Title: Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment.

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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 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% (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 % (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.

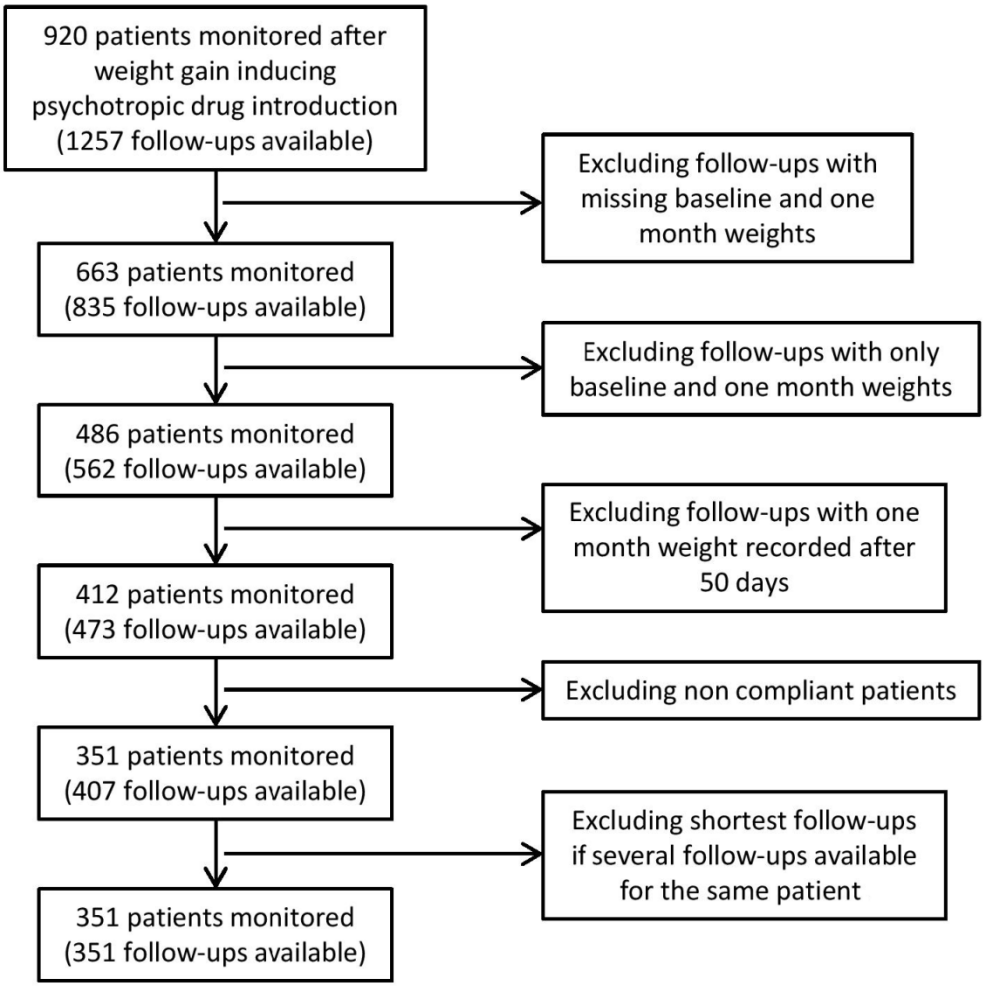
Weight change (%) at:	PPV	NPV	Sensitivity	Specificity	AUC
3 Months					
5	36	59	28	67	47
10	19	84	35	69	52
15	5	93	25	68	47
12 Months					
5	59	46	27	77	52
10	29	72	26	75	51
15	12	80	17	73	45

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.

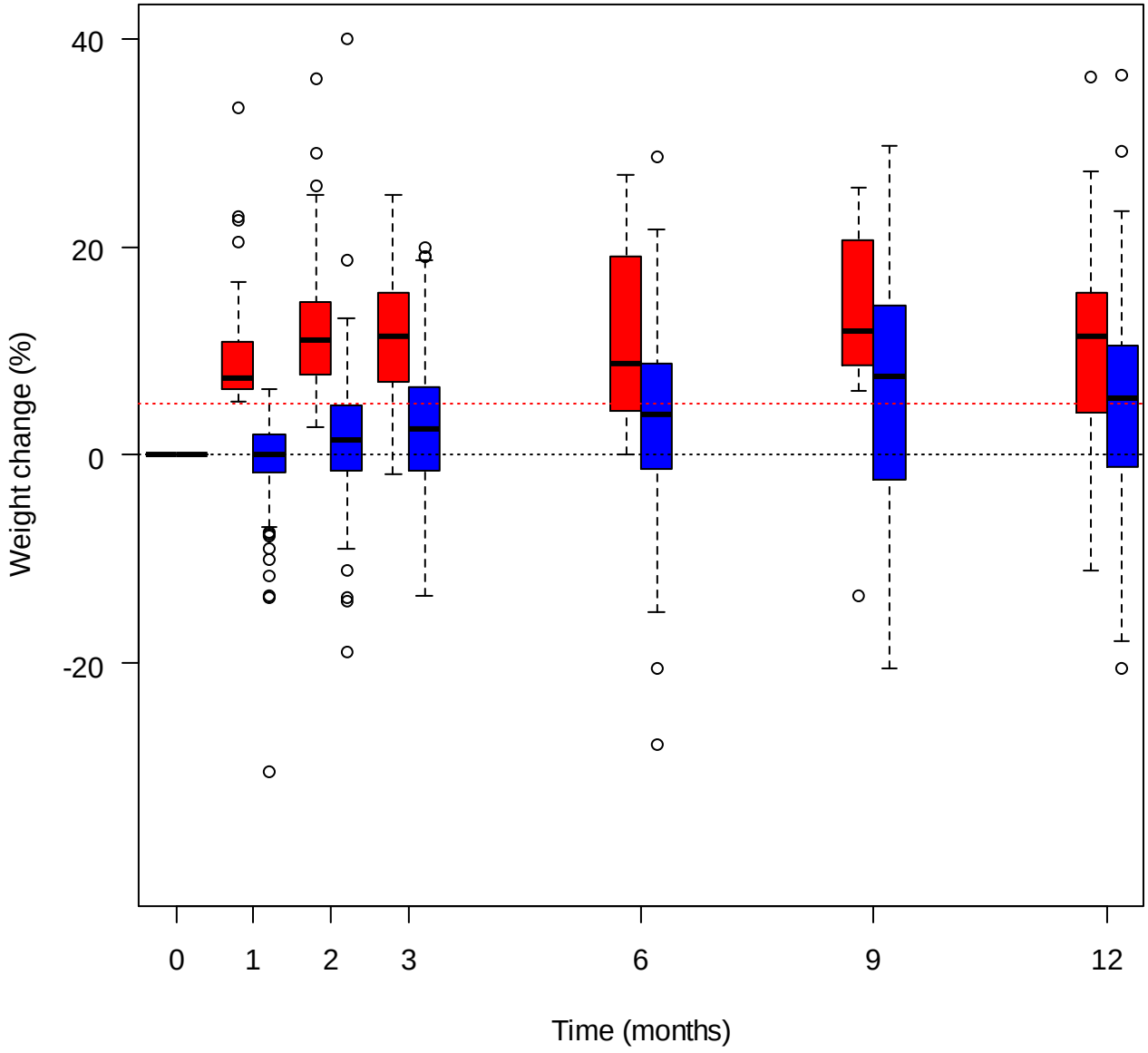
eTable 10: Co-medication possibly inducing weight gain[1, 2].

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.

REFERENCES:

1. Compendium Suisse des Medicaments. 2014 [cited 2014 24 février, 2014]; Available from: http://www.swissmedicinfo.ch
2. MICROMEDEX ® 1.0 (Healthcare series). 2011 [cited 2011 November 15, 2011]; Available from: http://www.micromedex.com/
3. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final report. Circulation 2002;106(25):3143-3421.
4. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005 Oct 25;112(17):2735-2752.
5. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006 May;23(5):469-480.
6. Choong E, Rudaz S, Kottelat A, Guillarme D, Veuthey JL, Eap CB. Therapeutic drug monitoring of seven psychotropic drugs and four metabolites in human plasma by HPLC-MS. J Pharm Biomed Anal 2009;50:1000-1008.
7. Hiemke C, Baumann P, Bergemann N, et al. AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Psychiatry: Update 2011. Pharmacopsychiatry 2011;44(6):195-235.
8. Pinheiro J, Bates D, DebRoy S, Sarkar D, Team RC. nlme: linear and nonlinear mixed effects models. 2013.
9. Pinheiro JC, Bates DM. Mixed-Effects Models in S and S-PLUS: Springer; 2000.
10. Davison AC, Hinkley DV. Bootstrap Methods and their Application. Cambridge, New York: Cambridge University Press; 1997.