91 (54%)	17/49 (35%)	32/42 (76%)	**0.0001**	43/68 (63%)	16/27 (59%)	27/41 (66%)	0.6	51/77 (66%)	13/22 (59%)	38/55 (69%)	0.4	**0.001**
M ≥ 102cm , F ≥ 88cm[(d,e)], n/total n (%)	9/64 (14%)	6/41 (15%)	3/23 (13%)	0.9	31/91 (34%)	7/49 (14%)	24/42 (57%)	**0.0001**	26/68 (38%)	8/27 (30%)	18/41 (44%)	0.3	33/77 (43%)	5/22 (23%)	28/55 (51%)	**0.04**	**0.002**
HDL-Cholesterol																	
Mean (se), mmol/l	1.32 (0.07)	1.3 (0.07)	1.37 (0.14)	0.9	1.3 (0.05)	1.26 (0.06)	1.35 (0.09)	0.6	1.51 (0.07)	1.42 (0.09)	1.58 (0.1)	0.3	1.45 (0.06)	1.35 (0.09)	1.49 (0.07)	0.3	0.05
M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l, n/total n (%)	12/38 (32%)	5/27 (19%)	7/11 (64%)	**0.02**	21/61 (34%)	7/33 (21%)	14/28 (50%)	**0.03**	11/43 (26%)	1/18 (6%)	10/25 (40%)	**0.01**	17/52 (33%)	2/14 (14%)	15/38 (39%)	0.1	0.8
Triglyceride																	
Mean (se), mmol/l	1.09 (0.12)	1.19 (0.18)	0.91 (0.09)	0.7	1.58 (0.17)	1.7 (0.3)	1.45 (0.16)	0.9	1.58 (0.19)	2 (0.42)	1.28 (0.11)	0.08	1.27 (0.08)	1.25 (0.16)	1.27 (0.1)	0.8	**0.004**
≥ 1.7mmol/l or lipid lowering treatment, n/total n (%)	3/38 (8%)	3/25 (12%)	0/13 (0%)		19/63 (30%)	11/35 (31%)	8/28 (29%)	0.9	14/44 (32%)	8/18 (44%)	6/26 (23%)	0.2	20/56 (36%)	6/15 (40%)	14/41 (34%)	0.8	**0.01**
Glucose																	
Mean (se), mmol/l	4.89 (0.07)	4.94 (0.09)	4.79 (0.08)	0.4	5.02 (0.08)	4.94 (0.12)	5.11 (0.1)	0.7	5.47 (0.25)	5.7 (0.47)	5.29 (0.26)	0.2	5.45 (0.13)	5.5 (0.17)	5.43 (0.16)	0.4	**0.01**
≥ 5.6mmol/l or antidiabetic treatment[(e,c)], n/total n (%)	4/43 (9%)	4/29 (14%)	0/14 (0%)		15/65 (23%)	7/34 (21%)	8/31 (26%)	0.8	10/45 (22%)	4/20 (20%)	6/25 (24%)	0.9	21/51 (41%)	7/14 (50%)	14/37 (38%)	0.5	**0.003**
≥ 6.1mmol/l or antidiabetic treatment[(d)], n/total n (%)	1/43 (2%)	1/29 (3%)	0/14 (0%)		7/65 (11%)	4/34 (12%)	3/31 (10%)	0.9	5/45 (11%)	3/20 (15%)	2/25 (8%)	0.6	12/51 (24%)	3/14 (21%)	9/37 (24%)	0.9	**0.02**
Blood pressure																	
Systolic, mean (se), mmHg	119 (2)	125 (2)	108 (3)	0.10	122 (1)	126 (2)	118 (2)	**0.003**	119 (2)	124 (4)	116 (3)	0.1	135 (2)	140 (4)	133 (3)	0.09	**0.00001**
Diastolic, mean (se), mmHg	72 (2)	75 (2)	66 (2)	**0.01**	79 (1)	79 (2)	78 (2)	0.5	80 (2)	84 (4)	77 (2)	0.09	75 (1)	78 (3)	74 (2)	0.3	**0.0002**
≥ 130/85mmHg or antihypertensive treatment, n/total n (%)	4/65 (6%)	3/43 (7%)	1/22 (5%)	0.9	12/96 (13%)	10/52 (19%)	2/44 (5%)	**0.03**	11/66 (17%)	7/25 (28%)	4/41 (10%)	0.09	31/78 (40%)	9/23 (39%)	22/55 (40%)	0.9	**0.001**
Prevalence of metabolic syndrome																	
ATP-III[f], n/total n (%)	1/32 (3%)	1/22 (5%)	0/10 (0%)		3/48 (6%)	0/25 (0%)	3/23 (13%)	0.1	6/38 (16%)	3/17 (18%)	3/21 (14%)	0.9	14/43 (33%)	2/12 (17%)	12/31 (39%)	0.3	**0.002**
ATP-III-A[g], n/total n (%)	1/32 (3%)	1/22 (5%)	0/10 (0%)		4/48 (8%)	1/25 (4%)	3/23 (13%)	0.3	7/38 (18%)	3/17 (18%)	4/21 (19%)	0.9	18/43 (42%)	4/12 (33%)	14/31 (45%)	0.7	**0.001**
IDF[h], n/total n (%)	2/32 (6%)	2/22 (9%)	0/10 (0%)		6/48 (13%)	2/25 (8%)	4/23 (17%)	0.4	8/38 (21%)	4/17 (24%)	4/21 (19%)	0.9	19/43 (44%)	3/12 (25%)	16/31 (52%)	0.2	**0.001**

[a]p-value were calculated using Kruskal-Wallis tests for continuous variables and Fisher's exact tests for categorical variables between age groups.
[b]p-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between genders.
[c]According to IDF definition for Caucasian.
[d]According to ATP-III definition.
[e]According to ATP-III-A definition.
[f] Metabolic syndrome is present if at least 3 criterias are present: central obesity (M ≥ 102 cm , F ≥ 88 cm); triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 6.1 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85mmHg or treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.
[g] Same as [f] but: glucose ≥ 5.6 mmol/l or type 2 diabetes treatment.
[h] Metabolic syndrome is present if: presence of central obesity (M ≥ 94 cm , F ≥ 80 cm) and at least two other following factors: triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 5.6 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85 mmHg of treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.

One year, (age range)	Young (age ≤ 25)				Young adult (age :]25-45])				Adult (age :]45-65])				Elderly (age : > 65)				Overal p[a]
Gender, (total n)	All (32)	Men (22)	Women (10)	P[b]	All (55)	Men (30)	Women (25)	P[b]	All (38)	Men (16)	Women (22)	P[b]	All (23)	Men (7)	Women (16)	P[b]	
BMI																	
Mean (se), kg/m^2	25.6 (0.9)	26.4 (1.1)	24 (1.9)	**0.03**	27.5 (0.8)	26.3 (0.8)	28.7 (1.3)	0.3	27.4 (1.1)	26.2 (1.0)	28.1 (1.6)	0.9	24.8 (1.3)	26.5 (2.7)	24.1 (1.5)	0.4	0.08
Overweight [25-30[kg/m^2, n/total n (%)	8/32 (25%)	7/22 (32%)	1/10 (10%)	0.4	11/48 (23%)	9/24 (38%)	2/24 (8%)	0.04	13/34 (38%)	9/13 (69%)	4/21 (19%)	**0.009**	4/21 (19%)	2/6 (33%)	2/15 (13%)	0.5	0.4
Obese ≥ 30 kg/m^2, n/total n (%)	5/32 (16%)	4/22 (18%)	1/10 (10%)	0.9	17/48 (35%)	4/24 (17%)	13/24 (54%)	**0.01**	7/34 (21%)	1/13 (8%)	6/21 (29%)	0.2	4/21 (19%)	1/6 (17%)	3/15 (20%)	0.9	0.2
Waist circumference																	
Mean (se), cm	91 (3)	94 (4)	83 (6)	0.05	94 (2)	94 (2)	95 (4)	1.0	98 (3)	101 (2)	96 (4)	0.1	97 (4)	102 (6)	95 (6)	0.6	0.2
M ≥ 94cm , F ≥ 80cm[(c)], n/total n (%)	14/31 (45%)	10/21 (48%)	4/10 (40%)	0.9	31/51 (61%)	16/30 (53%)	15/21 (71%)	0.2	31/36 (86%)	13/15 (87%)	18/21 (86%)	0.9	13/17 (76%)	4/5 (80%)	9/12 (75%)	0.9	**0.004**
M ≥ 102cm , F ≥ 88cm[(d,e)], n/total n (%)	9/31 (29%)	7/21 (33%)	2/10 (20%)	0.7	20/51 (39%)	8/30 (27%)	12/21 (57%)	**0.04**	18/36 (50%)	7/15 (47%)	11/21 (52%)	0.9	11/17 (65%)	3/5 (60%)	8/12 (67%)	0.9	0.07
HDL-Cholesterol																	
Mean (se), mmol/l	1.28 (0.08)	1.17 (0.09)	1.59 (0.11)	**0.01**	1.25 (0.06)	1.2 (0.08)	1.32 (0.08)	0.3	1.44 (0.12)	1.27 (0.11)	1.56 (0.18)	0.4	1.47 (0.08)	1.33 (0.09)	1.55 (0.11)	0.2	0.2
M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l, n/total n (%)	6/27 (22%)	6/20 (30%)	0/7 (0%)		14/43 (33%)	5/25 (20%)	9/18 (50%)	0.05	11/32 (34%)	2/13 (15%)	9/19 (47%)	0.1	4/20 (20%)	0/7 (0%)	4/13 (31%)	0.2	0.6
Triglyceride																	
Mean (se), mmol/l	1.27 (0.14)	1.41 (0.17)	0.86 (0.15)	0.07	1.7 (0.21)	2.09 (0.33)	1.19 (0.14)	0.2	1.66 (0.17)	1.72 (0.32)	1.63 (0.2)	0.9	1.53 (0.2)	1.33 (0.27)	1.65 (0.28)	0.4	0.2
≥ 1.7mmol/l or lipid lowering treatment, n/total n (%)	6/27 (22%)	6/20 (30%)	0/7 (0%)		13/44 (30%)	10/25 (40%)	3/19 (16%)	0.1	12/31 (39%)	5/13 (38%)	7/18 (39%)	0.9	11/21 (52%)	3/7 (43%)	8/14 (57%)	0.7	0.2
Glucose																	
Mean (se), mmol/l	5.19 (0.23)	5.33 (0.3)	4.83 (0.22)	0.3	5.43 (0.21)	5.55 (0.36)	5.27 (0.13)	0.9	5.63 (0.18)	5.81 (0.17)	5.51 (0.28)	0.08	5.63 (0.33)	6.09 (0.71)	5.34 (0.3)	0.6	0.05
≥ 5.6mmol/l or antidiabetic treatment[(e,c)], n/total n (%)	4/26 (15%)	3/19 (16%)	1/7 (14%)	0.9	19/45 (42%)	10/25 (40%)	9/20 (45%)	0.8	19/32 (59%)	10/13 (77%)	9/19 (47%)	0.1	11/19 (58%)	4/7 (57%)	7/12 (58%)	0.9	**0.003**
≥ 6.1mmol/l or antidiabetic treatment[(d)], n/total n (%)	2/26 (8%)	2/19 (11%)	0/7 (0%)	0.9	6/45 (13%)	4/25 (16%)	2/20 (10%)	0.7	7/32 (22%)	4/13 (31%)	3/19 (16%)	0.4	7/19 (37%)	2/7 (29%)	5/12 (42%)	0.7	0.07
Blood pressure																	
Systolic, mean (se), mmHg	122 (3)	130 (3)	107 (4)	**0.0002**	121 (3)	128 (4)	113 (3)	**0.007**	121 (2)	123 (3)	119 (3)	0.4	139 (4)	146 (5)	135 (5)	0.2	**0.001**
Diastolic, mean (se), mmHg	74 (2)	78 (3)	66 (2)	**0.005**	80 (2)	82 (3)	77 (2)	0.2	80 (2)	81 (2)	78 (2)	0.4	76 (2)	78 (3)	75 (2)	0.4	0.1
≥ 130/85mmHg or antihypertensive treatment, n/total n (%)	2/28 (7%)	2/18 (11%)	0/10 (0%)	0.5	8/47 (17%)	6/24 (25%)	2/23 (9%)	0.2	4/36 (11%)	3/16 (19%)	1/20 (5%)	0.3	13/23 (57%)	5/7 (71%)	8/16 (50%)	0.4	**0.001**
Prevalence of metabolic syndrome																	
ATP-III[f], n/total n (%)	2/22 (9%)	2/15 (13%)	0/7 (0%)		6/36 (17%)	4/21 (19%)	2/15 (13%)	0.9	9/29 (31%)	4/12 (33%)	5/17 (29%)	0.9	6/13 (46%)	2/5 (40%)	4/8 (50%)	0.9	**0.04**
ATP-III-A[g], n/total n (%)	3/22 (14%)	3/15 (20%)	0/7 (0%)		10/36 (28%)	6/21 (29%)	4/15 (27%)	0.9	9/29 (31%)	4/12 (33%)	5/17 (29%)	0.9	6/13 (46%)	2/5 (40%)	4/8 (50%)	0.9	0.21
IDF[h], n/total n (%)	3/22 (14%)	3/15 (20%)	0/7 (0%)		12/36 (33%)	7/21 (33%)	5/15 (33%)	0.9	11/29 (38%)	5/12 (42%)	6/17 (35%)	0.9	6/13 (46%)	2/5 (40%)	4/8 (50%)	0.9	0.14

[a]p-value were calculated using Kruskal-Wallis tests for continuous variables and Fisher's exact tests for categorical variables between age groups.
[b]p-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between genders.
[c]According to IDF definition for Caucasian.
[d]According to ATP-III definition.
[e]According to ATP-III-A definition.
[f] Metabolic syndrome is present if at least 3 criterias are present: central obesity (M ≥ 102 cm , F ≥ 88 cm); triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 6.1 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85mmHg or treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.
[g] Same as [f] but: glucose ≥ 5.6 mmol/l or type 2 diabetes treatment.
[h] Metabolic syndrome is present if: presence of central obesity (M ≥ 94 cm, F ≥ 80 cm) and at least two other following factors: triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 5.6 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85 mmHg of treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.

eTable 4: Receiver operating parameters for a one month weight change predicting a weight gain after 3 months of treatment (upper panel) and 12 months (lower panel) in all ages.

Weight change (%) at		PPV	NPV	Sensitivity	Specificity	AUC
1 Month	**3 Months**					
2	10	35	93	72	72	72
2	15	14	98	76	67	72
2	20	5	99	71	65	68
5	10	54	89	48	92	70
5	**15**	**29**	**97**	**67**	**88**	**79**
5	20	10	99	71	86	78
8	10	68	86	24	98	61
8	15	47	96	43	97	70
8	20	16	99	43	95	69
1 Month	**12 Months**					
2	10	52	78	55	76	66
2	15	35	89	62	73	66
2	20	21	94	65	70	66
5	10	61	73	29	91	60
5	15	39	85	31	89	60
5	**20**	**30**	**93**	**47**	**89**	**68**
8	10	56	70	10	96	53
8	15	33	82	10	95	53
8	20	33	90	18	96	57

The left column indicates the weight change after one month and the second left column indicates the weight change after 3 months (upper panel) and 12 months (lower panel).
In Bold, the retained prediction based on the highest AUC for 3 and 12 months.
Abbreviations: PPV = positive predictive values, NPV = negative predictive values, AUC = area under the curve.

eTable 5: Receiver operating parameters for a one month weight change predicting a weight gain after 3 months of treatment (upper panel) and 12 months (lower panel) for adults (]25-65] years old).

Weight change (%) at		PPV	NPV	Sensitivity	Specificity	AUC
1 Month	**3 Months**					
2	10	36	93	74	71	73
2	15	16	98	82	67	74
2	20	4	100	100	64	82
5	10	48	89	52	88	70
5	15	24	97	64	84	74
5	**20**	**7**	**100**	**100**	**82**	**91**
8	10	64	86	26	97	61
8	15	36	95	36	95	66
8	20	0	99	0	93	46
1 Month	**12 Months**					
2	10	27	88	59	64	62
2	15	46	77	57	68	62
2	20	19	93	64	63	64
5	10	55	74	37	86	61
5	15	35	86	41	83	62
5	**20**	**30**	**93**	**55**	**83**	**69**
8	10	25	82	12	92	52
8	15	50	69	13	94	53
8	20	25	89	18	93	55

The left column indicates the weight change after one month and the second left column indicates the weight change after 3 months (upper panel) and 12 months (lower panel).
In Bold, the retained prediction based on the highest AUC for 3 and 12 months.
Abbreviations: PPV = positive predictive values, NPV = negative predictive values, AUC = area under the curve.

eTable 6: Overall metabolic parameters (left column) and comparison between early and non early weight gainers.

	All	First month weight gain ≤ 5% (n=288)	First month weight gain > 5% (n=63)	P[a]
Weight, kg				
Baseline, mean (se)	69.24 (0.93)	70.1 (1)	65.47 (2.34)	**0.03**
Δ 3 months, mean (se)	2.81 (0.31)	2.05 (0.32)	6.95 (0.62)	**< 0.0001**
Δ 12 months, mean (se)[b]	4.37 (0.77)	3.73 (0.8)	7.71 (2.27)	**0.03**
Weight, %				
Δ 3 months (%), mean (se)	4.34 (0.44)	3.12 (0.45)	11.07 (0.97)	**< 0.0001**
Δ 12 months (%), mean (se)[b]	6.72 (0.94)	5.44 (0.91)	13.69 (3.12)	**0.0045**
BMI, kg/m2				
Baseline, mean (se)	24.4 (0.31)	25 (0.35)	22.2 (0.59)	**0.001**
Δ 12 months, mean (se)[b]	1.5 (0.26)	1.2 (0.26)	3.1 (0.8)	**0.01**
Waist circumference, cm				
Baseline, mean (se)	89 (0.83)	90 (0.91)	86 (1.97)	0.06
Δ 12 months, mean (se)[b]	4 (0.96)	4 (1.02)	5 (2.91)	0.7
HDL-Cholesterol, mmol/l				
Baseline, mean (se)	1.39 (0.03)	1.38 (0.04)	1.44 (0.06)	0.2
Δ 12 months, mean (se)[b]	-0.08 (0.03)	-0.02 (0.03)	-0.36 (0.07)	**0.0001**
Triglyceride, mmol/l				
Baseline, mean (se)	1.4 (0.08)	1.42 (0.09)	1.33 (0.11)	0.9
Δ 12 months, mean (se)[b]	0.3 (0.13)	0.06 (0.1)	1.46 (0.53)	**0.004**
Glucose, mmol/l				
Baseline, mean (se)	5.2 (0.07)	5.22 (0.08)	5.13 (0.19)	0.2
Δ 12 months, mean (se)[b]	0.2 (0.15)	0.1 (0.16)	0.73 (0.25)	**0.02**
Blood pressure, mmHg				
Baseline systolic (se)	124 (1.05)	124 (1.11)	122 (2.86)	0.5
Δ 12 months, mean (se)[b]	-0.71 (1.61)	-0.22 (1.7)	-3.11 (4.72)	0.8
Baseline diastolic (se)	77 (0.75)	77 (0.8)	76 (1.96)	0.6
Δ 12 months, mean (se)[b]	-0.09 (1.4)	-0.73 (1.5)	3. (3.84)	0.6

[a] p-value were calculated using Wilcoxon rank-sum between both groups.

[b] Difference between baseline and 12 months values.

eTable 7: Linear mixed effect model fitted on weight gain (%) over time.

	Difference of weight change (%) between ≤ 5% and >5% weight gain group (95%IC).	P
All sample[a]	6.4 % (3.6% to 9.0%)	0.0001
Gender stratification[b]:		
Men	6.6% (3.4% to 9.8%)	0.0002
Women	9.7% (6.9% to 12.5%)	<0.0001
Age stratification[b]:		
Young (≤ 25)	8.7 % (5.2% to 12.5%)	<0.0001
Young adult (]25-45])	7.3% (3.8% to 10.7%)	0.0001
Adult (]45-65])	7.4% (2.0% to 13.1%)	0.0051
Elderly (> 65)	13.6% (5.6% to 18.8%)	<0.01[c]
Diagnostic stratification[b] :		
Psychotic & schizoaffective disorder	7.0% (4.5% to 9.6%)	<0.0001
Bipolar disorder & depression	9.1% (4.2% to 14.1%)	0.0006
Others[d]	11.6% (3.9% to 19%)	<0.01[c]
Medication stratification[b] :		
Monotherapy	7.0 % (4.5% to 9.4%)	<0.0001
Polytherapy	7.7% (4.2% to 11.3%)	<0.0001
Amisulpride & aripiprazole	6.6% (2.2% to 11.2%)	0.003
Mirtazapine & lithium & quetiapine & risperidone	8.4% (4.8% to 12.1%)	<0.0001
Clozapine & olanzapine & valproate	7.4% (4.1% to 10.7%)	<0.0001

[a]Results were obtained by fitting a linear mixed model controlling for age, sex, time, baseline BMI, current psychotropic drug, co-medication possibly inducing weight gain, glucose levels, triglyceride levels, HDL levels .
[b]Results were obtained by fitting a linear mixed model controlling for age, sex, time, and baseline BMI if applicable.
[c]Due to low number of observations, one hundred boostraps were used for the analysis.
[d]Others include the following diagnostics :anxiety, drug addiction, mental retardation, personality disorder, organic disorders.

eTable 8: Receiver operating parameters for an activity > 30 minutes/day at month 1 predicting a weight gain at 3 and 12 months.

Weight change (%) at:	PPV	NPV	Sensitivity	Specificity	AUC
3 Months					
5	36	58	54	53	54
10	15	83	53	51	52
15	5	94	55	51	53
12 Months					
5	52	44	53	51	52
10	21	67	62	53	57
15	12	78	67	52	59

Upper panel indicates the weight increase at 3 months and the lower panel a weight increase at 12 months.
Abbreviations: PPV = positive predictive values, NPV = negative predictive values, AUC = area under the curve.

eTable 9: Receiver operating parameters for an appetite increase between baseline and one month predicting a weight gain at 3 and 12 months.

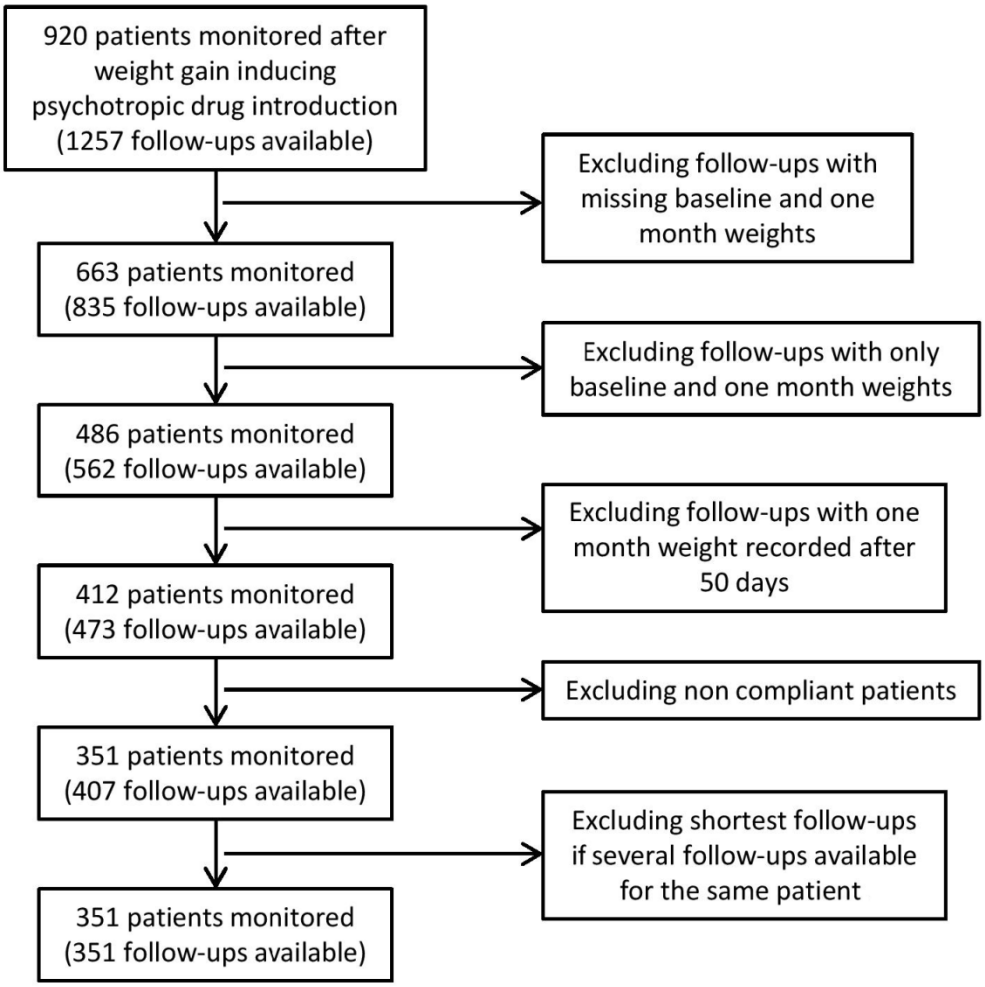
Weight change (%) at:	PPV	NPV	Sensitivity	Specificity	AUC
3 Months					
5	36	59	28	67	47
10	19	84	35	69	52
15	5	93	25	68	47
12 Months					
5	59	46	27	77	52
10	29	72	26	75	51
15	12	80	17	73	45

Upper panel indicates the weight increase at 3 months and the lower panel a weight increase at 12 months.
Abbreviations: PPV = positive predictive values, NPV = negative predictive values, AUC = area under the curve.

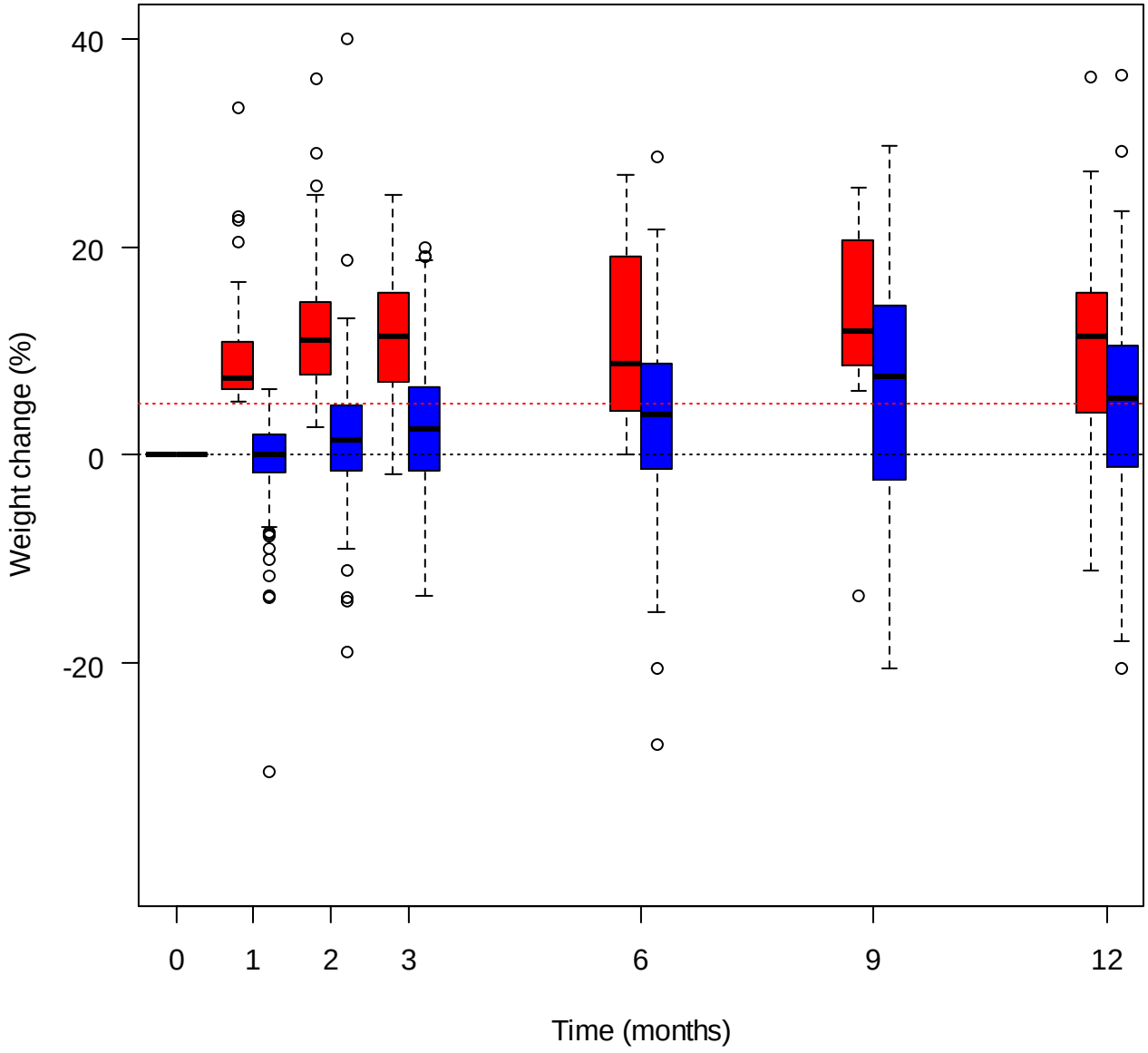
eTable 10: Co-medication possibly inducing weight gain[1, 2].

Anti-diabetic drug :		
pioglitazone	rosiglitazone	
Anti-histaminergic drug :		
cinnarizine	levocetirizine	
Contraceptive drugs :		
chlormadinone	desogestrel	ethinylestradiol
estradiol	gestodene	levonorgestrel
medroxyprogesterone	norelgestromin	
Psychotropic drugs (‡):		
carbamazepine	chlorprothixene	clomipramine
flupentixol	mianserine	pregabalin
zuclopenthixol		

‡ Investigated drugs (clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, lithium, valproate and mirtazapine) are not mentioned as co-medication if they are prescribed as monotherapy.



eFigure 1: Flow chart for selection of patients.



eFigure 2: Weight changes at 1 month (mean(se) 31(0.4) days), 2 months (mean(se) 64(1.8) days), 3 months (mean(se) 102(2) days), 6 months (mean(se) 189(2.3) days), 9 months (mean(se) 278(3.7) days) and one year (mean(se) 393(7.1) days). Red and blue box plots represent the patient's observation with a first month weight gain of more than 5% and less or equal to 5%, respectively. Dotted black line represents no weight change; red dotted line represents 5% weight increase.

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