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Antipsychotic-induced weight gain and birth weight in psychosis: A fetal programming model

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ABSTRACT

Antipsychotic induced weight gain is a frequent reason for treatment discontinuation in psychosis, subsequently increasing the risk of relapse and negatively affecting patient well-being. The metabolic effect of weight gain and the subsequent risk of obesity constitute a major medical problem on the long term. Despite its consequences, to date few risk factors have been identified (age, gender, body mass index at baseline), with some authors suggesting the implication of early life stressful events, such as perinatal conditions. We aim to describe if a surrogate marker of intrauterine environment (birth weight) might predict weight gain in a cohort of 23 antipsychotic naïve patients at the onset of the psychotic disease evaluated during 16 weeks with olanzapine treatment and in another cohort of 24 psychosis-resistant patients initiating clozapine assessed for 18 weeks.

Two independent linear mixed model analyses were performed in each cohort of patients, with prospective weight gain as the dependent variable, age, gender, body mass index, duration of treatment and time as independent variables.

Only in naïve patients, weight gain due to antipsychotics was significantly associated with birth weight, while male gender and body mass index at baseline were associated in both cohorts of patients. Treatment-resistant psychotic patients under clozapine were older, had previous antipsychotic treatment and more years of disease, confounders that might have influence a non significant association.

Our results suggest that early environmental events might be playing a role in weight evolution in naïve patients treated with antipsychotics.

1. Introduction

Antipsychotic induced weight gain (AIWG) is a common side effect affecting up to 72% of patients diagnosed with schizophrenia during acute or maintenance treatment (De Hert et al., 2011). Amongst them, clozapine and olanzapine are the most frequently associated with it (Manu et al., 2015). Family studies report a genetic risk of AIWG about 60–80% (Gebhardt et al., 2010), but its underlying mechanisms is not fully understood, being suggested receptor's pharmacology (Reynolds and Kirk, 2010), inflammatory (Fonseka et al., 2016), mitochondrial (Gonçalves et al., 2014), and striatal reward (Nielsen et al., 2016) pathways. Between the clinical factors associated to this phenomenon, gender, a younger age and baseline body mass index (BMI) have been found to be AIWG predictors due to atypical antipsychotics (Stefan Gebhardt et al., 2009; Harrison et al., 2017; Manu et al., 2015). Regarding gender, some studies suggest female patients are more prone to

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AIWG (Gebhardt et al., 2009; Harrison et al., 2017) while other show that male gender (Pérez-Iglesias et al., 2014) is more related, with others studies reporting no gender differences on AIWG (Bioque et al., 2018; Pons et al., 2013). Thus, AIWG has shown to be predicted by an increased baseline BMI in those exposed to previous antipsychotics while a low BMI prior to first antipsychotic treatment has proved to predict a higher acceleration of BMI change in drug naïve patients (Gebhardt et al., 2009; Harrison et al., 2017; Manu et al., 2015).

AIWG's consequences broaden the metabolic aspects, disturbing physical aspect, lowering self-esteem and quality of life (Malhotra et al., 2016), suffering from double stigma of obesity and mental disorder (Mizock, 2012). Indeed, the reduction in life expectancy about 20 years based mostly on cardiovascular disorders (Laursen et al., 2014) highlights the importance of AIWG and subsequent obesity in these patients. Obesity, a medical condition in which the accumulation of body fat mass represents a negative effect of health, might lead to an increased risk of medical co-morbidities, such as type 2 diabetes mellitus (T2DM), metabolic syndrome, atherosclerosis (Matsuda and Shimomura, 2013) and a reduced life expectancy (Flegal et al., 2013). Although it has been attributed to an increased energy intake and a reduced physical activity, the current state of knowledge mirrors the importance of early life stress (ELS) in determining long term fat storage (Eriksson et al., 2001). According to this, the fetal programming model posits that extremes on birth weight (BW) could influence on the later risk of obesity and metabolic diseases in the adolescence and adulthood (Hales and Barker, 1992). In general population, the modifier effect of BW on the later development of obesity and fat distribution has been found to be linear and positive associated in some studies while J- or U-shaped in others (Monasta et al., 2010; Rogers, 2003; Yu et al., 2011). Similar results have been found in relation to BW and T2DM (Hales and Barker, 1992; Harder et al., 2007; Whincup et al., 2008; Zhao et al., 2018), a medical condition highly associated with abdominal obesity.

The theoretical paradigm of the fetal programming has proved to be applicable not only to obesity and metabolic related diseases, but to the realm of mental health (O'Donnell and Meaney, 2017). An impaired fetal growth, measured as low BW ($\leq$2500 g), has been found to predict the later risk of psychopathology (Breslau and Chilcoat, 2000; Mathewson et al., 2017) and mental illness itself (Abel et al., 2010; Breslau and Chilcoat, 2000; Osler et al., 2005; Sucksdorff et al., 2015; Wiles et al., 2006). Moreover, it has been suggested that ELS might behave as a common risk factor for both, metabolic and psychiatric conditions in the same individual (Garcia-Rizo et al., 2015). Considering the example of schizophrenia, it has been proposed that those patients might present a vulnerability to develop both (the mental and metabolic disease), due to a higher epidemiologic ratio of diverse obstetric complications (Suvisaari et al., 2012), already present at the onset of the psychiatric illness (Fernandez-Egea et al., 2009). In this case, the use of antipsychotic treatment (the actual core treatment of the disease) will just increase the metabolic vulnerability present at the onset of the psychiatric illness (Fernandez-Egea et al., 2011).

As previously stated, olanzapine and clozapine are the two antipsychotics mainly related with AIWG (Manu et al., 2015). However, the role of BW in weight gain due to antipsychotics in mental ill populations has been barely studied with novel results from a cross-sectional study of antipsychotic adiposity in treatment resistant schizophrenic patients (Ziauddeen et al., 2016). In this study, low BW was a useful predictor of AIWG due to clozapine in comparison with antipsychotic naïve patients. However, there is a lack of prospective studies (where antipsychotic treatment is initiated) evaluating the possible effect of BW on AIWG.

With the previous rationale, we aim to extend the knowledge of risk factors contributing to AIWG. We hypothesize that there shall be a different weight gain (metabolic imprinting) depending on the intrauterine milieu (affected by known or unknown ELS) and reflected by BW. For this reason, we analyze two cohorts of psychotic patients, one with antipsychotic-naïve and other with treatment-resistant psychosis patients, hypothesizing that the possible role of BW on the later AIWG will be greater in the naïve cohort than in the treatment resistant, where other factors might have already co-occurred.

2. Material and methods

2.1. Subjects

For the current study, two cohorts of patients from two different studies that evaluated weight gain after initiating antipsychotics (olanzapine or clozapine) were included.

Cohort 1 (olanzapine cohort) involved 23 antipsychotic-naïve patients with newly diagnosed psychosis that were enrolled in a 16-week open label trial with olanzapine (Fernandez-Egea et al., 2011). They were recruited at the time of their first clinical contact for psychosis at Hospital Clinic (Barcelona, Spain) and had participated in a larger study of baseline metabolic abnormalities (Fernandez-Egea et al., 2009) and agreed to participate in a follow up olanzapine trial.

Cohort 2 (clozapine cohort) involved 24 treatment-resistant psychosis patients who initiated clozapine treatment and they were followed during the first 18 weeks of clozapine treatment. Those patients were recruited as a part of a grant designed to evaluate the longitudinal effects of clozapine in neuro-hormones and immunity in patients with treatment-resistant psychosis. All study subjects were recruited from the Clozapine Clinic of Hospital Clinic (Barcelona, Spain). Inclusion criteria were wide to be considered close to clinical practice: (1) patients diagnosed from schizophrenia, schizoaffective or bipolar disorder according to the DSM-IV-TR criteria; (2) aged from 18 to 65 years. The exclusion criteria were: (1) history of traumatic brain injury; (2) mental retardation.

For each study, subjects were informed of the purpose, procedures, and potential risks of their participation before signing an informed consent form. Both study protocols were approved by the local Ethical Committee and conducted in conformity with the Declaration of Helsinki.

2.2. Study design

Cohort 1 (olanzapine) patients participated in a 16-week open label trial with olanzapine. They were started on an oral dose of 5 mg/d, which was adjusted based on clinical response. Patients were evaluated with an oral glucose-tolerance test and anthropometric measures on weeks 4, 8, 12, and 16. Further methodological information was previously provided (Fernandez-Egea et al., 2011).

Cohort 2 (clozapine) patients were recruited from an analytic, observational prospective study of 18 weeks of follow up. A multidisciplinary team of two psychiatrist, two nurses and one psychologist conducted the study procedures. Because patients starting clozapine require weekly blood monitoring due to its risk of agranulocytosis in the first 18 weeks and then monthly, study visits were linked to those at their regular clozapine care. In this regard, three critical study visits were performed: a baseline visit (the day that clozapine was programmed to start), at week 8 and week 18 of treatment. Clozapine was initiated with a dose of 12.5–25 mg in the first day of treatment, followed by weekly upward adjustments of 25–50 mg (i.e., standard titration). The titration was continued until satisfactory symptom control or development of major side effects according to clinical impression. A complete blood count, metabolic evaluation and an electrocardiogram were obtained according to the regular monitoring on clozapine. Complete blood cell counting was checked weekly. All patients received a standard clinical care in the hospital and outpatient clinic in relation to the monitoring of clozapine treatment.

2.3. Study procedures and data collection: demographic, clinical, physical and anthropometric measures

Both study cohorts shared baseline visits including a complete set of demographic and clinical data. All subjects were clinically interviewed using the Spanish translation of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I Disorders (First and Spitzer, 1999). Clinical baseline assessment was also recorded using pre-planned structured interviews which included a review of the current medical and psychiatric history, details of psychiatric clinical status, family history, birth date, BW (in grams), and history of previous prescribed medication if proper. Vital signs and anthropometric evaluation included blood pressure and heart rate. Height, weight and waist circumference were measured for each patient and BMI was calculated (BMI = weight [kg]/height^2 [m^2]). In this regard, cohort 1 (olanzapine) recorded vital signs and anthropometric measures on baseline, weeks 4, 8, 12 and 16. Further information was provided in previous article (Fernandez-Egea et al., 2011). In the cohort 2 (clozapine), those measures were recorded at baseline, week 8 and week 18 of follow up.

Olanzapine (cohort 1) and clozapine (cohort 2) oral dosages were recorded at each study visit to be considered of interest in relation to weight gain. No olanzapine plasma levels were collected as the technique was not available in our clinical setting, however, clozapine and nor-clozapine blood levels were performed in cohort 2 (measured at week 8 and week 18).

2.4. Statistical analysis

The demographic and baseline clinical variables were described by treatment group and the total population. For continuous variables the mean, median, standard, maximum and minimum deviation was calculated. Discrete and categorical variables were analyzed by analysis of absolute and relative frequencies.

Linear mixed model analysis (LMMA) to analyze repeated measurements was used to compare the different weight gain pattern in time course for the two cohorts of patients (with time as a repeated measure factor). The LMMA is strongly recommended and a standard way to handle the dependencies of the longitudinal data at hand and the model with maximum likelihood estimation has the advantage of coping with drop-outs in an efficient way (Gueorguieva and Krystal, 2004). They also have the advantage of allowing the investigation of variability between patients (heterogeneity) and simultaneously adjusting for the within-subject correlation. For repeated covariance type, the unstructured covariance matrix was selected based on lowest Akaike information criteria and the Bayesian Schwarz information criterion after considering unstructured, compound symmetry and autoregressive covariance structure matrices.

To explore prospective differences in weight gain in each cohort, an initial unadjusted LMMA (model 1), which considered weight as the dependent variable and time as the independent factor, was performed. Then, we performed two sets of LMMA with the different independent variables, separately. A backward stepwise method was used for selecting which variables are suitable to be included in the model, while only variables with a p value < 0.05 remained in the final model (Model 7). Test statistics for fixed effects were based on F values. After an unadjusted model was applied, later adjusted models for each cohort were developed with weight as the dependent variable and time-invariant covariates (gender, BMI at baseline, age, olanzapine dosage/nor-clozapine plasma levels, and years on antipsychotic treatment in cohort 2) and time were independent factors. In a later fully adjusted LMMA (model 7) for each cohort, BW was included as another independent factor to the previous valid model.

To evaluate the shape of the association between weight gain and BW, we used the predictive values derived from model 7. They were plotted correlated with BW, to graphically describe the predicted value of weight gain over time given any birth weight.

Table 1
Cohort characteristics.

M ± (SD)	Cohort 1 (Olanzapine) N = 23	Cohort 2 (Clozapine) N = 24
Age (years old)	27.3 ± 6.1	34.3 ± 9.4
Gender (% male/female)	14(61%)/9(39%)	15(63%)/9(37%)
BW (Kg)	3.3 ± 0.3	3.3 ± 0.4
Weight baseline (Kg)	65.3 ± 13.9	81.7 ± 19.0
Δ Weight end follow-up (Kg)	4.5 ± 4.4	1.3 ± 4.2
BMI baseline (Kg/m2)	22.0 ± 3.1	27.7 ± 5.2
Δ BMI end follow-up (Kg/m2)	1.0 ± 1.2	0.5 ± 1.5
Time on antipsychotics (years)[a]	–	6.1 ± 6.8

M: Mean; SD: Standard Deviation; BMI: Body Mass Index; BW: Birth Weight.
[a] Only assessed in cohort 2 (clozapine).

3. Results

3.1. Description of the sample

A total of 23 patients were included in the cohort 1 and 24 in the cohort 2. At the end of follow-up of the olanzapine (cohort 1) and clozapine (cohort 2) treatment, the drop-out ratios were 30.4% (n = 7) and 25% (n = 6), respectively. Sample characteristics are summarized in Table 1 for both cohorts. None of the participants presented values of BW compatibles with low BW (≤2500gr) or high BW (> 4000gr) in any of the cohorts.

3.2. Prospective association between demographic and clinical factors and AIWG

The first unadjusted LMAA model (model 1) showed that, in both cohorts, there was a significant weight increase over time (cohort 1: $F = 20.98$; $df = 16$; $p < 0.001$; cohort 2: $F = 3.649$, $df = 19$, $p = 0.045$). For each time frame (5 time frames in cohort 1, baseline, week 4, week 8, week 12 and week 16 and 3 in cohort 2, baseline, week 8 and week 18) specific fixed effects estimates were obtained (data not shown). At the end of follow-up, weight gain was on average 4.53 Kg in cohort 1 and 1.25 Kg in cohort 2 with a BMI baseline ≥30Kg/m2 in 8 patients (33.3%) of cohort 2 while none in cohort 1.

After adjusting for covariates in models 2 and 3, it was found that male gender (cohort 1: $F = 28.7$, $df = 10$, $p < 0.001$; cohort 2: $F = 18.5$, $df = 21$, $p < 0.001$) and BMI at baseline (cohort 1: $F = 84.4$, $df = 11$, $p < 0.001$; cohort 2: $F = 202.0$, $df = 21$, $p < 0.001$) were prospectively associated with weight gain in both cohorts. In model 4 when age was included in the model, it did not reach a significant association, age (cohort 1: $F = 0.087$, $df = 8$, $p = 0.775$; cohort 2: $F = 0.02$, $df = 20$, $p = 0.962$). In model 5, for cohort 1: olanzapine olanzapine dosage ($F = 0.054$, $df = 22$, $p = 0.819$) and in cohort 2: norclozapine levels ($F = 0.03$, $df = 32$, $p = 0.864$) was not found to be significantly associated. In model 6, and only for cohort 2, time of antipsychotics was included and did not reach any significant association ($F = 0.02$, $df = 20$, $p = 0.891$).

3.3. Prospective association with AIWG after additional adjustment for BW

Further adjustment in the LMMA, including BW as a covariate (see Table 2, model 7), showed similar associations found in model 3 for male gender (cohort 1: $F = 31.2$, $df = 15$, $p < 0.001$; cohort 2: $F = 17.2$, $df = 20$, $p < 0.001$), baseline BMI (cohort 1: $F = 72.1$, $df = 16$, $p < 0.001$; cohort 2: $F = 196.2$, $df = 20$, $p < 0.001$) and time (cohort 1: $F = 21.4$, $df = 16$, $p < 0.001$ and cohort 2: $F = 3.4$, $df = 19$, $p = 0.055$). Thus, according to this model, BW was associated with AIWG (only in cohort 1: $F = 5.3$, $df = 9$, $p = 0.047$, not in cohort

Table 2
Linear Mixed Model Analysis for the association between AIWG and different demographic, anthropometric, clinical and birth variables over the study period.

		Cohort 1 (Olanzapine) N = 23			Cohort 2 (Clozapine) N = 24		
		Estimation ± SE	95% CI	p-value	Estimation ± SE	95% CI	p-value
Unadjusted: (Model 1) [a]				< 0.001			0.045
Adjusted (Model 2)				< 0.001			0.052
	Gender (Male)	16.2 ± 4.7	6.2, 26.1	< 0.001	17.1 ± 6.7	2.7,31.6	0.022
Adjusted (Model 3)				< 0.001			0.055
	Gender (Male)	13.6 ± 2.6	8.0,19.1	< 0.001	9.9 ± 2.3	5.1,14.7	< 0.001
	BMI baseline (Kg/m2)	3.5 ± 0.4	2.7, 4.4	< 0.001	3.1 ± 0.2	2.6,3.5	< 0.001
Adjusted (Model 7)				< 0.001			0.055
	Gender (Male)	15.0 ± 2.6	9.0,20.1	< 0.001	9.8 ± 2.4	4.9,14.7	< 0.001
	BMI baseline (Kg/m2)	4.0 ± 0.5	3.0,5.0	< 0.001	3.1 ± 0.2	2.6,3.5	< 0.001
	Birth Weight (Kg)	−7.4 ± 3.2	−14.7,-0.1	0.047	1.8 ± 2.5	−3.5,7.0	0.485

As stated in the methods and results section: Model 4 included age, Model 5 included olanzapine dosage for cohort 1/Norclozapine Levels for cohort 2, Model 6 included time on antipsychotics. The variables were excluded from the final model because $p < 0.05$.
[a] Model includes time.

2: F = 0.5, df = 20 p = 0.485).

To describe the shape of the associations for the continuous relations between BW and AIWG, predicted values of weight gain (Kg) resulted from the previous LMMA (model 7) were plotted correlated with BW (see Fig. 1). A curvilinear regression analysis was conducted where both, linear and quadratic models were included. Only in cohort 1, but not in cohort 2, it was able to significantly predict the variance in the increment of weight gain on the study period. Linear correlation between BW and predicted weight gain over the study period in cohort 1 ($R^2 = 0.048$; BW: $\beta = 0.219$, $t = 2.391$; $p = 0.018$) and quadratic correlation ($R^2 = 0.127$; BW: $\beta = -4.099$; $t = -3.006$; $p = 0.003$; BW squared: $\beta = 4.328$, $t = 3.173$; $p = 0.002$) were significant (see Fig. 1).

4. Discussion

Our results suggest that BW, a surrogate marker of intrauterine milieu, is associated with weight induced gain in a cohort of naïve patients initiating antipsychotic treatment with olanzapine, despite several confounding factors. Also BW was found to correlate with AIWG with a quadratic relationship in the same cohort. However, this association was not found in another cohort of psychosis-resistant patients switching to clozapine.

Our findings also suggest that known clinical factors involved in AIWG such as male gender and baseline BMI, remain positively and significantly associated with weight increase in both subsets, naïve (cohort 1) and psychosis-resistant (cohort 2) patients. Similar results have been previously described on male gender in first episode psychosis (Pérez-Iglesias et al., 2014) and high baseline BMI on the

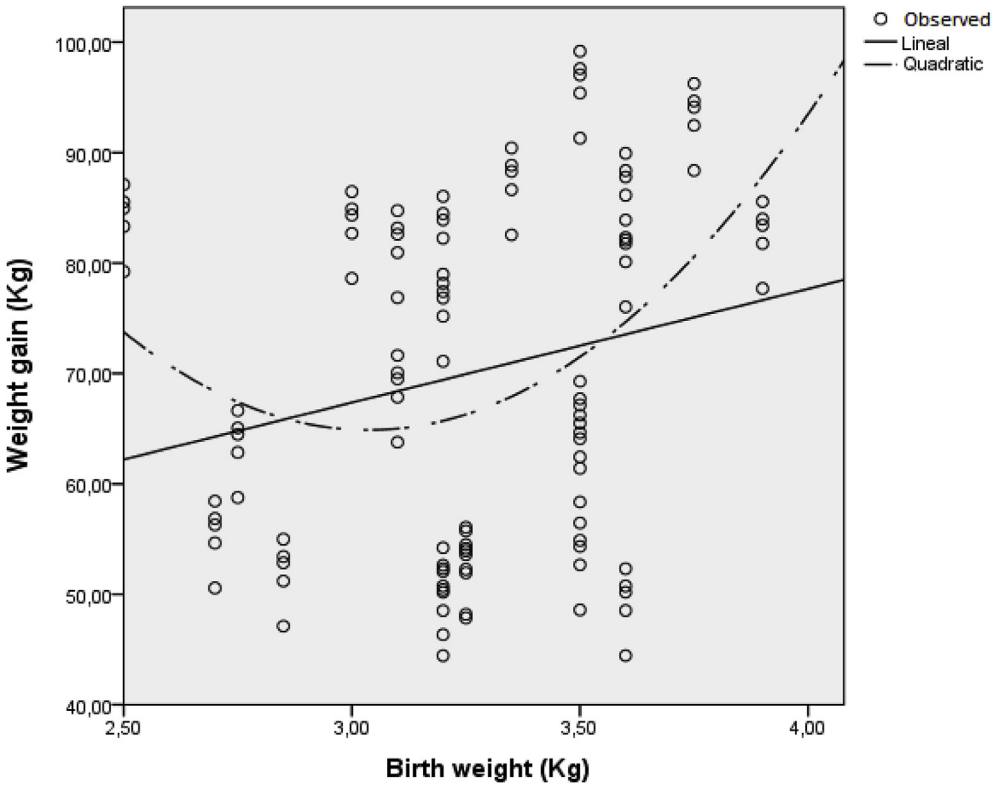

Fig. 1. Predicted values for weight gain (Kg) over 16 weeks in first episode naïve patients treated with olanzapine (cohort 1) regarding BW and displayed in a linear ($R^2 = 0.040$) and quadratic relationship ($R^2 = 0.127$).

prediction of AIWG in treated-patients (Gebhardt et al., 2009). We did not find any association with age, a finding also described in first episode psychotic patients not naïve (Bioque et al., 2016) and in clozapine treatment resistant patients (Lau et al., 2016). However, it has been described in the literature that children and adolescents appear to have an increased risk (Martínez-Ortega et al., 2013) for AIWG in comparison with adult populations. Our negative results towards antipsychotic dosage or levels were also previously reported (Lau et al., 2016). As expected, in our sample, there was a significant weight increase in both samples, with a higher AIWG in the naïve subjects (cohort 1, olanzapine).

Further, our research suggests that BW might play a role in the weight gain of patients initiating their first antipsychotic treatment (cohort 1), while its role might not be so clear in patients that had been already suffering from other adverse factors such as unhealthy lifestyle, older age, medical co-morbidities or previous antipsychotic medication (cohort 2). The fact that BW is only associated in naïve subjects and not in psychosis-resistant patients suggests that the effect of BW on AIWG seems to get diluted over time after starting antipsychotic treatment. Treatment-resistant psychosis patients could also present a metabolic load in comparison with naïve patients that might attenuate the possible role of BW. Thus, in our sample, treatment resistant patients (cohort 2) are older, displayed baseline higher rates of overweight and obesity and presented a lower average of weight gain (possibly mediated for years of mental illness and psychopharmacological treatment). This cumulative load may underlie the fact that early environmental factors (indirectly measured by BW) would minimally apply to those patients. Indeed, quadratic relationship in Fig. 1 suggests that, in our model, the 12.7% of the variation of AIWG can be attributed to BW in cohort 1 after controlling for the described confounders. However, this variation might be underestimated for sample characteristics such as none of the patients present extreme BW ($\leq$2500gr or $>$ 4000gr), which might drive to a more conservative model. Overall, the use of BW as an indirect marker of the intrauterine milieu seems a useful predictive tool to detect patients at risk of developing higher weight increase due to antipsychotics over time in our model, but only in those naïve for medication. BW differences across subjects have proved, not only an effect in anthropometric parameters but, also an effect in other conditions, such as brain development (Walhovd et al., 2014). BW has already been studied in patients with schizophrenia as a predictor of cognitive functioning (Haukvik et al., 2014; Torniainen et al., 2013) or as a risk factor related to parental psychosis (Keskinen et al., 2013). It has also shown correlation with clinical symptomatology (Wegelius et al., 2013), with genetic risk (Wegelius et al., 2015) and as a link between maternal inheritance and parental age (Lin et al., 2010). However, a recent large cohort study did not find any association from BW with clinical psychiatric outcomes (Rautio et al., 2016).

Several limitations apply to our study. Our study lacks a control group which might describe possible differences between BW and weight over a period in the absence of antipsychotic treatment. Indeed, current literature presented at the introduction, reflects a similar association however with much higher number of subjects. Our cohort of psychosis-resistant patients (cohort 2), included patients diagnosed with bipolar disorder and schizoaffective disorder. Although it might seem unspecific, some percentages of patients with a first episode of non-affective psychosis end up with an affective diagnosis (Salvatore et al., 2009). Our results in psychosis-resistant cohort were confounded by time on antipsychotics, not by cumulative dosage of antipsychotic. This variable did not account for non-compliance periods, number of previous antipsychotics, or even treatment dosage. Also, BW is a crude marker and indirect measure of the intrauterine period, influenced by gestational age which was not recorded (Eide et al., 2005). Another limitation is the lack of information regarding two important factors affecting weight gain such as dietary intake and physical activity. Our negative results in cohort 2 might be a type II error (false negative finding). In order to get a significant result, we must increase the number of subjects as the effect found in naïve might be surpassed by other confounders which not apply in naïve subjects (Kirkpatrick et al., 2012).

The provided results rely in a theoretical framework (Garcia-Rizo et al., 2015) applied not only to schizophrenia but to serious mental illnesses with a described common metabolic pathway (Garcia-Rizo et al., 2016). Our model highlights the fact that ELS promotes the development of metabolic abnormalities and mental health disorders in the same subject probably due to epigenetic modifications. Our results guide to a new approach in daily clinical practice, suggesting that ELS (such as obstetric complications during the pregnancy) must be described and considered as a possible marker of AIWG (Mezquida et al., 2018). We suggest that in these circumstances where ELS apply, a risk towards higher AIWG is an epiphenomenon already present in subjects who initiate antipsychotic treatment for a psychiatric diagnosis. So intervention strategies promoting healthy life-style must be oriented to those at-risk subjects. Further studies replicating our findings in larger cohorts are required to confirm the influence of BW in the later adverse metabolic development.

5. Conclusions

Our results suggest the effect of BW in the latter development of increased weight gain due to antipsychotics, pointing out to a new approach towards metabolic abnormalities at least in naïve subjects with a first episode of psychosis. The evaluation not only of BW but also different ELS events during pregnancy and initial years, such as infant/childhood trauma (Hepgul et al., 2012), might help understand which patients will develop greater AIWG and implement specific intervention strategies in selected patients.

Conflicts of interest

MG: has received grants and served as consultant or advisor for Ferrer, Lundbeck, Janssen, Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III through a 'Rıo Hortega' contract (CM17/00102), FEDER, and Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM).

EFE: has received consultancy fee honoraria from Angelini and Recordati.

AM, LS, CO has nothing to disclose.

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BK: has a financial relationship with ProPhase, LLC, for teaching and dissemination of the Brief Negative Symptom Scale; support by Walsh Medical Media for editorial work on Clinical Schizophrenia and Related Psychoses; payment by the Journal of Clinical Psychiatry for continuing education articles; and consulting with Genentech/Roche.

EV: has received grants, CME-related honoraria, or consulting fees from Alexza, Almirall, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmith-Kline, Janssen, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Pierre-Fabre, Qualigen, Roche, Sanofi-Aventis, Schering-Plough, Servier, Shire, Solvay, Takeda, Teva, CIBERSAM, the Seventh European Framework Programme (ENBREC), the Stanley Medical Research Institute, United Biosource Corporation, and Wyeth.

MB: has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, Somatics and has obtained research funding from the Ministry of Education, Culture and Sport, the Spanish Ministry of Economy, Industry and Competitiveness (CIBERSAM), by the Government of Catalonia, Secretaria d'Universitats i Recerca del Departament

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Contributors

MG and EFE: acquisition and interpretation of data, drafting the manuscript, and revising critically for contents.

AM and LS: acquisition and interpretation of data, revising critically for contents.

CO, EP, BK, EV and MB: revising the manuscript critically for intellectual content and approved the final version of the manuscript.

CGR: conception and design of the article, revising the manuscript critically for intellectual content and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.05.004.

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