Evolution of metabolic risk factors over a two-year period in a cohort of first episodes of psychosis

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Abstract

Patients with a first episode of psychosis (FEP) display a broad range of metabolic risk factors related to the development of diverse medical comorbidities. Initial stages of these disorders are essential in understanding the increased vulnerability of developing cardiometabolic disturbances, associated with a reduced life expectancy. This study aimed to evaluate the metabolic profile of a cohort of patients with a FEP and its evolution during a two year follow-up, as well as the factors that influence the changes in their metabolic status.

16 participating centers from the PEPs Project recruited 335 subjects with a FEP and 253 matched healthy controls, aged 9-35 years. We investigated a set of anthropometric measures, vital signs and laboratory data obtained from each participant over two years in a prospective, naturalistic study.

From the beginning of the study the FEP group showed differences in the metabolic profile compared to the control group, together with a progressive worsening in the major part of the analyzed variables during the follow-up period, with higher rates of obesity and metabolic syndrome. Certain risk factors were related to determinate clinical variables such as male gender, the presence of affective symptoms or an early onset or to treatment variables such as the use of antipsychotic polypharmacy, antidepressants or mood stabilizers.

Our results highlight the extremely high risk of patients at early phases of schizophrenia and other psychotic disorders of developing cardiovascular comorbidity and the fast worsening of the metabolic profile during the first two years.

Introduction

Patients with a first episode of psychosis (FEP) display a wide array of metabolic disturbances (Fleischhacker et al., 2013), which over time might predict the development of diverse medical conditions, such as metabolic syndrome (MetS) or cardiovascular diseases (CVD). Those medical co-morbidities seem to underlie the increased mortality in those patients detected even at the onset of a mental disorder (Laursen et al., 2013; Nordentoft et al., 2013). Part of this increased risk might also be related to the metabolic side effects of antipsychotics, already present after few weeks of treatment (Fernandez-Egea et al., 2011; Tek et al., 2016).

Initial stages of psychotic disorders are essential in understanding the increased risk of developing metabolic disturbances (Fernandez-Egea et al., 2009; Perez-Iglesias et al., 2014). Two meta-analyses reflect that the risk for MetS is low in FEP but increases over time (Mitchell et al., 2013; Mitchell et al., 2011), with high prevalence in chronic patients (Arango et al., 2008). The determination of MetS rates at initial stages might underscore the risk of developing CVD, so further analysis must be implemented (Garcia-Rizo et al., 2017). At initial stages, glucose abnormalities are the most replicated findings (Anto et al., 2017; Garcia-Rizo et al., 2016; Greenhalgh et al., 2016; Perry et al., 2016; Pillinger et al., 2017; Ryan et al., 2003; Spelman et al., 2007). Besides, other CVD risk factors have been assessed: (i) blood pressure, through increased pulse pressure (Fernandez-Egea et al., 2009); (ii) lipid profile has been reported to be altered (Keinanen et al., 2015) or subclincal (Misiak et al., 2017), while other studies did not find differences(Kirkpatrick et al., 2010); and (iii) abdominal obesity (Ryan et al., 2004), but other studies failed to replicate (Fernandez-Egea et al., 2009; Keinanen et al., 2015). In this context, the study of the population with a FEP is of great interest because it avoids the effect of confounding variables, such as somatic comorbidities, prolonged antipsychotic treatment or chronicity (Bernardo and Bioque, 2014; Bernardo et al., 2013).

The PEPs Project was a multicenter, prospective, longitudinal, naturalistic study, conducted in 16 research sites in Spain designed to follow a cohort of 335 subjects with a FEP, matched with 253 healthy controls (Bernardo et al., 2013; Bioque et al., 2016). The aim of the present study was to evaluate the metabolic profile of patients at the FEP and its evolution during the two year follow-up, aiming to identify the factors that influence in these early changes. This study offers a unique opportunity to extend previous research by investigating the prevalence of metabolic abnormalities in a real-world cohort of patient with a FEP treated with commonly-used drugs during a follow-up of two years.

Methods

Subjects

During the recruitment period (2009-2012), every patient who met the inclusion criteria that was attended at the PEPs project participating sites facilities was invited to participate in the study, either inpatient or outpatient. The rationale and the complete clinical protocol used in the PEPs project were previously published (Bernardo et al., 2013) (free text available both in English and Spanish).

The inclusion criteria for patients were: presence of a FEP in the last 12 months, age between 7 and 35, and speak Spanish correctly. The Spanish translation of the K-SADS-PL (Kaufman et al., 1997) was used to assess current and past psychopathology in children and adolescents according to DSM-IV criteria (American Psychiatric Association (Washington), 1994), and the SCID-I & II, with a Spanish translation available, for adults (First et al., 1994, 1999). In order to retrospectively characterize and date the initial symptoms of a psychotic illnesses the Symptom Onset in Schizophrenia (SOS) inventory was used (Perkins et al., 2000).

The exclusion criteria for patients were: (1) mental retardation according to DSM-IV criteria (American Psychiatric Association (Washington), 1994), (2) history of head trauma with loss of consciousness and (3) presence of an organic disease with mental repercussions.

Healthy controls were matched by age (± 10%), gender and parental socio-economic status (SES), measured by the Hollingshead-Redlich scale (±1 level). They also had to speak Spanish fluently. The exclusion criteria for controls were the same as for patients plus having a personal antecedent of psychotic and/or major affective disorder and having a first degree relative with psychotic disorder history.

With the above mentioned criteria, a cohort of 335 subjects who have suffered a FEP within the previous 12 month and 253 healthy controls were included in the PEPs Project, with an age between 9 and 35 years. 198 patients and 158 control subjects were kept in the study until the two year follow-up final visit.

Being a naturalistic study, there were no specific guidelines for treatments, so patients received antipsychotic treatment based on the clinician's choice. Dosing, co-medications or treatment changes were based on clinical necessity. Following the inclusion/exclusion criteria, treatment with antipsychotics did not exceed 12 months at study entry, with a mean duration of untreated psychosis (DUP) of 106.21 days (Bernardo et al., 2017). As the majority of the participating centres were tertiary university hospitals a large majority of the patients included in the study were recruited during their first hospitalization, when the first antipsychotic treatment was indicated. The major part of the patients (n=304, 90.7%) were under antipsychotic treatment by the time they were included in the study, with a mean of 54.08 days taking antipsychotic treatment (Bioque et al., 2016). Only a small proportion (n=49, 14.6% of the sample) had been taking antipsychotic for more than three months before the inclusion. A previous report gave a full description of the psychopharmacological treatment used in this study (Bioque et al., 2016).

The study was approved by the investigation ethics committees of all participating centers and informed consent was obtained from all participants or legal guardians.

Study assessments and biochemical determinations

At baseline, a complete medical history was taken. Body weight, blood pressure and waist circumference were assessed at baseline and at 2, 6, 12 and 24 months visits. Laboratory data was obtained at every visit in patients and at baseline and at 24 months in controls. In all the participating sites, blood glucose, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides (TG) were directly analyzed by enzymatic procedures with an Automatic Chemical Analyzer. Glycated hemoglobin was analyzed by high-performance liquid chromatography (HPLC). The reference values at each site were recorded in a common database called GIDSAM, where individual values were homogenized and included (Bernardo et al., 2013).

Metabolic and cardiovascular risk assessment

Taking each individual's anthropometric measures, vital signs and laboratory data, the presence of MetS and/or obesity was established for each participant at baseline and 24 month's visit. As subjects included in the PEPs project were aged from 9 to 35, both conditions were defined with available criteria which have different definitions for underage and adult. Thus, the presence of Mets was defined using

the International Diabetes Foundation (IDF) criteria (Alberti et al., 2005; Zimmet et al., 2007). In subjects aged 10 to 16 years, the MetS criteria were abdominal obesity ≥90th percentile (or adult cut-off if lower), fasting glucose ≥ 100 mg/dL, triglycerides ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL and blood ≥ 130/85 mmHg. In subjects ≥ 16 years the criteria were abdominal obesity >94 cm in men and >80 cm in women, fasting glucose ≥ 100 mg/dL, triglycerides ≥ 150 mg/dL, HDL cholesterol <40 mg/dL in men and <50 mg/dL in women and blood pressure ≥ 130/85 mmHg, or being under pharmacological treatment for any of the previous conditions. In all subjects, the presence of the abdominal obesity criteria was mandatory, plus 2 of the other 4 criteria (Alberti et al., 2005; Zimmet et al., 2007).

Also the overweight/obesity definition was different for underage or adult subjects, following the WHO charts (http://www.who.int/growthref/who2007_bmi_for_age/en/).

Diabetes was considered present if the participant was under treatment with insulin or oral hypoglycemic agents or whether fasting blood glucose exceeded 126 mg/dl.

Statistical analysis

Differences in categorical variables were assessed using a two-tailed Chi-square test. Baseline differences on continuous variables with approximately normal distributions were assessed using a two-tailed t test.

A multivariate analysis of covariance (MANCOVA) was conducted to compare baseline anthropometric, vital signs and metabolic measures between patient and control groups. The number of days of the antipsychotic treatment previous to the baseline assessment was used a covariate in this analysis, as we found positive correlations between the length of previous antipsychotic treatment and some of the metabolic measures.

Differences between cases and controls on continuous variables at the endpoint were assessed using a lineal mixed model.

Within the FEP group, a one-way repeated measures ANOVA was conducted to compare patient's anthropometric, vital signs and metabolic measures between every visit.

A mixed between-within subjects analysis of variance was conducted to assess the impact of gender, diagnosis (affective vs. non-affective psychoses) and age of onset (underage vs. adult) on these measures. A Chi-square test for independence was used to explore the relationship between gender, diagnosis, age of onset, antipsychotic treatment, antipsychotic polytherapy, obesity, significant body weight gain (>7%) or MetS at the study final visit.

The relationship between the metabolic outcomes and antipsychotic mean daily doses (in chlorpromazine equivalents) was investigated using Pearson correlation coefficient.

A value of $p<0.05$ was taken to be statistically significant in all analysis. Data was managed and analyzed with the IBM SPSS Statistics v.23.

Results

Baseline clinical characteristics, anthropometric, vital signs and metabolic measures

335 patients with a FEP and 253 healthy controls completed the baseline visit. 57 (17,6%) patients and 32 (12.6%) controls were underage. Demographic and clinical characteristics and baseline metabolic measures are presented in Table 1.

(Table 1 about here)

At baseline, the FEP group presented statistically significant higher total and LDL cholesterol and lower HDL cholesterol mean levels (Table 1). At this point, patients and control showed differences in two of the five IDF MetS criteria (glucose and HDL cholesterol).

Anthropometric, vital signs and metabolic measures in the follow-up visits

After two years, the FEP group showed higher mean levels of glucose, triglycerides, diastolic blood pressure and lower HDL cholesterol, together with higher body weight, BMI and waist circumference measures (table 2). There were differences between groups in overweight, obesity and MetS rates, with statistical significant differences in 4 of the 5 IDF MetS criteria.

(Table 2 about here)

Within the group of FEP, there were statically significant increases of glycated hemoglobin, triglycerides, total cholesterol, HDL cholesterol, body weight, BMI and abdominal circumference measures thorough the five follow-up visits (table 3), with a moderate to large effect size, according to commonly used guidelines (Cohen, 1988), these increases showed. The proportion of subjects with overweight and obesity also significantly increased across the follow-up.

(Table 3 about here)

A total of 55.1% (103/187) of the FEP subjects gained ≥7% of body weight during the 2-years follow-up. This relevant body weight gain was not associated with diagnosis, gender or age of onset.

Effect of gender

At baseline, the male subgroup of FEP patients showed statistically significant higher systolic blood pressure mean measures (122.91 vs. 113.78 mmHg, $t=-6.02$, $p<0.001$) and lower HDL cholesterol mean levels (47.11 vs. 54.43 mg/dL, $U=5721$, $p=0.002$). While a larger proportion of male patients filled the IDF MetS criteria of hypertension (30 vs. 10.57%, $\chi2=14.57$, $p<0.001$), more female patients fulfilled criteria of abdominal circumference (60.71 vs. 21.02%, $\chi2=39.62$, $p<0.001$) and low HDL cholesterol (45.78 vs. 23.62%, $\chi2=13.19$, $p=0.001$).

After two years, the male group of FEP patients kept showing statistically significant higher systolic blood pressure mean measures (123.89 vs. 114.08 mmHg, t=-4.67, p<0.001), lower HDL cholesterol mean levels (44 vs. 55.20 mg/dL, t=5.51, p<0.001) and a larger proportion the IDF MetS hypertension criteria (31.29 vs. 13.55%, $\chi 2$=6.69, p=0.007). Besides, the male group also showed statistically significant higher diastolic blood pressure mean measures (72.25 vs. 68.86 mmHg, t=-2.17 p<0.036), LDL cholesterol mean levels (107.13 vs. 94.62 mg/dL, t=-2.68, p=0.008) and glycated hemoglobin mean levels (5.40 vs. 5.17, U=4894.5, p<0.001). On the other hand, female patients kept showing a larger proportion of IDF MetS criteria of abdominal circumference (62.96 vs. 39.51%, $\chi 2$=12.67, p<0.001).

A mixed between-within subjects analysis of variance showed no significant interaction between gender and BMI, body weight, waist circumference, glycated hemoglobin, total cholesterol and triglycerides, but there was a substantial main effect for time (p<0.05), suggesting that all these parameters increased during the follow up period in a similar way in both genders (Figures 1A-E, supplemental info 1). Male patients showed statistically significant major decreases of HDL cholesterol mean values than women over the study (Wilks' Lambda = 0.9, F=2.97, p=0.023) (Figure 1F).

(Figure 1 about here)

We found no significant association between gender and the presence of obesity ($\chi 2$=0.63, p=0.28, phi=-0.55), body weight gain >7% ($\chi 2$=0.22, p=0.64, phi=-0.03), or MetS ($\chi 2$=0.12, p=0.92, phi=-0.029) at the study final visit.

Effect of diagnosis

Two hundred and eighty patients (83.6%) were diagnosed of "non-affective psychosis" and 55 subjects (16.4%) were diagnosed of DSM-IV "affective psychosis" (unipolar depression or bipolar disorder with psychotic features and schizoaffective disorder). At baseline, the group of patients with an affective psychosis showed a significant proportion of subjects with obesity (15.4 vs. 6.61%, $\chi 2$=4.55, p=0.048) and lower HDL cholesterol mean levels (44.31 vs. 50.28 mg/dL, t=2.71, p=0.007), compared to the group of patients with a "non-affective psychoses". There were no differences in the proportion of cases with MetS.

After two years the proportion of cases with MetS was significantly higher in the affective psychosis group (26.66 vs. 11.57%, $\chi 2$=4.41, p=0.046, phi=0.17). We found no significant association between gender and the presence of obesity ($\chi 2$=3.23, p=0.079, phi=-0.13) or body weight gain >7% ($\chi 2$=0.07, p=0.85, phi=0.02).

We found no significant interaction between diagnosis and any of the CV risk factors measures, suggesting similar evolution both in affective and non-affective psychoses (supplemental info 2).

Effect of the age of onset

Fifty-seven subjects were underage (<18 years) when their FEP started. At baseline, this subgroup showed lower mean body weight (61.68 vs. 70.39 kg, t=-4.27, p<0.001), BMI (21.9 vs. 23.8 kg/m^2, t=-3.01, p=0.002) and abdominal perimeter (79.58 cm vs. 87.12, t=-4.02, p<0.001). They also showed

statistically significant lower total cholesterol (152.80 vs. 163.87 mg/dL, U=8278, p=0.041), LDL cholesterol (88.16 vs. 27.18 mg/dL, U=6307, p=0.048) and glycated hemoglobin mean levels (5.05 vs. 5.23%, t=-2.25, p=0.025). After two years, this subpopulation stilled showed significant lower total cholesterol mean levels (161.10 vs. 173.35 mg/dL, t=-1.99, p=0.047).

Patients with early onset showed a statistically significant major increase in fasting glucose mean values along the study (Wilks' Lambda =0.91, F=3.19, p=0.017; supplemental info 3). We found no statistical association between the age of onset and the probability of presenting obesity ($\chi2$=0.026, p=1.0, phi=-0.012), body weight gain >7% ($\chi2$=2.17, p=0.18, phi=-0.11) or MetS ($\chi2$=0.13, p=0.77, phi=-0.03) at the two-year visit.

Psychopharmacological treatment

Psychopharmacological treatment registered in the baseline and final visits is resumed in table 4.

(Table 4 about here)

At baseline, patients had been treated with antipsychotics a mean of 54.08 days. Thirty-one patients (9.2%) were not receiving antipsychotics, including those never treated and those who had already discontinued previous treatments. Compared to the subgroup of patients who were under antipsychotic treatment, this subgroup of patients who were not receiving antipsychotics at baseline showed significant lower rater of diabetes (0.35%, vs. 4.16%, $\chi2$=4.76, p=0.029) and lower levels of LDL cholesterol (94.40 vs. 106.15 mg/dL, t=-1.98, p=0.049) and waist circumference (80.95 vs. 86.28 cm, t=1.99, p=0.047). Mean diastolic blood pressure were significantly higher in the non-treated group (75.77 vs. 71.47 mmHg, U=3883, p=0.033).

There were no statistical differences in any metabolic parameter between the groups of patients being treated or not with antipsychotics (n=20/116; 17.2%) at the end of the study.

Patients receiving an antipsychotic polytherapy regimen at the beginning of the study presented statistically significant higher mean body weight (72.28 vs. 68.45 kg, t=2.02, p=0.044), BMI (24.69 vs. 23.28 kg/m^2, t=2.49, p=0.015), glucose levels (87.08 vs. 83.48 mg/dL, t=2.07, p=0.039) and glycated hemoglobin levels (24.69 vs. 23.28 kg/m^2, t=-2.04, p=0.043). Those differences between the antipsychotic monotherapy vs. polytherapy groups were not maintained at the end of the follow up period.

At baseline, higher body weight was statistically associated with higher baseline antipsychotic dose (r=0.12, p=0.042). At the 2-year visit there wasn't any significant correlation between the antipsychotic dosage and metabolic parameters.

There were no group differences in any metabolic parameter depending if patients were receiving an antidepressant treatment at baseline. However, a statistical significant higher proportion of patients who were under antidepressant treatment in the 2-year follow up visit presented a body weight gain >7% (81,3 vs. 54,7%, $\chi2$= 3.94, p=0.047, phi=0.19), overweight criteria (62,5 vs. 30,2%, $\chi2$=7.99, p=0.018) and MetS (41,2 vs. 9,2%, $\chi2$=10.31, p=0.001, phi=-0.35) and higher mean systolic pressure blood levels (126.12 vs. 118.41 mmHg, t=2.28, p=0.024).

The subgroup of patients receiving mood stabilizers at baseline (46/335: 13.7%) presented higher basal mean levels of triglycerides (102.21 vs. 86.07 mg/dL, t=2.09, p=0.038), which kept being the only significant difference in two-year follow up visit (144.45 vs. 103.58 mg/dL, t=2.16, p=0.033).

Discussion

These results highlight the extremely high risk of patients at early phases of schizophrenia and other psychotic disorders of developing CVD risk factors and the rapid worsening of the metabolic profile during two years period. From the beginning of the study, the FEP group showed differences in metabolic parameters compared to the control group (table 1). After two years of follow-up, the metabolic status of the FEP group clearly worsened compared to the control group in almost all metabolic measures (figure 1, table 2), with higher rates of overweight/obesity and MetS.

The baseline findings support the existence of underlying predisposition of FEP patients to present such alterations from the very beginning of the disorder or even before starting the psychopharmacological treatment (Fernandez-Egea et al., 2009; Verma et al., 2009; Zhai et al., 2016).

The results in the follow-up are in the line of previous works, showing how first months of treatment are critical in terms of body weight gain and metabolic syndrome rates (Fleischhacker et al., 2013; Patel et al., 2009; Perez-Iglesias et al., 2014; Tek et al., 2016). Indeed, we observed a quick increase of body weight gain and waist circumference during the first year with a subsequent stabilization afterwards. Our results summarize in the same cohort, MetS differences found in meta-analysis between naïve patients (Vancampfort et al., 2013) and FEP (Mitchell et al., 2013) as a continuum in the rate of increasing risk over time.

By genders, both subgroups of patients showed a similar metabolic deterioration during the two year follow-up after a FEP, but the male group started from a worse metabolic profile in certain measures (Figure 1), similarly to previous results reported from the CAFE Study in the US (Patel et al., 2009).

The affective psychoses subgroup presented higher rates of MetS at the end of the follow-up, possibly mediated by the coadjuvant use of antidepressant and mood stabilizers, more frequent in this subgroup (Bioque et al., 2016). A higher proportion of patients who were under antidepressant treatment in the 2-year follow up visit presented relevant body weight gain, overweight and MetS, together with higher systolic pressure blood levels, while those receiving mood stabilizers higher mean levels of triglycerides. The relatively low number of subjects in this subgroup of affective psychosis (n=55) is another factor to consider when interpreting these results.

A key feature of this study is that the age of inclusion is wider than in other previous works. Globally, the subgroup of early onset showed a pattern of metabolic worsening similar with the adult subpopulation, being a consistent finding with previous studies (Correll et al., 2009). However, the early onset was associated with a greater worsening in the glucose metabolism. This vulnerability should be considered when treating this population and in guidelines design (Galling and Correll, 2015).

Another aim of this study was to determine the effect of psychopharmacological treatment on the metabolic profile in a real-world setting. Those patients who were not receiving antipsychotic treatment at baseline showed significant lower rates of diabetes, together with lower waist circumference, glucose and LDL cholesterol levels, in the line of previous findings reported in the literature with antipsychotic-naïve populations (Fernandez-Egea et al., 2009; Greenhalgh et al., 2016; Perry et al., 2016; Pillinger et al., 2017; Verma et al., 2009).

One point in which we have focused our study is in the effects of antipsychotic polytherapy, which is a common practice in everyday clinical practice (Bernardo et al., 2012; Tani et al., 2013). Polytherapy regimens at the beginning of the study were associated to higher body weight, BMI, glucose and glycated hemoglobin levels. Besides, the baseline daily dose of antipsychotic correlated with the body weight.

Some limitations should be taken into account when analyzing these results. Firstly, patients could be under antipsychotic treatment for a maximum of 12 months at the study baseline, as the inclusion/exclusion criteria allowed to include subjects diagnosed of a FEP in the previous year. Although only a small proportion of the sample (n=49, 14.6%) had been taking antipsychotics for more than three months before the inclusion, the number of days of the antipsychotic treatment previous to the baseline assessment was used a covariate in that analysis, as we found positive correlations between the length of previous antipsychotic treatment and some of the metabolic measures. Secondly, the PEPs project was a naturalistic study, not a randomized controlled trial, so patients could be changing treatments during the follow-up period according to the clinician's choice; Thirdly, the major part of the participant sites are tertiary care centers linked to the Spanish network of translational research (CIBERSAM), so patient samples and therapeutic strategies may differ from those used in other areas; Fourthly, the relatively high number of drop-out during the follow-up period (40.9% of the cases and 37.6% % of the controls) may have limited the capability to detect differences between groups at the end of the study. Finally, another aspect that should be taken into account when interpreting these results is that the proportion of patients with an early onset included in our study (17%, 57/335) was higher compared to other similar studies made in subjects with a FEP in Australia (11.2%, 41/366) or with schizophrenia in Finland (4.7%, 19/400) (Amminger et al., 2011; Cannon et al., 1999).

A strength of this study is that that the diagnostic evaluation was performed with a very comprehensive protocol, with strict inclusion-exclusion criteria, with a wide age of inclusion better reflecting the natural history of the disorders, making this sample much closer to the "real life" FEP population (Bernardo et al., 2013). To our knowledge, there are no previous similar studies with this broad range of age and including patients with criteria which might be excluded in other ones (suicide ideation, drug use). Besides, the Spanish public health system universal coverage suggests that the population studied gives a good perspective of what is presently the clinical practice in this country (Bioque et al., 2016).

These findings may help clinicians to detect subgroups of patients with an incremented risk to develop certain cardiovascular comorbidities according to accessible clinical variables such as gender, diagnosis or age of onset. Besides, the torpid evolution of the major part of the metabolic measures during the follow-up visits, with higher rates of overweight/obesity and MetS, highlights the importance of an adequate clinical management (both for mental illness and metabolic comorbidities) in this population. These results indicate the need for and can help guide primary and secondary prevention strategies for metabolic risk factors in early phases of psychotic disorders.

Figure 1 Title: Evolution of BMI, body weight, waist circumference, glycated hemoglobin, triglycerides, high density lipoprotein (HDL) cholesterol and total cholesterol in male and female patients during the two-year follow-up period.

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Table(s)

Table 1. Demographic and clinical characteristics and baseline metabolic measures.

	First Episode Psychosis (n=335)	Control (n=253)	Statistic	P-value
Age – years [mean (sd)]	23.6 (6)	24.2 (6.4)	t=-1.26	0.21
Subjects <18 years old – no. (%)	57 (17)	32 (12.6)	χ^2=2.14	0.16
Gender – no. (%)				
Female	110 (32.8 %)	91 (36 %)	χ^2=0.63	0.43
Male	225 (67.2 %)	162 (64 %)		
Ethnic Group – no. (%)				
Caucasian	284 (84.8 %)	228 (90.1 %)		
Gipsy	6 (1.8 %)	0 (0)		
Maghrebian	8 (2.4 %)	2 (0.8 %)		
Sub-Saharan	4 (1.2 %)	0 (0)	χ^2=11.95	0.11
Asian	4 (1.2 %)	1 (0.4 %)		
Caribbean	8 (2.4 %)	4 (1.6 %)		
Hispanic	17 (5.1 %)	14 (5.5 %)		
Other	4 (1.2 %)	4 (1.6 %)		
Metabolic measures - mean (sd)				
Glucose (mg/dL)	84.9 (16.2)	83.7 (10.5)	F=0.082	0.775
Glycated hemoglobin (%)	5.2 (0.5)	5.2 (0.5)	F=1.365	0.243
Triglycerides (mg/dL)	88.4 (47.7)	80.9 (41.7)	F=0.067	0.795
Total Cholesterol (mg/dL)	161.9 (36.5)	169.6 (37.9)	F=8.381	0.004*
HDL Cholesterol (mg/dL)	49.4 (12.7)	55 (13.8)	F=6.410	0.012*
LDL Cholesterol (mg/dL)	95.5 (28.9)	98.1 (33.1)	F=5.452	0.020*
Body weight (Kg)	68.9 (14.1)	69.1 (12.7)	F=1.439	0.231
BMI (kg/m^2)	23.5 (4.2)	23.5 (3.4)	F=1.577	0.210
Abdominal circumference (cm)	85.7 (11.5)	84.8 (9.5)	F=0.037	0.848
Systolic blood pressure (mmHg)	119.9 (13.3)	119.8 (14.8)	F=0.139	0.710
Diastolic blood pressure (mmHg)	71.9 (10.1)	69.9 (9.6)	F=0.748	0.388
IDF Metabolic Syndrome criteria – % (no.)	6.6 % (13/197)	3.8 % (7/184)	F=0.361	0.55
Abdominal obesity	34 % (88/259)	42.9% (66/213)	F=0.839	0.36
Glucose	5.5 % (17/309)	0.9 % (2/226)	F=3.945	0.048*
Triglycerides	7.5 % (23/306)	6.2 % (14/225)	F=0.11	0.74
HDL Cholesterol	30.6 % (81/265)	15.7 % (34/216)	F=10.155	0.002*
Blood Pressure	23.6 % (74/314)	25.8 % (59/229)	F=0.141	0.71
Overweight – % (no.)	23.1% (75/324)	19.8 % (48/243)	F=0.4	0.53
Obesity – % (no.)	8% (26/324)	6.6% (16/243)	F=0.113	0.74
Diabetes – % (no.)	0.64 % (2/309)	0.44 % (1/226)	F=0.324	0.57

Abbreviations: BMI, body mass index; HDL, High-Density Lipoprotein; IDF, International Diabetes Federation criteria; LDL, Low-Density Lipoprotein.

*p<0.05. [a] Affective psychosis includes DSM-IV diagnosis of unipolar depression or bipolar disorder with psychotic features and schizoaffective disorder.

Table 2. Anthropometric, vital signs and metabolic measures comparison between the patients and healthy controls groups at the two year follow-up visit.

	First Episode Psychosis (n=198)	Control (n=158)	Statistic	p-value
Metabolic measures - mean (sd)				
Glucose (mg/dL)	86.4 (10.7)	83.1 (11.9)	F=7.45	0.006*
Glycated hemoglobin (%)	5.3 (0.9)	5.2 (0.4)	F=1.27	0.26
Triglycerides (mg/dL)	108.1 (80.3)	82.3 (52.6)	F=10.86	0.001*
Total Cholesterol (mg/dL)	170.8 (35.2)	170.6 (33.9)	F=3.08	0.79
HDL Cholesterol (mg/dL)	47.6 (13.5)	54.5 (14.8)	F=40.48	<0.001*
LDL Cholesterol (mg/dL)	103.2 (29.0)	100.1 (28.4)	F=0.002	0.96
Body weight (Kg)	76.6 (15.9)	69.6 (12.9)	F=5.14	0.024*
BMI	26.1 (4.8)	23.7 (3.2)	F=7.94	0.005*
Abdominal circumference (cm)	90.8 (12.8)	84.2 (9.3)	F=14.46	<0.001*
Systolic blood pressure (mmHg)	120.8 (14.1)	118.8 (12.9)	F=0.74	0.39
Diastolic blood pressure (mmHg)	71.2 (10.3)	69.1 (9.2)	F=8.57	0.004*
Metabolic Syndrome – % (no.)	14.6 % (22/151)	3.4 % (4/118)	χ^2=9.48	0.001*
IDF Abdominal obesity	48.3 % (86/178)	26.2 % (34/130)	χ^2=15.52	<0.001*
IDF Glucose	8.6 % (17/198)	3.2 % (5/157)	χ^2=4.39	0.045*
IDF Triglycerides	18.4 % (36/196)	7.6 % (12/158)	χ^2=8.66	0.002*
IDF HDL Cholesterol	34.7 % (60/173)	18.4 % (28/152)	χ^2=10.84	0.001*
IDF Blood Pressure	25.8 % (49/190)	21.9% (30/137)	χ^2=0.66	0.44
Overweight – % (no.)	33% (63/191)	24.6% (34/138)	χ^2=25.43	<0.001*
Obesity – % (no.)	20.4% (39/191)	4.3% (6/138)		
Diabetes – % (no.)	0.5 % (1/198)	0.6 % (1/157)	χ^2=0.027	0.99

Abbreviations: BMI, body mass index; HDL, High-Density Lipoprotein; IDF, International Diabetes Federation criteria; LDL, Low-Density Lipoprotein.

*p<0.05.

Table 3. Anthropometric, vital signs and metabolic mean measures for patients along all the visits of the PEPs study.

Anthropometric, vital signs and metabolic mean measures - mean (sd)	Baseline (n=335)	2-months (n=283)	6-months (n=260)	12-months (n=237)	24-months (n=198)	Statistics	p-value	Partial eta Squared*
Glucose (mg/dL)	84.9 (16.2)	87.1 (16.2)	87.1 (18.2)	87.2 (13.1)	86.4 (10.7)	WL=0.95, F=1.79	0.134	0.51
Glycated hemoglobin (%)	5.2 (0.5)	5.2 (0.4)	5.2 (0.4)	5.3 (0.5)	5.3 (0.9)	WL=0.77, F=8.13	**<0.001**	**0.23**
Triglycerides (mg/dL)	88.4 (47.7)	101.9 (62.1)	107.2 (67.4)	100.6 (86.6)	108.1 (80.3)	WL=0.92, F=2.88	**0.025**	**0.08**
Total Cholesterol (mg/dL)	161.9 (36.5)	169.3 (35.9)	169.1 (35.6)	164.4 (34.9)	170.8 (35.2)	WL= 0.88, F=4.84	**0.001**	**0.12**
HDL Cholesterol (mg/dL)	49.4 (12.7)	48.4 (12.4)	47.8 (12.9)	45.6 (11.6)	47.6 (13.5)	WL=0.87, F=4.18	**0.003**	**0.13**
LDL Cholesterol (mg/dL)	95.5 (28.9)	100.5 (30.9)	100.5 (31.5)	100.9 (28.3)	103.2 (29.0)	WL=0.93, F=1.97	0.104	0.07
Body weight (Kg)	68.9 (14.1)	72.1 (13.5)	74.4 (14.6)	76.4 (15.5)	76.6 (15.9)	WL=0.57, F=27.37	**<0.001**	**0.43**
BMI (kg/m^2)	23.5 (4.2)	24.5 (3.8)	25.3 (4.1)	25.9 (4.6)	26.1 (4.8)	WL=0.57, F=28.57	**<0.001**	**0.44**
Abdominal circumference (cm)	85.7 (11.5)	88.1 (11.4)	90.7 (11.6)	90.8 (12.2)	90.8 (12.8)	WL= 0.69, F=12.88	**<0.001**	**0.30**
Systolic blood pressure (mmHg)	119.9 (13.3)	119.8 (15.3)	119.5 (13.6)	120.2 (13.1)	120.8 (14.1)	WL=0.98 , F= 0.66	0.62	0.019
Diastolic blood pressure (mmHg)	71.9 (10.1)	70.6 (10.3)	70.8 (9.6)	71.5 (9.7)	71.2 (10.3)	WL=0.94 , F=2.04	0.092	0.057
Metabolic Syndrome – % (no.)	6.6 % (13/197)	11.4% (21/185)	14.6% (29/198)	14.6% (26/178)	14.6 % (22/151)	CQ=6.00	0.20	-
Overweight – % (no.)	23.1% (75/324)	26.5% (74/279)	39.7% (102/257)	36.8% (85/231)	33% (63/191)	CQ=13.85	**0.008**	-
Obesity – % (no.)	8% (26/324)	12.2% (34/279)	13.2% (34/257)	19% (44/231)	20.4% (39/191)	CQ=33.77	**<0.001**	-
Diabetes – % (no.)	0.6 % (2/309)	0.8% (2/255)	2.4% (6/249)	0.9% (2/220)	0.5 % (1/198)	CQ=4.00	0.41	-

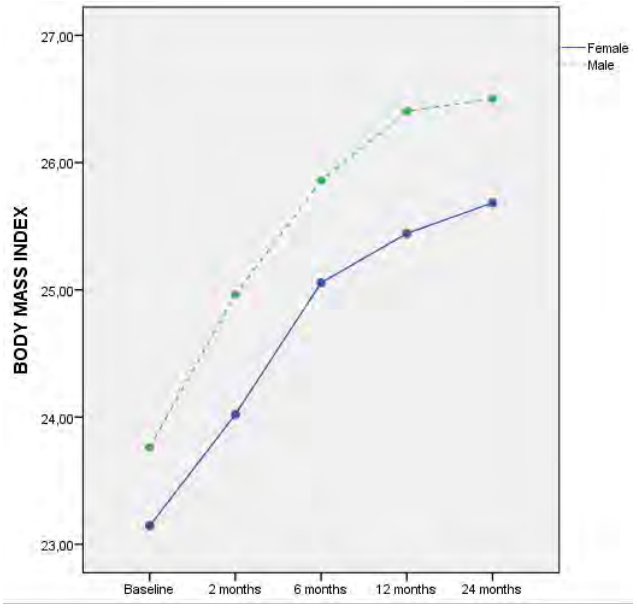
CQ: Cochran's Q ; WL: Wilk's Lambda. *Partial Eta Squared value of effect size (0.01-0.05=small, 0.06-1.3=moderate, >0.14=large).

Table 4. Psychopharmacological treatment in the baseline and in the two year follow-up visit.

	Baseline	2-year follow-up visit
Subjects Antipsychotic treatment		
No antipsychotics	31/335 (9.2%)	20/116 (17.2%)
Antipsychotic Monotherapy	231/335 (69%)	84/116 (72.4%)
Antipsychotic Polytherapy	73/335 (21.8%)	12/116 (10.4%)
Route of antipsychotic		
Only oral	288/304 (94.7)	86/96 (89.6%)
Only Long Acting Injection	1/304 (0.3)	9/96 (9.4%)
Both	15/304 (4.9)	1/96 (1%)
Chlorpromazine equivalent mean dose	599.08 (±442.56)	345.02 (±292.79)
Subjects with other treatments		
Anticholinergics	41/335 (12.2%)	5/116 (4.3%)
Antidepressants	41/335 (12.2%)	18/116 (15.5%)
Mood stabilizers	46/335 (13.7%)	30/116 (25.9%)
Benzodiazepines	130/335 (38.8%)	18/116 (15.5%)

Figure(s)

A



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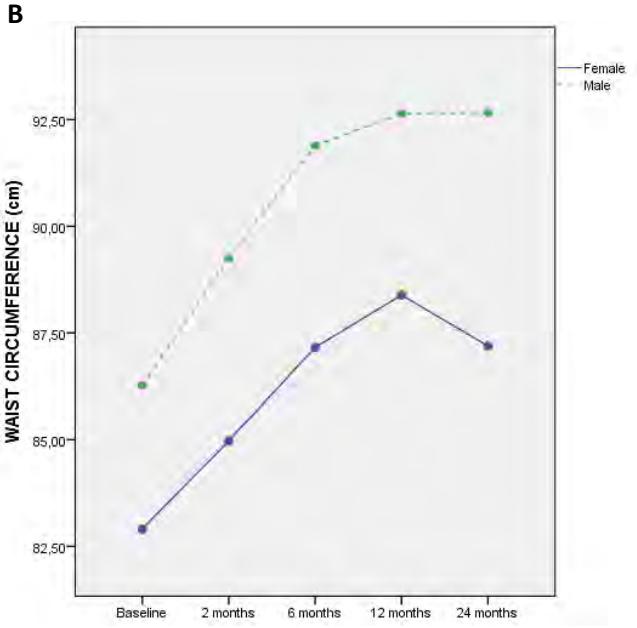

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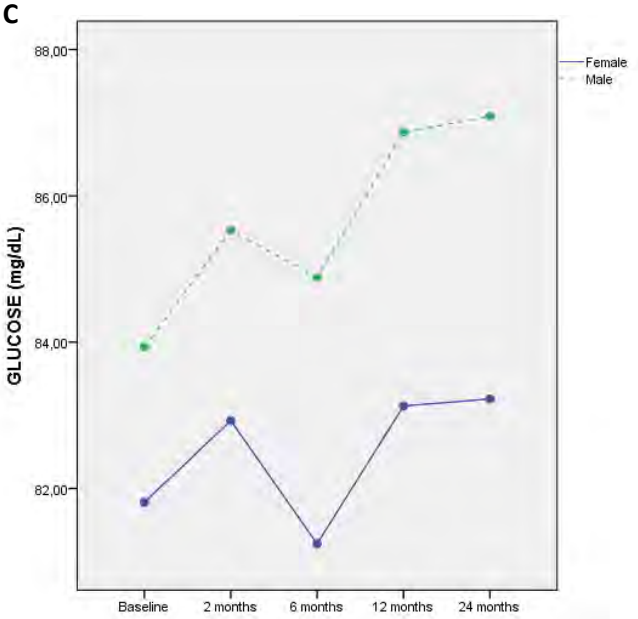

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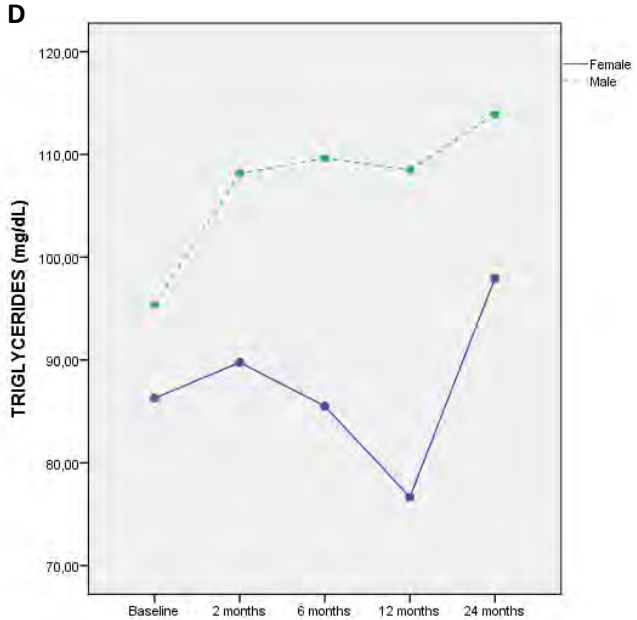

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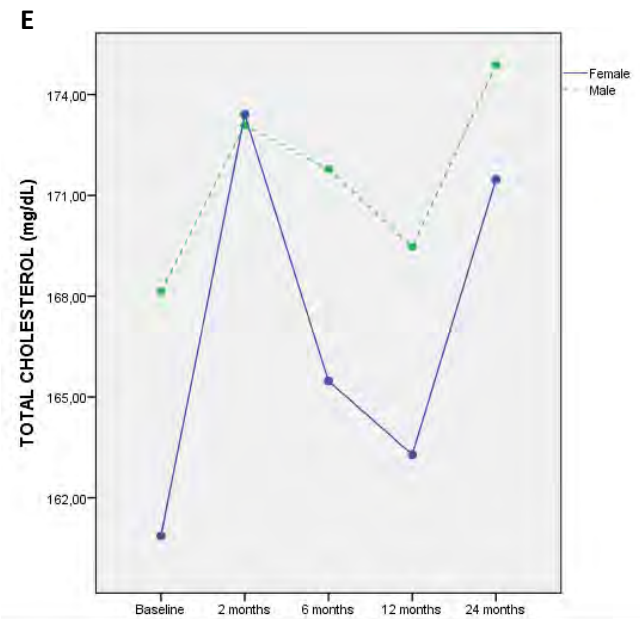

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