

## REGULAR RESEARCH ARTICLE

# Aripiprazole and Risperidone Present Comparable Long-Term Metabolic Profiles: Data From a Pragmatic Randomized Controlled Trial in Drug-Naïve First-Episode Psychosis

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## Abstract

**Objective:** Aripiprazole and risperidone are 2 of the most used second-generation antipsychotics (SGAs) worldwide. Previous evidence shows a similar effect of these SGAs on weight and metabolic changes in the short term. However, a longer period is necessary for a better assessment of the SGA's metabolic profile. We aimed to compare the long-term (1-year) metabolic profile of these 2 antipsychotics on a sample of drug-naïve first episode-psychosis (FEP) patients.

**Methods:** A total 188 drug-naïve patients, suffering from a first episode of non-affective psychosis (FEP), were randomly assigned to treatment with either aripiprazole or risperidone. Weight and glycemic/lipid parameters were recorded at baseline and after 1-year follow-up.

**Results:** We observed significant weight increments in both groups (9.2 kg for aripiprazole and 10.5 kg for risperidone) after 1 year of treatment. Despite this, weight and body mass index changes did not significantly differ between treatment groups ( $P > .05$ ). Similarly, both treatment groups presented similar metabolic clinical impact with a comparable increase in the proportion of participants meeting criteria for metabolic disorders such as obesity or hypercholesterolemia, but not for metabolic syndrome ( $\Delta 9.2\%$  vs  $\Delta 4.3\%$ ) or hypertriglyceridemia ( $\Delta 21.9\%$  vs  $\Delta 8.0\%$ ), where aripiprazole showed worse outcomes than risperidone.

Received: November 8, 2021; Revised: April 29, 2022; Accepted: May 26, 2022

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## Significance Statement

We studied, in a cohort of patients with a first episode of non-affective psychosis, the changes in body weight and glucose/lipid metabolisms observed during the first year after the diagnoses of psychosis and the initiation of antipsychotic treatment. At study entry, patients were randomized to either aripiprazole or risperidone, so we were able to run head-to-head comparisons between antipsychotic treatments. The results showed a significant increase in mean body weight in the whole cohort. Despite this, aripiprazole and risperidone showed a similar metabolic profile and produced comparable weight gain at long term in individuals with a first episode of psychosis. Secondary analyses showed that women had a statistically significant greater increase in body mass index than men. We did not observe sex-treatment interactions in weight gain or metabolic changes. Early preventive measures to avoid weight gain should be put in place when treating individuals for a first episode of psychosis.

**Conclusion:** This study shows that aripiprazole and risperidone share a similar long-term metabolic profile. After 1 year of antipsychotic treatment, drug-naïve FEP patients in both treatment groups presented a significant increase in weight and metabolic changes, leading to a greater prevalence of metabolic disorders.

**Keywords:** Metabolism, weight gain, treatment-naïve, second-generation antipsychotic, schizophrenia

## Introduction

Schizophrenia is a neuropsychiatric disorder characterized by a chronic progression and lifetime prevalence of approximately 1% (Kahn et al., 2015). The primary treatment for schizophrenia is second-generation antipsychotics (SGAs) (Goff, 2021). After symptoms have been controlled in individuals with their first episode of psychosis (FEP), it is strongly advised to reduce SGA treatment to the lowest effective dose as soon as possible. This praxis not only ensures symptomatic stability but also reduces the likelihood of emergent adverse events, which would result in poor treatment acceptability and compliance (Goff et al., 2017; Correll et al., 2018). In this regard, SGAs have been widely linked to weight gain, which, along with other lifestyle risk factors, contributes to an increased risk of dyslipidemia, glucose intolerance, diabetes mellitus, metabolic syndrome (MetS), and, ultimately, cardiovascular disease (Henderson et al., 2015; Nielsen et al., 2021). These physical conditions are underlying causes of up to 70% of the excess mortality seen in schizophrenia, resulting in a life expectancy reduction of up to 20 years (Owen et al., 2016; Kurdyak et al., 2021). Recent evidence, however, indicates that there are differences in the side effects profile of antipsychotics in terms of weight gain (Leucht et al., 2013; Huhn et al., 2019). A recent meta-analysis described gradual but marked differences between a wide range of antipsychotic treatments regarding weight gain (Huhn et al., 2019).

Aripiprazole (a D2 and 5-HT1A receptor partial agonist and 5-HT2A receptor antagonist) and risperidone (a D2, 5-HT2, and NE alpha-2 receptor antagonist) are 2 of the most widely used SGAs (Toto et al., 2019; Taipale et al., 2020). As a result, head-to-head comparisons of tolerability, particularly in terms of metabolic profiles, are timely but currently scarce (Kishimoto et al., 2019). Moreover, literature on this topic showed contradictory results when comparing aripiprazole and risperidone metabolic profiles. A recent meta-analysis of patients with chronic schizophrenia found significant differences in weight gain between aripiprazole and risperidone, with the former being more effective (Huhn et al., 2019). Previous research on FEP patients found that aripiprazole (Vazquez-Bourgon et al., 2018) and risperidone (Perez-Iglesias et al., 2009) had metabolic profiles similar to other SGAs such as olanzapine or quetiapine. Similarly, a recent pooled analysis in FEP patients that included 6 different SGAs (haloperidol, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) and focused on treatment

effectiveness found that aripiprazole and risperidone demonstrated clear advantages in effectiveness without demonstrating significant differences in weight gain after long-term follow-up (Gomez-Revuelta et al., 2020). Another recent study carrying head-to-head comparison of aripiprazole and risperidone in the acute-phase treatment of FEP patients (6 weeks after FEP diagnosis) showed no significant differences in weight gain between treatment groups (Gomez-Revuelta et al., 2021). Furthermore, Josiassen et al. (2010) demonstrated that after 8 weeks of treatment, FEP patients receiving aripiprazole gained similar weight to those receiving risperidone (7% vs 7.3% from baseline body weight).

Nonetheless, a longer timeframe may be required to properly observe clinically relevant changes in weight and metabolic parameters. Long-term studies on FEP patients show that the majority of this weight gain occurs within the first year of FEP diagnosis, indicating that this is the critical period for these side effects (Bioque et al., 2018; Vázquez-Bourgon et al., 2021).

As a result, the first aim of this study was to elucidate whether aripiprazole and risperidone may have distinct tolerability profiles in medication-naïve FEP patients in the first year of treatment.

Our main hypothesis was that based on the previous research, aripiprazole and risperidone would present with similar metabolic profiles. Second, we hypothesized that after the first year of antipsychotic treatment, FEP drug-naïve patients would have a significant increase in weight and metabolic measures.

## MATERIALS AND METHODS

The study was carried out in an early-psychosis intervention program in northern Spain (Programa Asistencial de las Fases Iniciales de Psicosis [PAFIP] program); this is a clinical and research program aimed at providing intensive and specialized treatment to people in Cantabria who have experienced their first episode of non-affective psychosis (Pelayo-Terán et al., 2008). Furthermore, the study formed part of a pragmatic clinical trial to compare the effectiveness of aripiprazole and risperidone in a sample of drug-naïve FEP patients (NCT02532491) (Son et al., 2021). The PAFIP program involves clinical and research activity at the outpatient and inpatient psychiatric units of the University Hospital Marqués de Valdecilla (Santander, Spain).

The hospital serves as a reference center for a 580000-person catchment area and houses the province's only psychiatric acute inpatient unit as well as a 24-hour emergency care service. Regular meetings with all community mental health teams in Cantabria were maintained in an attempt to reach all persons suffering from FEP in Cantabria to provide them with adequate specialized treatment.

## Participants

The sample for the present study was recruited between February 2011 and October 2018. These patients were referred to the PAFIP program when presenting a FEP and were admitted if they fulfilled the following criteria: (1) aged 15–60 years; (2) met the DSM-IV criteria (according to the Structured Clinical Interview for DSM-IV) 6 months after inclusion for a principal diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, brief reactive psychosis, or psychosis non-otherwise specified; (3) habitually living in the catchment area; (4) no prior treatment with antipsychotic medication; and (5) current psychotic symptoms of at least moderate severity, as assessed by 1 of the 5 items of the Scale for the Assessment of Positive Symptoms (SAPS). Patients were not admitted to the program if they had any of the following conditions: (1) intellectual disability, (2) a neurological disorder, or (3) a drug dependence (DSM-IV criteria). Prior to their inclusion in the study, all participants provided written informed consent, which was approved by the regional ethics committee (Clinical Research Ethics Committee of Cantabria).

## Study Design

Patients entering the clinical trial (NCT02532491) were randomly assigned to treatment with aripiprazole (D2 and 5-HT<sub>1A</sub> receptor partial agonist, and 5-HT<sub>2A</sub> receptor antagonist) or risperidone (D2, 5-HT<sub>2</sub>, and NE alpha-2 receptor antagonist). A statistician created a computer-generated randomization list. The treatment dose ranges for aripiprazole were 5–30 mg/d and 1–6 mg/d for risperidone. Doses could be adjusted within the prescribed range as clinically indicated to target the lowest effective dose. Certain concomitant medications, such as lorazepam and clonazepam (benzodiazepine receptor agonists, non-selective GABA-A receptor-positive allosteric modulators), were permitted for the management of agitation, general behavior disturbances, and/or insomnia. Only if clinically significant extrapyramidal symptoms occurred was anticholinergic medication (biperiden, at a dose of up to 8 mg/d) permitted. If clinically necessary, antidepressants (sertraline, a SERT reuptake inhibitor) and mood stabilizers (lithium; enzyme interactions) were also permitted. Those patients who did not respond after 6 weeks of treatment [ $<30\%$  total improvement measured by SAPS (Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) scales] or who experienced significant side effects, measured by the Udvalg für Kliniske Undersogelser (UKU) scale (Lingjaerde et al., 1987), were switched to a different antipsychotic. Patients were clinically evaluated by a senior psychiatrist at baseline and at the following time-points after initiating the treatment: 6 weeks, 12 weeks, and 1 year.

The NCT02532491 is a clinical trial aimed to evaluate and compare the effectiveness of aripiprazole and risperidone in FEP patients at long term (1 year). The clinical trial outcomes were discontinuation rates, changes in psychopathological (e.g., Brief Psychiatric Rating Scale, SAPS, and SANS) and side effects (e.g., UKU, Barnes Akathisia Scale) scales, and relapse and remission

rates. Taking advantage of the clinical trial implementation and the systematic measure of anthropometric and metabolic parameters carried out in the patients included in the PAFIP program, we were able to set the following outcomes for the present exploratory analyses associated with the clinical trial. The primary outcome measures for the current study were changes in weight and body mass index (BMI), and the secondary outcomes were changes in metabolic (lipid and glyceemic) parameters from baseline to 1 year after starting antipsychotic treatment.

## Laboratory Analysis

All determinations were performed in our hospital, including both biochemical and endocrinology analysis. All measurements were obtained after an overnight fast. Patients and family members reported on their fasting state as well as treatment adherence. Glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using automated methods on a TechniconDax (Technicon Instruments Corp, Tarrytown, NY, USA), with reagents provided by Boehringer-Mannheim (Mannheim, Germany). Low-density lipoprotein cholesterol was determined by the Friedewald et al. calculation (Friedewald et al., 1972):

$$\text{Low-density lipoprotein} = \text{total cholesterol} - (\text{HDL} + [\text{triglycerides}/5])$$

Insulin levels were determined using an immunoradiometric assay (Immunotech, Beckman Coulter Company, Prague, Czech Republic) with a 3.3% average interassay coefficient of variation and a 2.8% intraassay coefficient of variation. The sensitivity of the method was 0.5  $\mu\text{U}/\text{mL}$ . Values for normal-weight participants were 2–17  $\mu\text{U}/\text{mL}$ . This assay does not show any cross-reactivity with human proinsulin and C-peptide. Homeostasis model assessment (HOMA) was used to assess insulin resistance (IR). The HOMA index was calculated using a previously described formula (Matthews et al., 1985):

$$\text{HOMA} = [\text{fasting insulin } (\mu\text{U}/\text{mL}) \times \text{fasting glucose } (\text{mmol}/\text{L})] / 22.5$$

Furthermore, as proposed by McLaughlin and colleagues (McLaughlin et al., 2005), we calculated the triglyceride to HDL cholesterol ratio as a predictor of IR using the optimal cutpoint of 3.5.

## Statistical Analysis

We investigated the relationship between antipsychotic treatment and changes in metabolic parameters. For comparison between groups, an analysis of variance for continuous variables and a chi-square test for categorical variables were used first. A paired *t* test was used to determine if there were any statistically significant changes in glyceemic and lipid parameters after 1 year of antipsychotic treatment. When exploring differences in longitudinal changes between antipsychotic groups, we compared mean differences resulting from 1-year data minus baseline data.

General linear model ANCOVA analyses were performed to explore longitudinal differences in weight and metabolic parameters between antipsychotic treatment groups. Measurements of each parameter at baseline, 3 months, and 1 year were entered as the dependent variable; the type of medication (treatment group) as the independent variable; and BMI at baseline, gender, and age as covariates. This analysis was carried out following an Intention-to-treat (ITT) approach (per protocol analysis was also performed). We additionally calculated the percentage of participants with pathologic values in weight and glucose and lipid

parameters (according to the reference values of our laboratory) at baseline and 1 year. To evaluate significant changes in these percentages, we used the McNemar test for repeated measures.

Finally, we conducted post-hoc analysis to explore a possible differentiated effect of antipsychotic treatment regarding gender. We used ANCOVA analyses to accomplish this.

For statistical analyses, the Statistical Package for Social Science version 23.0 (IBM Corp, Armonk, NY, USA) was used. All statistical tests were 2-tailed, and significance was set at .05.

## RESULTS

### Enrollment and Characteristics of Study Population

A total of 299 patients were screened and offered to enter the clinical/research program between February 2011 and October

2018. A total of 28 of these individuals were excluded because they did not meet the inclusion criteria or refused to be treated in the program. Another 41 patients were excluded from the statistical analyses for the current study solely because they were not drug free (having been on antipsychotic treatment for >2 days before entering the program). A total of 230 patients were included in the study; they had been randomized to receive (Fig. 1) aripiprazole (n=114; 49.6%) or risperidone (n=116; 50.4%). We had a 17.9% dropout rate at 1 year (41 patients were lost to follow-up or refused to be evaluated: 23 on the aripiprazole arm and 18 on the risperidone one). As a result, 189 patients entered the current study to assess the long-term changes in the main metabolic values. To avoid data distortion, 9 participants with outlier values for at least 1 of the glycemic/lipid parameters at baseline (value >3 SDs) were excluded from the analysis (4 of these patients were on aripiprazole and 5 on

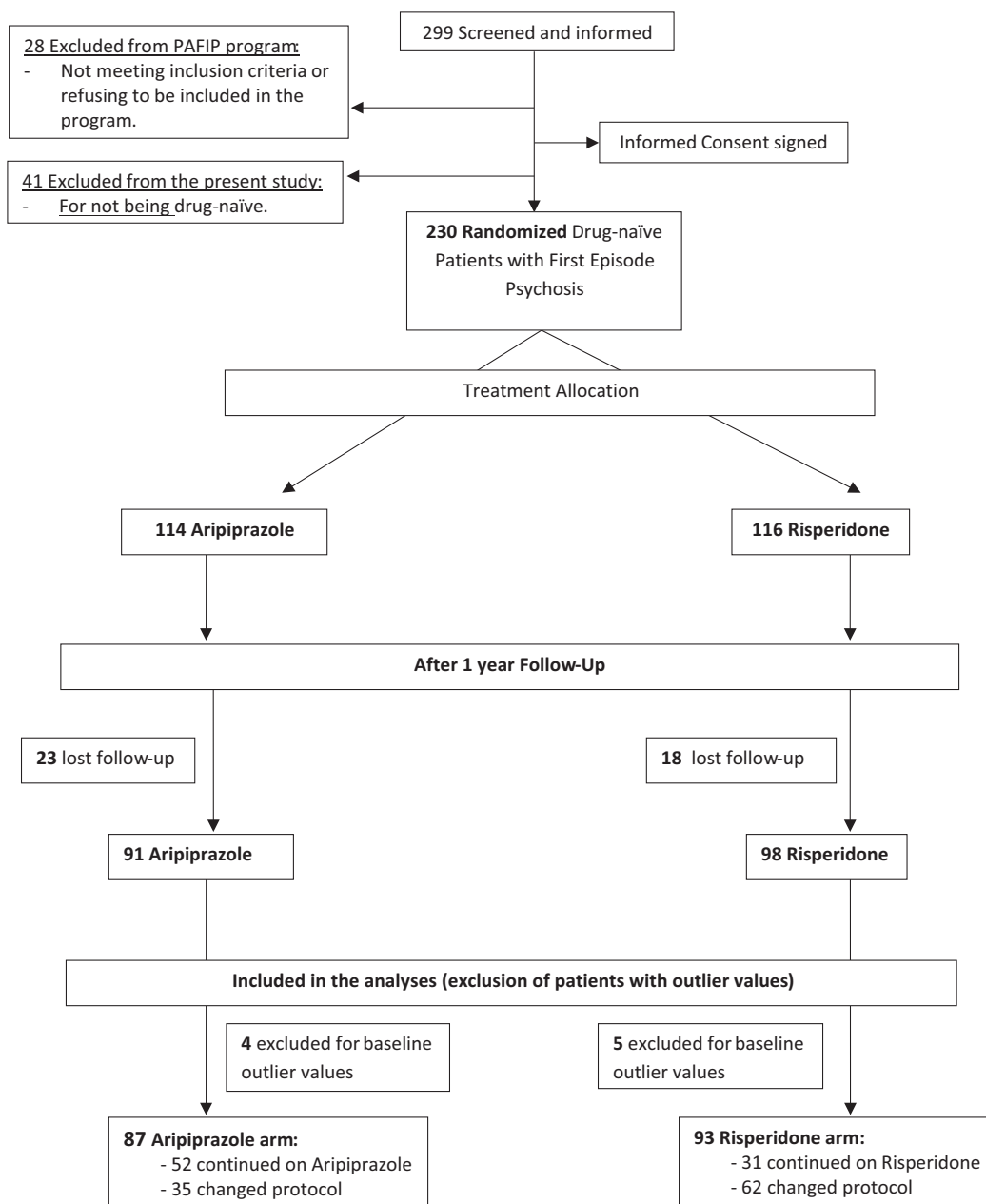


Figure 1. Participant flow in the randomized clinical trial.

risperidone). Post-hoc statistical analyses that included the outlier participants revealed that their exclusion did not affect the reported results.

The clinical and socio-demographic characteristics of the sample are shown in Table 1. The 2 treatment groups were comparable on a wide range of baseline data, including age, ethnicity, substance use, and clinical severity.

At the end of follow-up, 46.1% (n=83) of the 180 patients evaluated continued with the same antipsychotic treatment assigned at baseline (59.8% of aripiprazole group vs 33.3% of risperidone group). After 1 year of treatment, 97 patients did not complete the treatment protocol (supplementary Material, Tables 1, 2, 3A, 3B). The reasons for the treatment switch included side effects (41.2%), inefficacy (38.1%), non-adherence (16.5%), and others (4.1%). Despite the high rate of treatment switches due to side effects, neither weight gain nor metabolic disorders

were among the reasons for antipsychotic change. Detailed data on the reasons for the antipsychotic switch in both treatment groups, as well as data on which treatments were prescribed to those patients who discontinued the initial treatment protocol, are available (supplementary Table 1).

Mean daily baseline doses (after initial titration) were 9.1 mg (SD=2.5) for aripiprazole and 2.0 mg (SD=.4) for risperidone. At the 1-year follow-up (per protocol), mean daily doses were 8.3 mg (SD=3.9) for aripiprazole and 2.3 mg (SD=1.3) for risperidone. Mean antipsychotic doses using chlorpromazine equivalents (Gardner et al., 2010) (where 600 mg chlorpromazine is equivalent to 30 mg aripiprazole or 6 mg risperidone) at baseline were 181.6 mg (SD=49.5) aripiprazole and 203.2 mg (SD=40.2) risperidone ( $P < .001$ ); at 1-year follow-up (intention-to-treat [ITT]), doses were 243.4 mg (SD=133.0) in the aripiprazole group and 287.3 mg (SD=200.9) in the risperidone group ( $P > .05$ ).

Table 1. Socio-Demographic and Clinical Characteristics of Study Population

Patients' characteristics	Aripiprazole (n=87)		Risperidone (n=93)		Total (n=180)	
	Mean	SD	Mean	SD	Mean	SD
Age at inclusion, y	32.01	10.69	32.50	10.21	32.26	10.42
DUP, mo	10.60	25.70	15.01	42.93	12.91	35.74
Weight at inclusion, kg	65.24	14.13	63.72	15.66	64.46	14.91
BMI at inclusion, kg/m <sup>2</sup>	22.43	3.76	22.47	4.44	22.45	4.12
SAPS at inclusion	15.03	5.00	15.85	5.23	15.46	5.12
SANS at inclusion	5.81	6.23	4.78	5.46	5.28	5.85
	n	%	n	%	n	%
Sex, male	49	56.32	49	52.69	98	54.44
Student	23	27.06	19	20.65	42	23.73
Education level, secondary or lower	43	51.19	39	42.39	82	46.59
Family socioeconomic status, low	42	50.60	55	61.11	97	56.07
Living with family	67	79.76	66	71.74	133	75.57
Single	63	74.12	59	64.13	122	68.93
Unemployed	33	39.29	35	38.46	68	38.86
Obesity at inclusion	3	3.45	7	7.61	10	5.59
Diagnosis, schizophrenia	41	47.13	36	38.71	77	42.78
Hospitalization at inclusion	68	78.16	74	79.57	142	78.89
Drug consumption						
Tobacco	38	45.78	46	51.69	84	48.84
Cannabis	34	39.08	36	38.71	70	38.89
Alcohol	27	31.76	32	35.96	59	33.91
Concomitant treatments						
Anticholinergics 3 mo	26	32.10	26	28.57	52	30.23
Anticholinergics 6 mo	13	16.46	14	16.09	27	16.27
Anticholinergics 1 y	9	11.11	12	13.48	21	12.35
Antidepressants 3 mo	10	12.35	19	20.88	29	16.86
Antidepressants 6 mo	19	24.05	28	31.82	47	28.14
Antidepressants 1 y	21	25.30	26	29.21	47	27.33
Benzodiazepines 3 mo	19	23.46	29	31.87	48	27.91
Benzodiazepines 6 mo	14	17.72	23	26.14	37	22.16
Benzodiazepines 1 y	15	18.07	19	21.35	34	19.77
Mood stabilizers 3 mo	3	3.70	4	4.40	7	4.07
Mood stabilizers 6 mo	2	2.53	5	5.68	7	4.19
Mood stabilizers 1 y	2	2.41	4	4.49	6	3.49
Hypnotics 3 mo	20	24.69	20	21.98	40	23.26
Hypnotics 6 mo	14	17.72	8	9.09	22	13.17
Hypnotics 1 y	12	14.46	14	15.73	26	15.12

Abbreviations: BMI, body mass index (obesity defined as BMI  $\geq 30$  kg/m<sup>2</sup>); DUP, duration of untreated psychosis; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

Statistical analyses: Un-adjusted ANOVA for continuous variables and chi-square test for categorical variables. Non-significant group differences, all  $P > .05$ .

## Weight and Metabolic Changes After the First Year of Antipsychotic Therapy

Results from paired *t* tests in the whole FEP sample showed significant changes in weight as well as glycemic and lipid parameters after 1 year of antipsychotic treatment (Table 2). Thus, FEP patients had a significant increase in weight and BMI ( $t=16.49$ ,  $P<.001$  and  $t=16.62$ ,  $P<.001$ , respectively), with a mean increase of 9.9 kg in the first year after starting antipsychotic treatment, reflected in a 3.5-point increase in BMI.

These changes were also observed when we separately examined both treatment groups and also maintained statistical significance in most of the parameters (Table 2). For example, in the first year of treatment, patients in the aripiprazole and risperidone groups gained 9.2 kg and 10.5 kg, respectively ( $t=11.19$ ,  $P<.001$  and  $t=12.12$ ,  $P<.001$ , respectively), increasing their mean BMI by 3.2 and 3.7 points.

## Comparison Between Treatment Groups on Weight and Metabolic Longitudinal Changes During the First Year of Antipsychotic Therapy

Through general linear model ANCOVA tests, we explored whether there were significant differences between

treatment groups in longitudinal changes in weight and metabolic parameters.

These tests revealed no significant differences (all  $P>.05$ ) in any of the weight and metabolic measures compared between treatment groups (aripiprazole vs risperidone) (Table 3). Following per protocol analysis approach, no significant differences were observed between treatment groups (supplementary Material 2; supplementary Table 2).

Both treatment groups followed comparable trajectories of weight and BMI gain throughout the first year of antipsychotic treatment (Fig. 2).

## Clinical Impact of Weight and Metabolic Changes

Similarly, after the first year of antipsychotic treatment, McNemar tests revealed a significant increase in the percentage of FEP patients meeting clinical criteria for obesity and metabolic disorders (Table 4). For example, after comparing the rate of patients with pathological levels before and 1 year after initiating antipsychotic treatment, we found a significant increase in the percentage of patients with MetS (2.8% vs 9.4%,  $P=.010$ ), obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) (5.6% vs 15.3%;  $P<.001$ ), hypercholesterolemia (cholesterol  $>200$  mg/dL) (14.5% vs 35.3%;  $P<.001$ ), and hypertriglyceridemia (triglycerides  $>150$  mg/dL) (3.4% vs 18.2%;

**Table 2.** Changes in Weight and in Glycemic and Lipid Parameters After 1 Year of Antipsychotic Treatment in a Population of Drug-Naïve Patients

Weight and metabolic parameters	1-Year follow-up		Baseline		Change	n	t	P
	Mean	SD	Mean	SD				
Anthropometric parameters								
Weight, kg	74.22	16.49	64.35	14.95	9.873	177	16.487	<.001
Aripiprazole	74.38	14.83	65.17	14.20	9.208	86	11.193	<.001
Risperidone	74.07	18.00	63.57	15.68	10.502	91	12.118	<.001
BMI, kg/m <sup>2</sup>	25.90	4.67	22.44	4.14	3.463	177	16.618	<.001
Aripiprazole	25.60	4.02	22.42	3.78	3.189	86	11.378	<.001
Risperidone	26.18	5.22	22.46	4.47	3.721	91	12.170	<.001
Glycemic parameters (fasting)								
Glucose, mg/dL	89.17	11.66	84.11	9.27	5.057	175	5.347	<.001
Aripiprazole	88.21	11.97	85.27	8.84	2.941	85	2.182	.032
Risperidone	90.08	11.36	83.02	9.59	7.056	90	5.430	<.001
Insulin, $\mu$ U/mL	11.40	9.15	9.35	9.28	2.049	174	2.362	.019
Aripiprazole	10.30	4.94	9.06	7.06	1.236	85	1.551	.125
Risperidone	12.45	11.80	9.63	11.02	2.825	89	1.863	.066
HOMA index	2.61	2.71	2.02	2.16	0.590	173	2.509	.013
Aripiprazole	2.24	1.13	1.96	1.62	0.277	85	1.480	.143
Risperidone	2.96	3.61	2.06	2.58	0.892	88	2.102	.038
Triglyceride/HDL index	2.46	1.98	1.68	0.94	0.780	143	5.269	<.001
Aripiprazole	2.53	1.84	1.79	0.99	0.740	71	4.067	<.001
Risperidone	2.39	2.11	1.57	0.88	0.821	72	3.501	.001
Lipid parameters (fasting)								
Cholesterol, mg/dL	190.51	41.57	170.10	33.53	20.410	173	7.341	<.001
Aripiprazole	190.81	46.16	167.44	30.86	23.376	85	5.253	<.001
Risperidone	190.23	36.86	172.68	35.92	17.545	88	5.200	<.001
LDL-cholesterol, mg/dL	116.51	35.78	101.06	28.70	15.443	140	6.254	<.001
Aripiprazole	117.71	40.26	100.41	28.80	17.300	70	4.409	<.001
Risperidone	115.30	30.89	101.71	28.79	13.586	70	4.512	<.001
HDL-cholesterol, mg/dL	51.89	13.32	52.33	13.27	-0.441	143	-0.394	.694
Aripiprazole	51.38	13.86	50.92	12.83	0.465	71	0.338	.736
Risperidone	52.39	12.85	53.72	13.64	-1.333	72	-0.758	.451
Triglycerides, mg/dL	111.91	72.20	79.51	32.03	32.399	148	5.976	<.001
Aripiprazole	114.34	66.74	82.34	31.35	32.000	73	4.456	<.001
Risperidone	109.53	77.51	76.75	32.64	32.787	75	4.024	<.001

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein. Statistical analyses: paired *t* test comparison.

Table 3. Comparison of Longitudinal Changes in Weight and Metabolic Parameters Between Treatment Groups

Weight and metabolic parameters	n	Aripiprazole						Risperidone						Total									
		Baseline		3M		1Y		Baseline		3M		1Y		Baseline		3M		1Y					
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
<b>Anthropometric changes</b>																							
Weight, kg	81	64.9	14.1	69.6	14.9	74.2	15.1	87	63.5	15.9	69.1	15.4	74.1	17.9	168	64.2	15.0	69.3	15.1	74.2	16.5	0.050	.824
BMI, kg/m <sup>2</sup>	81	22.5	3.8	24.0	4.0	25.7	4.1	87	22.4	4.5	24.4	4.3	26.2	5.2	168	22.4	4.2	24.2	4.1	25.9	4.7	0.315	.576
<b>Lipid parameters</b>																							
Cholesterol, mg/dL	80	168.5	30.7	187.3	35.0	191.6	47.1	81	171.7	34.4	191.0	35.5	191.7	37.5	161	170.1	32.5	189.2	35.2	191.6	42.4	0.196	.658
Triglycerides, mg/dL	69	83.4	31.8	99.4	41.6	116.3	67.7	70	77.2	33.0	94.5	43.3	111.7	79.7	139	80.3	32.4	97.0	42.4	114.0	73.7	0.294	.588
HDL cholesterol, mg/dL	67	51.0	13.1	52.4	13.1	51.7	14.1	67	53.1	13.1	56.1	15.4	52.6	13.2	134	52.0	13.1	54.3	14.4	52.1	13.6	0.406	.525
LDL cholesterol, mg/dL	66	100.9	29.0	114.3	31.8	118.4	41.3	65	102.1	28.9	114.6	32.5	116.5	31.3	131	101.5	28.8	114.5	32.0	117.5	36.6	0.014	.905
<b>Glycemic parameters</b>																							
Glucose, mg/dL	80	85.3	8.9	86.0	8.7	88.4	12.3	83	82.9	9.9	85.3	8.2	89.8	11.5	163	84.1	9.4	85.6	8.4	89.1	11.8	0.326	.569
HOMA index	79	2.0	1.7	2.2	1.2	2.3	1.2	79	2.1	2.7	2.1	1.3	2.9	3.8	158	2.0	2.2	2.1	1.2	2.6	2.8	1.142	.287
HOMA index men	42	1.9	1.7	2.4	1.4	2.5	1.4	40	2.4	3.4	2.3	1.3	3.1	3.7	82	2.2	2.7	2.4	1.4	2.7	2.8	1.121	.293
HOMA index women	37	2.0	1.7	2.0	0.9	2.0	0.9	39	1.8	1.6	1.8	1.2	2.8	3.9	76	1.9	1.6	1.9	1.1	2.4	2.8	0.170	.681
Triglyceride/HDL index	67	1.8	1.0	2.1	1.2	2.6	1.9	67	1.6	0.9	1.9	1.2	2.4	2.2	134	1.7	1.0	2.0	1.2	2.5	2.0	0.192	.662
Insulin total, $\mu$ U/mL	79	9.0	7.3	10.4	5.1	10.3	5.1	80	9.9	11.6	9.8	5.9	12.4	12.2	159	9.4	9.6	10.1	5.5	11.4	9.4	0.967	.327
Insulin men	42	9.0	8.1	11.1	6.0	11.0	5.9	41	11.4	14.8	10.9	6.4	12.9	11.0	83	10.2	11.9	11.0	6.2	12.0	8.8	1.247	.268
Insulin women	37	9.1	6.3	9.7	3.9	9.5	3.8	39	8.3	6.6	8.7	5.1	11.9	13.5	76	8.7	6.4	9.1	4.5	10.7	10.0	0.029	.865
<b>Hormonal levels</b>																							
Leptin total, ng/mL	77	10.4	12.5	12.8	14.4	14.5	11.6	80	8.9	11.6	13.7	13.6	16.3	14.3	157	9.6	12.0	13.3	14.0	15.4	13.0	0.023	.880
Leptin men	41	7.6	10.3	8.0	8.8	9.5	8.2	41	5.7	6.2	9.1	7.9	12.8	11.4	82	6.6	8.5	8.5	8.3	11.1	10.0	0.447	.506
Leptin women	36	13.6	14.1	18.3	17.5	20.3	12.3	39	12.3	14.7	18.6	16.5	20.0	16.1	75	12.9	14.3	18.5	16.9	20.1	14.3	0.073	.787

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein. Statistical analyses: GLM ANCOVA model, where measures of each parameters at baseline, 3 months, and 1 year were the dependent variable; treatment group the independent variable; and baseline BMI, sex, and age were the covariates.

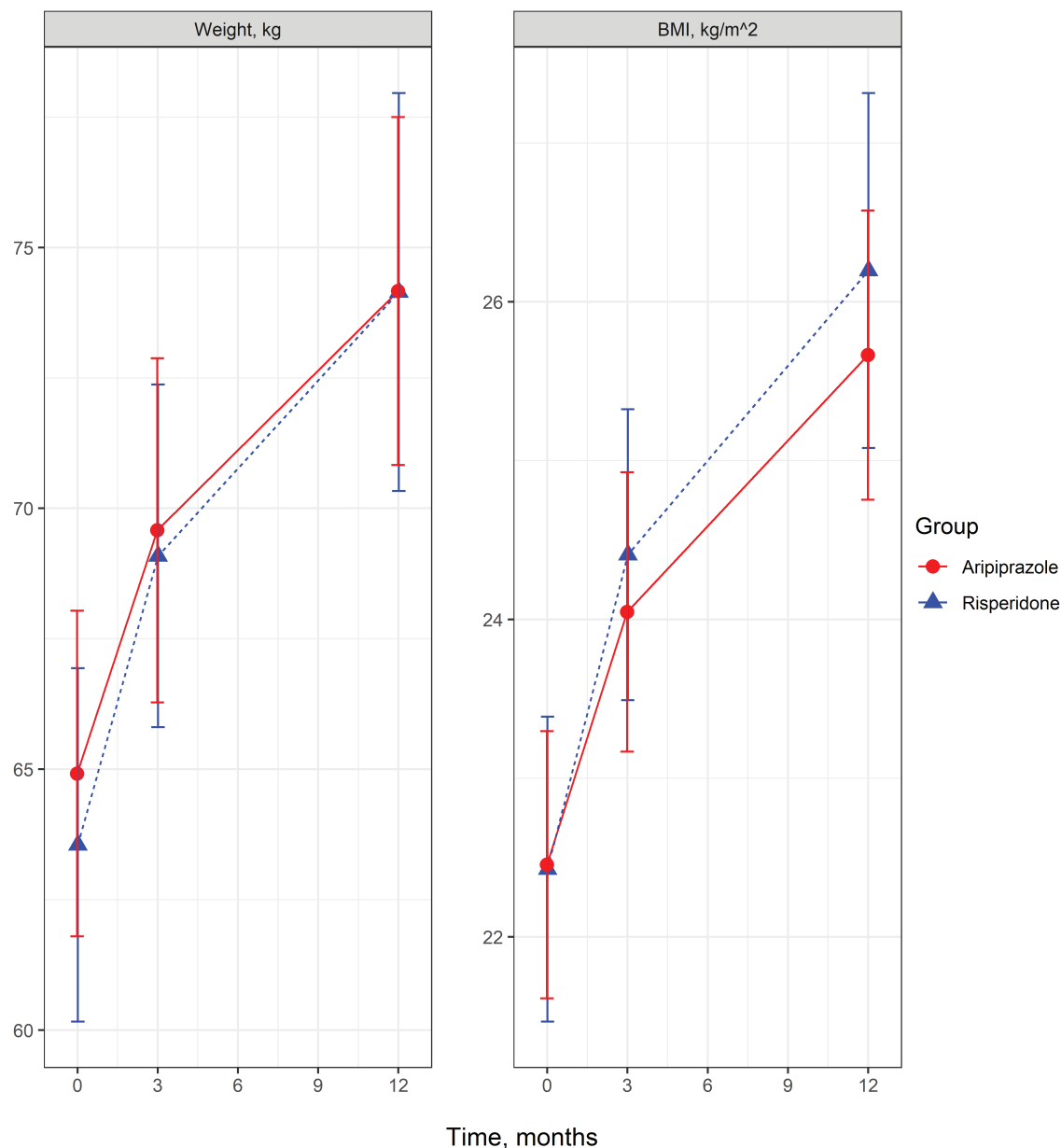


Figure 2. Differences in weight and body mass index (BMI) changes between treatment groups.

$P < .001$ ). Except the triglyceride to HDL IR index (6.3% vs 21%,  $P < .001$ ), we did not find a significant increase in the percentage of patients with pathological criteria for glycemic metabolism measures.

When looking at each treatment group separately, we observed similar results in both groups, with increments after 1 year in the proportion of the participant reaching the criteria for obesity and other metabolic disorders. However, although the increase in the percentage of patients meeting MetS criteria (from 1.1% to 10.3%,  $P = .027$ ) and hypertriglyceridemia (from 1.4% to 23.3%,  $P < .001$ ) was statistically significant in the aripiprazole group, it was not statistically significant in the risperidone group (MetS: from 4.3% to 8.6%,  $P = .289$ ; hypertriglyceridemia: from 5.3% to 13.3%,  $P = .149$ ).

### Post-Hoc Analyses Exploring Sex-Treatment Interaction on Metabolic and Weight Changes

Secondary analysis carried out dividing the sample according to sex did not find sex-treatment interaction in weight/BMI or metabolic changes after 1 year of treatment. Complete data are available as supplementary material ([supplementary material 3](#); [supplementary Tables 3A and 3B](#)).

### Discussion

We discovered that aripiprazole and risperidone have a similar long-term metabolic profile in FEP patients, resulting in a comparable increase in weight gain and an analogous incidence of metabolic alterations after a long-term follow-up.



**Table 4.** Comparison of Proportion of Participants With Pathologic Parameters in Weight, Fasting Glucose, and Lipid Levels at Baseline and at 1-Year Follow-up in Each Treatment Group

Metabolic conditions	1-Year follow-up	Baseline	% Difference	n	P <sup>a</sup>
	% (n)	% (n)			
<b>BMI ≥30 kg/m<sup>2</sup></b>					
Aripiprazole group	10.5 (9)	3.5 (3)	10.0	86	.041
Risperidone group	19.8 (18)	7.7 (7)	12.1	91	.003
Total	15.3 (27)	5.6 (10)	9.6	177	<.001
<b>Metabolic syndrome</b>					
Aripiprazole group	10.3(9)	1.1(1)	9.2	87	.027
Risperidone group	8.6(8)	4.3(4)	4.3	93	.289
Total	9.4(17)	2.8(5)	6.7	180	.010
<b>Glucose&gt;110 mg/dL</b>					
Aripiprazole group	2.4 (2)	0	2.3	85	.480
Risperidone group	3.3 (3)	0	3.3	90	.248
Total	2.9 (5)	0	2.9	175	.074
<b>Insulin, μU/mL; men&gt;15.7, women&gt;17.3</b>					
Aripiprazole group	9.4(8)	7.1(6)	2.4	85	.773
Risperidone group	14.6(13)	7.9(7)	6.7	89	.211
Total	12.1(21)	7.5(13)	4.6	174	.186
<b>HOMA; men&gt;3.5, women&gt;3.9</b>					
Aripiprazole group	7.1(6)	5.9(5)	1.2	85	1.000
Risperidone group	12.5(11)	8.0(7)	4.5	88	.423
Total	9.8(17)	6.9(12)	2.9	173	.424
<b>Triglyceride/HDL index&gt;3.5</b>					
Aripiprazole group	22.5 (16)	7.0 (5)	15.5	7	.010
Risperidone group	19.4 (14)	5.6 (4)	13.9	72	.009
Total	21.0 (30)	6.3 (9)	14.7	143	<.001
<b>Cholesterol &gt;200mg/dL</b>					
Aripiprazole group	36.5 (31)	11.8 (10)	24.7	85	<.001
Risperidone group	34.1 (30)	17.0 (15)	17.1	88	.002
Total	35.3 (61)	14.5 (25)	20.8	173	<.001
<b>LDL cholesterol &gt;130mg/dL</b>					
Aripiprazole group	34.3 (24)	14.3 (10)	20.0	70	.002
Risperidone group	28.6 (20)	12.9 (9)	15.7	70	.010
Total	31.4 (44)	13.6 (19)	17.9	140	<.001
<b>HDL cholesterol &lt;40mg/dL</b>					
Aripiprazole group	19.7 (14)	18.3 (13)	1.4	71	1.000
Risperidone group	12.5 (9)	12.5 (9)	0	72	1.000
Total	16.1 (23)	15.4 (22)	0.7	143	1.000
<b>Triglycerides &gt;150mg/dL</b>					
Aripiprazole group	23.3 (17)	1.4 (1)	21.9	73	<.001
Risperidone group	13.3 (10)	5.3 (4)	8.0	75	.149
Total	18.2 (27)	3.4 (5)	14.9	148	<.001

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein.

<sup>a</sup>McNemar test for repeated measures.

### Head-to-Head Comparison Regarding Weight and Metabolic Changes

When we explored the possible differential effect of treatments on weight gain and related metabolic side effects, both through intention-to-treat and per-protocol analysis, we observed no significant differences between aripiprazole and risperidone treatment groups (Tables 2 and 3; supplementary Material 2). The analogous trajectories of weight and BMI gain throughout the first year of treatment demonstrate this similarity in the metabolic impact of both antipsychotic treatments (Fig. 2).

The lack of significant differences between aripiprazole and risperidone metabolic profiles is contrary to previous evidence in multi-episode schizophrenia patients. A recent meta-analysis found significant differences in weight gain between aripiprazole and risperidone, where the latter was associated with a greater

weight gain (Huhn et al., 2019). In this regard, risperidone has been widely described as one of the antipsychotics linked to increased weight gain and metabolic changes, whereas aripiprazole has traditionally been associated with a lower weight gain. Actually, it was even proposed that aripiprazole may be a weight gain-neutral drug (Kane et al., 2002; McEvoy et al., 2007). Furthermore, several studies have shown that switching from certain antipsychotic treatments to aripiprazole improves weight and metabolic parameters (Siskind et al., 2021). In contrast, studies on FEP patients that excluded confounding factors such as chronicity and antipsychotic polypharmacy found similar results to those found in our study. The current study's significant increase in weight and BMI matches previous long-term studies from other FEP samples (Perez-Iglesias et al., 2009; Vazquez-Bourgon et al., 2018). In those studies, FEP patients presented significant increments in body weight and

significant changes in metabolic variables, reaching pathological values. Former long-term follow-up studies conducted by our group on different FEP samples discovered that aripiprazole (Vazquez-Bourgon et al., 2018) and risperidone (Perez-Iglesias et al., 2009) had metabolic profiles similar to other SGAs such as olanzapine or quetiapine. Consistent with these findings, a recent pooled analysis comparing the efficacy of 6 different antipsychotics found that aripiprazole and risperidone had clear advantages in terms of efficacy, with no significant differences in weight gain after a 3-year follow-up (Gomez-Revuelta et al., 2020). Furthermore, Mustafa and colleagues (2019) studied predictors of antipsychotic discontinuation in FEP patients and did not find significant differences in weight change among 3 SGAs (olanzapine, risperidone, and aripiprazole) after 1 year of initiating antipsychotic treatment (Mustafa et al., 2019).

In any case, given the high rate of treatment switch in our sample and the differences in protocol discontinuation characteristics between both treatment groups, our findings should be interpreted with caution. For instance, patients initially randomized to risperidone discontinued the protocol more frequently than those randomized to aripiprazole. Those discontinuing aripiprazole, on the other hand, did so sooner and due to poor response, whereas those discontinuing risperidone did so primarily due to side effects and more evenly throughout the 1-year follow-up. Interestingly, in none of the groups was weight gain or other metabolic changes cited as the primary reason for protocol discontinuation. The same number of patients in each group ( $n=20$ ) switched to olanzapine or clozapine, 2 antipsychotics known to produce greater weight gain.

### Head-to-Head Comparison Regarding Clinical Impact

After 1 year of treatment, we observed an increase in the proportion of participants meeting the criteria for obesity in both treatment groups ( $\Delta 12.1\%$  in the risperidone group and  $\Delta 10.0\%$  in the aripiprazole group). Contrary to our results, Cheng and colleagues (2019) reported significant differences in the short term (8 weeks) in FEP patients between aripiprazole and risperidone, with a lower prevalence of patients with clinically significant (i.e.,  $\geq 7\%$ ) weight gain (17% vs 32.5%) in the aripiprazole group compared with the risperidone group (Cheng et al., 2019). According to a recent systematic review and meta-analysis (Barton et al., 2020), although all antipsychotic groups (including aripiprazole and risperidone) significantly increased weight gain, aripiprazole did not cause clinically significant weight gain. Furthermore, the risk of presenting clinically relevant weight gain was higher in risperidone patients than in aripiprazole patients with established schizophrenia (relative risk 3.64 vs 1.86) (Huhn et al., 2019).

Our results revealed some differences concerning the metabolic clinical impact between treatment groups. The aripiprazole group showed a greater increase in the proportion of participants with MetS ( $\Delta 9.2\%$ ,  $P=.027$ ), whereas this increment in the risperidone group ( $\Delta 4.3\%$ ,  $P>.05$ ) did not reach statistical significance. Equally, the increments in the proportion of patients with hypertriglyceridemia were statistically significant in the aripiprazole group ( $\Delta 21.9\%$ ,  $P<.001$ ), but not in the risperidone group ( $\Delta 8.0\%$ ,  $P<.05$ ). A previous study of 151 FEP patients discovered that the prevalence of MetS was comparable between the aripiprazole and risperidone groups (18.2% vs 23.5%) (Ventriglio et al., 2018). However, recent research on established schizophrenia found that risperidone was associated

with a higher risk of MetS than aripiprazole (odds ratio=2.21 and 1.74, respectively) (Zhang et al., 2020).

### Head-to-Head Comparison in Other Populations

Our results are consistent with studies comparing risperidone and aripiprazole in other patient populations. The use of antipsychotics in the treatment of other disorders and populations, such as children and adolescents with behavioral disorder or autism, has allowed researchers to compare their metabolic impact on these populations. A recent large-scale systematic meta-review showed that both treatments presented an increased risk for weight gain in children and adolescents (Solmi et al., 2020). In this regard, there has been an increase in evidence comparing the effects of these 2 antipsychotics on these populations in recent years (Ishitobi et al., 2013; Wink et al., 2014; Nicol et al., 2018; Schoemakers et al., 2019; Cicala et al., 2020). Head-to-head comparison studies between aripiprazole and risperidone in these populations showed similar results on weight gain and lipid/glycemic parameters, in both the short term (6–12 weeks) (Ishitobi et al., 2013; Nicol et al., 2018) and long-term (1 year) (Wink et al., 2014; Schoemakers et al., 2019; Cicala et al., 2020).

### Strengths and Limitations

The study has several limitations. Firstly, its design, as a pragmatic clinical trial, makes it difficult to control for confounding factors with a possible effect on weight changes. For example, diet and physical activity have a clear impact on weight changes (Erickson et al., 2016; Nyboe et al., 2019) but were not recorded in this study. Secondly, because of the significant percentage of patients who discontinued the protocol treatment during the study period, the results for head-to-head comparisons (ITT approach) should be interpreted with caution. In addition, although the results from the per protocol analyses followed the same direction, the all-cause discontinuation rate was higher for risperidone than for aripiprazole. Thirdly, we conducted multiple (uncorrected) comparisons in this exploratory study, so the results should be interpreted with caution. On the other hand, this study presents several strengths. First, its longitudinal prospective design enables reliable analysis of the changes and progression of weight and metabolic parameters. Second, such a long-term follow-up period (1 year) is uncommon and aids in the detection of metabolic disturbances, which typically take a long time to develop. Third, by limiting the study to drug-naive patients with FEP, we were able to avoid the confounding effect of chronicity and long-term exposure to previous medications (van der Esch et al., 2020). Finally, the results of this study may be highly generalizable due to its pragmatic randomized clinical trial design and high retention rate for a long-term follow-up study, which may reflect real-world clinical practice.

### Conclusions

In this study, we demonstrated that aripiprazole and risperidone caused similar weight changes and had a similar metabolic profile. The study highlights the significant and rapid weight gain associated with both treatments in the first year following the psychosis diagnoses as well as the early metabolic repercussions produced in these young patients. As a result, greater efforts must be made to prevent these weight and metabolic changes from the earliest phases of the psychosis.

## Acknowledgments

This study was conducted as part of the randomized clinical trial “Effectiveness of Second Generation Antipsychotics in First Episode Psychosis Patients: 1-Year Follow-up (PAFIP3\_1Y).” ClinicalTrials.gov Identifier: NCT02532491. The authors thank all Programa Asistencial de las Fases Iniciales de Psicosis (PAFIP) research team and all patients and family members who participated in the study.

This work was supported by the Instituto de Investigación Sanitaria Valdecilla (INT/A20/04, INT/A21/10) and the Instituto de Salud Carlos III (PI020499, PI050427, PI060507). Unrestricted educational and research grants from AstraZeneca, Pfizer, Bristol-Myers Squibb, Janssen Johnson & Johnson, and Lundbeck provided support for PAFIP activities. No pharmaceutical industry or institutional sponsors participated in the study concept and design, data collection, analysis and interpretation of the results, or drafting the manuscript.

## Contributors

B.C.-F. designed the study, wrote the protocol, obtained the financial support, and evaluated the patients. J.M.-v.S. and M.G.-R. evaluated the patients and collected the study variables. V.O.-G. built and maintained the dataset. J.V.-B. managed the literature searches and wrote the first draft of the manuscript. J.V.-B. and V.O.-G. undertook the statistical analyses. B.C.-F., M.G.-R., M.J.-R., and N.G.-T. contributed to the interpretation of the data and critically revised the manuscript. All authors revised and approved the final manuscript.

## Interest Statement

J.V.-B has received funding support from IDIVAL and honoraria for his participation as a consultant and/or speaker at educational events from Janssen, Johnson & Johnson, and Lundbeck. V.O.-G.F., J.M.-v.S., M.G.-R., M.J.-R., and N.G.-T. report no conflicts of interest. B.C.-F. has received unrestricted research funding from ISCIII, MINECO, Gobierno de Cantabria, CIBERSAM, the 7th European Union Framework Program, and Lundbeck. He has also received honoraria for his participation as a consultant and/or speaker at educational events from Janssen, Johnson & Johnson, Lundbeck, and Otsuka Pharmaceuticals.

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