# MC4R methylation and antipsychotic-related metabolic changes in early psychosis: findings from two prospective cohorts

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# MC4R methylation and antipsychotic-related metabolic changes in early psychosis: findings from two prospective cohorts

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ABSTRACT

Metabolic side effects represent a major long-term concern in antipsychotic (AP)-treated early psychosis. We evaluated the weight gain and changes in related metabolic parameters in patients followed up for 12 months. We also explored DNA methylation of four genes associated with weight gain (*ADRA2A, INSIG2, LEP*, *MC4R*). We included patients aged 15–64 years followed in the Ribeirão Preto Early Intervention in Psychosis Program from two different cohorts (Clinical sample, $n = 147$; Epigenetic sample, $n = 59$). DNA methylation was analysed by pyrosequencing only at baseline, after several weeks of AP exposure. In both cohorts, 40% of patients initially received second-generation antipsychotics (SGAs), increasing to over 70% after one year. Clinical sample: At follow-up, patients exhibited significant increases in body mass index ($p < 0.001$), triglycerides ($p < 0.001$), HDL-c ($p = 0.001$) and LDL-c ($p < 0.001$). Patients predominantly on SGAs during the 12 months had almost three times higher chance of weight gain than those using haloperidol. Other factors associated with weight gain included non-white skin colour (OR = 2.6), fewer years of schooling (OR = 2.5) and a weight gain of at least 7% at three months (OR = 3.1). Epigenetic sample: Patients receiving SGA treatment (median = 23.4 weeks) at baseline showed hypermethylation within the *MC4R* promoter region in relation to patients using haloperidol (median = 18.6 weeks). No changes in the baseline methylation of other genes related to weight gain or AP drugs were observed longitudinally. *MC4R* promoter hypermethylation in SGA-treated patients suggests drug-induced metabolic alterations and a potential role of *MC4R* as a biomarker for predicting AP-related metabolic risk.

## 1. Introduction

People with schizophrenia and other psychoses show a greater increase in mortality rates compared to the general population, with a reduction in life expectancy ranging from 15 to 25 years (Hjorthøj et al., 2017; Leite da Roza et al., 2022). These effects are mainly due to increased risk of physical illness, especially metabolic and cardiovascular diseases.

A study analysing 11,000 schizophrenia and other psychoses patients showed that elevated body mass index (BMI) represented one of the greatest cardiovascular risk factors in these patients compared with the general population (Rossom et al., 2022). One of the reasons for the elevated BMI in patients may be a consequence of antipsychotic (AP) treatment, particularly those known as second-generation APs (SGAs). In addition to weight gain, which is most frequently observed with the use of olanzapine and clozapine (Barton et al., 2020; Huhn et al., 2019; Shamshoum et al., 2021), APs can also contribute to worsening cholesterol and triglyceride levels (Bernardo et al., 2021), effects observed in the very first few weeks of treatment (Zhang et al., 2020).

Weight gain and metabolic syndrome are complex, multifactorial

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conditions shaped by diverse risk factors whose prevalence is strongly influenced by the socioeconomic and cultural contexts. Metabolic syndrome is a major contributor to cardiovascular and metabolic morbidity and develops in approximately one-third of individuals with psychosis, nearly doubling the odds compared to the general population (Vancampfort et al., 2015). The diagnosis of metabolic syndrome involves central obesity, increased fasting glucose, hypertriglyceridemia, HDL hypocholesterolemia and hypertension (Lemieux and Després, 2020).

Despite growing evidence of the association between APs and metabolic disturbances, most research has been conducted in high-income countries, with limited data from individuals living in the Global South. Beyond the country's social inequalities, the Brazilian public healthcare system presents a particular regulatory framework that may provide valuable insights into the relationship between AP use and metabolic outcomes. Under the Brazilian Ministry of Health guidelines, first-generation APs (FGAs) – primarily haloperidol – are the recommended first-line treatment for psychosis within the public health system, due to their lower costs and the availability in long-action injectable formulation. Access to SGAs is generally reserved for situations where FGAs prove ineffective or cause side effects. This policy context creates a unique naturalistic setting to examine how different APs treatment pathways influence metabolic health, particularly in low and middle-income countries (LMICs).

A fast-moving area of research involving psychiatric disorders and AP-induced weight gain is epigenetics. One major mechanism of epigenetic modification is DNA methylation, through which environmental triggers may alter the gene expression pattern (silenced or inactive), resulting in behavioural modifications. Changes in DNA methylation can be reversible, offering the chance to control gene expression by environmental factors (Joseph et al., 2018; Pacchierotti and Spanò, 2015). The interaction between DNA methylation and AP treatment is a two-way relationship: not only may these drugs alter methylation patterns and subsequent gene expression, but an individual's unique methylation profile may influence AP efficacy (Reynolds and Fachim, 2016). For these reasons, epigenetic markers can be exploited to predict therapeutically effective strategies, to reduce side effects, and to develop novel pharmacotherapies.

Epigenome-Wide Association Studies (EWAS) have identified methylated genes associated with metabolic effects (Lokmer et al., 2023; Womersley et al., 2022). Womersley et al. (2022) linked early-life stress to methylation changes in stress-response and metabolic genes, while Lokmer et al. (2023) and Dubath et al. (2024) identified treatment-induced methylation shifts in immune, neuronal, and metabolic pathways following AP exposure. Together, these findings highlight genome-wide CpG methylation variation across gene-coding and non-coding regions, underscoring shared epigenetic mechanisms underlying metabolic dysregulation. However, there has been a paucity of research on longitudinal studies (Delacrétaz et al., 2019) investigating the methylation profile of AP-induced weight gain, particularly in early-stage psychosis, or exploring methylation profiles as predictive markers. Identifying these epigenetic markers may contribute to a better understanding of the underlying mechanisms, serving as a predictive tool to identify the individuals at high risk of AP-induced weight gain.

Relevant genes, such as adrenoceptor alpha-2A receptor (*ADRA2*A), insulin-Induced gene 2 (*INSIG2*), leptin (*LEP*), and melanocortin-4 Receptor (*MC4R*) seem to be related to weight gain due to AP treatment (Li et al., 2020; Libowitz and Nurmi, 2021; Zhang et al., 2016). The *ADRA2*A plays an important role in energy expenditure and lipolysis (Garenc et al., 2002); *LEP* can be related to the AP-induced leptin resistance, reflecting in weight gain (Endomba et al., 2020); *INSIG2* has an important role in regulating cholesterol and lipid fatty acid biosynthesis (Dong and Tang, 2010; McPherson and Gauthier, 2004); and *MC4R* is a transmembrane G protein-coupled receptor expressed in hypothalamus and peripheral tissues, representing the most common single-gene effect of human obesity (Hainer et al., 2020).

This study comprised human clinical data collected from two Brazilian cohorts involving patients in the early stages of schizophrenia and other psychosis (early psychosis, EP). Early psychosis typically refers to individuals within the first 2–5 years of illness onset or treatment for a psychotic disorder, rather than exclusively to those experiencing their initial psychotic episode (Breitborde et al., 2009), irrespective of chronological age. Although early intervention programs primarily target adolescents and young adults (Solmi et al., 2021), some guidelines, such as in the UK, have extended eligibility to adults up to 65 years of age (Ferrara et al., 2024).

This study had two main objectives. We initially aimed to identify demographic and clinical predictors of weight gain and metabolic changes of EP patients followed up for 12 months, with emphasis on the time of exposure to haloperidol or SGAs. Second, in a different sample, we investigated the DNA methylation in four genes (*ADRA2A*, *INSIG2*, *LEP* and *MC4R*) related to weight gain to explore their associations with (a) exposure for a few weeks to haloperidol or SGAs; and (b) weight gain in a 12-month follow-up period.

Our primary hypotheses were: (a) weight gain would be associated with longer exposure to SGAs, although not exclusively, as demographic and clinical factors would also contribute to weight gain over the 12-month follow-up; and (b) methylation of metabolic genes might be altered after a few weeks of treatment with APs and would be associated with weight gain at 12 months. By addressing these aims, our findings may help improve understanding of the biological and clinical mechanisms underlying AP related metabolic effects, contributing to better pharmacological treatment adherence, minimizing the risk of adverse effects, and, consequently, improving the quality of life of schizophrenia and other psychoses patients.

## 2. Methods

### 2.1. Context

EP patients were recruited from the Ribeirão Preto Early Intervention Program for Psychosis (Ribeirão Preto-EIP) (Corrêa-Oliveira et al., 2022; Scarabelot et al., 2024), and matched the following inclusion criteria between 01st January 2015 and 31st December 2021 (Clinical sample); and 1st April 2012 to 31st May 2015 (Epigenetic sample): (a) the first contact with any of the mental health services of the catchment area due to psychotic symptoms; (b) aged between 15 and 64 years old; (c) clinical and metabolic data available at the study entry (baseline) and 12 months later. None of the participants included in epigenetic sample were from the sample used in clinical sample.

We included 206 (Clinical sample, $n = 147$; Epigenetic sample, $n = 59$), collectively referred to as the EP patients with diagnosis of schizophrenia spectrum (ICD-10 codes F20, F22, F25, F28, F29), affective disorders with psychotic features (F31.2, F32.3), and psychotic disorders induced by psychoactive substances (F1X.5). Patients with psychotic symptoms due to other medical conditions were excluded. The clinical sample included patients with demographic, clinical, and metabolic data to characterize treatment and metabolic outcomes. The epigenetic sample consisted of patients who provided peripheral blood samples for DNA methylation analysis, allowing the exploration of epigenetic mechanisms underlying clinical and metabolic alterations.

We obtained approval from the local Ethics Committee (Process numbers 5.964.832; 12,606/2012) and all patients signed a consent form.

### 2.2. Clinical assessments

The diagnosis was established by applying the “Structured Clinical Interview for DSM IV-TR axis I disorders”, clinician version - SCID (Del-Ben et al., 2001; First et al., 1997). To ensure the reliability of the data, all the possible sources of information were consulted, i.e., available medical records, patient-referrals from health professionals or

professionals' team, and family members.

*Variables of interest*: Data included patient identification (sex at birth, age, years of schooling, skin colour and marital status); anthropometric measurements [body weight (Kg), height (cm), and BMI (Kg/m$^2$)]; and biochemical results associated with metabolic indices [overnight fasting: blood glucose and fasting lipids such as low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides and total cholesterol]; and pharmacological treatment (type and duration of drugs). This information is among those recorded as routine care in the medical records.

*Exposure to APs*: At the end of the 12-month follow-up, patients were divided into two groups based on their cumulative exposure to haloperidol or SGAs. To determine group allocation, the AP medications prescribed at five follow-up time points (baseline, and three, six, nine and 12 months) were considered. Patients who were prescribed haloperidol on at least three of these occasions were classified as having "exclusive or predominant use of haloperidol". Conversely, patients who received risperidone, olanzapine, quetiapine, or clozapine on at least three occasions were classified as having "exclusive or predominant use of SGAs".

*Weight gain in the follow-up*: To characterize the weight gain at the end of the 12-month follow-up, we adopted the criterion of a 7% increase from baseline weight, as previously proposed (Bak et al., 2014). Additionally, an intermediate criterion of a 7% weight increase at three months was used, given the well-established evidence that weight gain tends to occur early during pharmacological treatment (Zhang et al., 2020).

### 2.3. Epigenetics

Biological data (epigenetic analysis) were measured only at baseline using DNA stored in a biobank approved by the local ethics committee (12606/2012).

For DNA methylation, we considered the genes identified by the review of Li et al. (2020), combined with the findings of a systematic review (Libowitz and Nurmi, 2021) providing evidence for significant and consistent individual response variability to AP-related weight gain. We selected four genes, namely *ADRA2A*, *INSIG2*, *LEP* and *MC4R*.

We collected 5 mL of peripheral blood using disposable tubes containing EDTA. Following the manufacturer's instructions, the genomic DNA was extracted from all human peripheral blood according to standard protocols (AllPrep DNA/RNA Mini Kit, Qiagen, CA/USA) and was stored at −20 °C.

We modified the DNA with bisulfite treatment to convert unmethylated cytosine residues to uracil using the EpiTect Fast DNA Bisulfite Conversion Kit (Qiagen, CA/USA) with a calculated mean conversion of 99%. Afterwards, the PCR reactions were carried out with bisulfite-converted DNA using the PyroMark PCR Kit. DNA sequences for each gene were identified in the 5′ region that contains transcription factor binding sequences identified using Allgen-Promo specific for humans (https://alggen.lsi.upc.es/cgi-bin/promo_v3/promo/promoinit.cgi?dirDB=TF_8.3).

Primers for amplification and sequencing were designed using the Qiagen Pyromark Q48.exe (Supplemental Material, Table S1). A pyrosequencing method was developed for the determination of methylation at the CpG sites within sequences of interest. Methylation status in the promoter sequence of the target genes was determined with a PyroMark Q48 pyrosequencer (Qiagen, UK) using the PCR product and a sequencing primer. We used the Pyrosequencer, considered a gold standard method to evaluate DNA methylation.

### 2.4. Statistical analysis

Statistical analyses were conducted using the program *Statistical Package for Social Sciences* version 27.0 (SPSS) (IBM Corp: Armonk, NY, USA) and R studio. Data were checked for normality using the Kolmogorov-Smirnov test.

#### 2.4.1. Sociodemographic and clinical variables

Sociodemographic, clinical and metabolic data were submitted to descriptive statistical analysis to compare differences between EP patients receiving haloperidol or SGAs treatment at baseline and in the 12-month follow-up; categorical variables were evaluated using the Chi Square or Fisher's exact tests (frequencies), and continuous variables were analysed using *t*-tests (mean ± SD or mean ± SEM) or Mann-Whitney *U* tests (median).

For follow-up analyses, General Linear Models (GLM) Repeated Measures were performed to compare the mean change from baseline to each specified post-baseline time point in the metabolic parameters (i.e., BMI, glucose, and fasting lipids) measures between and within AP.

Binary logistic regression models were used to identify possible predictors of weight gain (<7% or ≥ 7%) in the 12-month follow-up (Crude Model). For the multivariate analysis (adjusted model), we considered all variables statistically significant in the crude model and adjusted for sex at birth and baseline BMI. We considered alpha criterion<0.05 as significant.

#### 2.4.2. Exploring the DNA methylation markers

To test the overall difference between the type of AP (haloperidol vs. SGAs) on the target gene methylation, we used Generalized Linear Model (GzLM), controlling for sex at birth, age of onset of psychosis, skin colour, years of school, baseline BMI, concomitant psychotropic medications (antidepressants or mood stabilizers) and duration of AP treatment until blood collection. For multiple test errors, the Bonferroni's test was used, considering an adjusted *p*-value (0.05/number of DNA methylation at CpG sites) statistically significant.

We also performed GzLM analysis separately for each gene and their correspondent DNA methylation at CpG sites as predictors for weight gain at 12 months follow-up (<7% or ≥ 7%), adjusted for the sex at birth, education level, skin colour, age of onset psychosis, and type of AP treatment at baseline (haloperidol or SGAs), as well as concomitant psychotropic medications.

## 3. Results

### 3.1. Sample characteristics

In the clinical sample, 147 patients (63.3% male) were diagnosed with non-affective psychotic disorders (F20 to F29 and F1X.5). The median DUP was 6.1 (0–257) weeks and the median treatment time at study entry was 3.6 weeks (0–177). Regarding the epigenetic sample ($n$ = 59), 64.4% patients were men, and 44.1% received a non-affective psychosis diagnosis (F20 to F29). The median DUP was 7.0 (0–256) weeks and the median treatment time at study entry was 20.7 weeks (0−112).

In both samples, the mean BMI in the baseline was 24.4 (SD = 5.9) kg/m$^2$, with 17.0% and 13.6% of obese (BMI ≥ 30 kg/m$^2$), respectively, and 26.5% and 23.7% meeting criteria for overweight (BMI ≥ 25, <30 kg/m$^2$). No missing data were observed for any metabolic variables at either baseline or follow-up assessments.

Demographical and clinical features of both samples at study entry, according to the type of AP in use are described in Table 1. At the study entry, 40.1% of EP patients from the clinical sample and 28.8% from the epigenetic sample were using SGAs. In both samples, no significant differences were observed in the clinical demographic variables in relation to the type of AP.

### 3.2. BMI and metabolic markers on the 12-month follow-up

There were significant changes in metabolic parameters over the 12-month follow-up independent of the type of AP. EP patients from the clinical sample showed a significant increase in BMI from baseline (24.6

**Table 1**
Demographic and clinical parameters of EP patients according to AP treatment at baseline.

| | Clinical sample ($n = 147$) | | | | Epigenetic sample ($n = 59$) | | | |
|---|---|---|---|---|---|---|---|---|
| Sociodemographic and clinical variables | Haloperidol ($n = 86$) | SGAs ($n = 61$)[a] | Effect size[1,2,3] | p-value | Haloperidol ($n = 42$) | SGAs ($n = 17$)[b] | Effect size[1,2,3] | p-value |
| Sex at birth (male), n (%)[1] | 52 (60.5) | 41 (67.2) | 0.7 (0.4–1.5) | 0.488 | 27 (64.3) | 11 (64.7) | 1.0 (0.3–3.2) | 1.000 |
| Self-reported ethnicity (non-white), n (%)[1] | 25 (29.1) | 17 (27.9) | 0.9 (0.5–2.0) | 1.000 | 17 (40.5) | 7 (41.2) | 1.0 (0.3–3.2) | 1.000 |
| Marital status (living without partner), n (%)[1] | 68 (79.1) | 53 (86.9) | 0.6 (0.2–1.4) | 0.275 | 30 (71.4) | 12 (70.6) | 1.0 (0.3–3.6) | 1.000 |
| Years of education (≤9), n (%)*[1] | 42 (49.4) | 29 (48.3) | 1.0 (0.5–1.9) | 1.000 | 16 (38.1) | 9 (52.9) | 1.8 (0.6–5.7) | 0.386 |
| Age, mean (SD)[2] | 30.8 (14.1) | 25.8 (12.8) | 0.36 | 0.077 | 30.5 (13.5) | 35.5 (17.5) | 0.34 | 0.235 |
| Age of psychosis, mean (SD)*[2] | 29.9 (13.5) | 25.9 (12.9) | 0.30 | 0.103 | 29.6 (13.2) | 34.7 (17.0) | 0.36 | 0.221 |
| DUP (weeks), median (min-max)[3] | 8.6 (0–257) | 5.9 (0–256) | 0.06 | 0.505 | 5.7 (0–256) | 9.1 (0−223) | 0.06 | 0.627 |
| Duration of psychosis (weeks), median (min-max)[3] | 19.1 (0–261) | 14.0 (0–260) | 0.05 | 0.525 | 44.4 (2−322) | 40.0 (0−310) | 0.004 | 0.973 |
| Pharmacological treatment (weeks), median (min-max)[3] | 3.7 (0–81) | 3.6 (0–177) | 0.005 | 0.146 | 18.6 (0–112) | 23.4 (0–87) | 0.04 | 0.831 |
| Primary diagnosis (non-affective psychosis), n (%)[1] | 86 (100.0) | 61 (100.0) | NA | | 20 (47.6) | 6 (35.3) | 1.7 (0.5–5.3) | 0.563 |
| Metabolic markers | | | | | | | | |
| Baseline body weight (Kg), mean (SD)[2] | 72.4 (18.2) | 68.7 (15.3) | 0.21 | 0.187 | 70.1 (18.2) | 68.0 (17.9) | 0.12 | 0.695 |
| Baseline BMI (kg/m$^2$), mean (SD)[2] | 25.2 (6.5) | 23.8 (4.8) | 0.23 | 0.152 | 24.1 (6.4) | 23.4 (5.3) | 0.11 | 0.669 |
| Overweight (BMI ≥ 25, <30 kg/m$^2$), n (%)[1] | 21 (24.4) | 18 (29.5) | 0.7 (0.2–2.3) | 0.749 | 10 (23.8) | 4 (23.5) | 1.1 (0.2–6.4) | 0.180 |
| Obese (BMI ≥ 30 kg/m$^2$), n (%)[1] | 19 (22.1) | 6 (9.8) | 1.9 (0.5–7.5) | 0.07 | 6 (14.3) | 2 (11.8) | 1.3 (0.2–10.5) | 0.289 |
| Glucose (mg/dl), mean (SD)[2] | 97.8 (23.4) | 92.6 (19.7) | 0.23 | 0.160 | 88.3 (11.4) | 84.0 (5.4) | 0.43 | 0.139 |
| Cholesterol (mmol/L), mean (SD)[2] | 176.0 (42.2) | 164.6 (40.4) | 0.27 | 0.100 | 170.0 (28.2) | 171.2 (38.9) | 0.04 | 0.897 |
| Triglycerides (mmol/L), mean (SD)[2] | 114.6 (62.8) | 101.8 (48.9) | 0.22 | 0.185 | 131.6 (57.8) | 126.1 (64.6) | 0.09 | 0.749 |
| LDL-c (mmol/L), mean (SD)[2] | 103.8 (34.2) | 100.2 (33.0) | 0.11 | 0.523 | 101.4 (24.2) | 101.5 (23.9) | 0.004 | 0.979 |
| HDL-c (mmol/L), mean (SD)[2] | 44.5 (12.1) | 41.9 (9.6) | 0.23 | 0.151 | 40.6 (5.9) | 41.4 (6.1) | 0.13 | 0.630 |

Abbreviations: BMI: Body Mass Index; DUP: Duration of Untreated Psychosis; EP: Early psychosis; HDL: High-Density Lipoprotein Cholesterol; LDL: Low-Density Lipoprotein Cholesterol; SGAs: Second-generation antipsychotics; SD: Standard Deviation; NA: Not Applicable. *Years of education, $n = 2$ missing; *Age of psychosis, n = 4 missing.

[a] SGAs, clinical sample: n = 1 ziprasidone; $n = 2$ aripiprazole; $n = 2$ clozapine; n = 4 quetiapine; $n = 13$ olanzapine; and $n = 39$ risperidone.

[b] SGAs, epigenetic sample: n = 1 aripiprazole; n = 2 quetiapine; $n = 3$ olanzapine; and $n = 11$ risperidone.

[1] Fisher's Exact Test [Effect size: Odds Ratio (OR) 95% CI].

[2] T-test (Effect size: Cohen's d).

[3] Mann-Whitney (Effect size: r). Significant results are depicted in bold ($p < 0.05$).

± 5.9 kg/m$^2$) to 12 months (27.2 ± 6.3 kg/m$^2$, $p < 0.001$) (Fig. 1A). We also found a significant increase in triglycerides, HDL-c and LDL-c ($p = 0.005$; $p = 0.002$ and $p = 0.039$, respectively). No significant differences were observed between other metabolic markers (glucose, $p = 0.079$; cholesterol, $p = 0.055$) (Fig. 1B).

At the end of the 12 months of follow-up, most patients ($n = 101$; 68.7%) of the clinical sample had been exposed exclusively or predominantly to SGAs (Table 2). Patients using SGAs presented higher BMI changes (follow-up − baseline) when compared to those receiving exclusively or predominantly haloperidol during the longitudinal period [mean = 3.1 (SD = 4.1) vs. 1.5 (SD = 4.0); $p = 0.036$]. No significant differences were found in other metabolic variables between EP patients receiving exclusively or predominantly haloperidol versus SGAs treatment during 12-month follow-up (Supplemental Material, Table S2).

### 3.3. Identifying predictive clinical variables for weight gain during follow-up

EP patients who were exclusively or predominantly exposed to SGAs during the 12 months had almost three times (OR = 2.9; 95%CI 1.2–6.9) higher chance of weight gain than those exposed exclusively or predominantly to haloperidol. Other factors identified in the multivariable model as predictors of weight gain after 12 months of follow-up included non-white skin colour [OR = 2.6 (95%CI 1.1–5.8)], fewer years of schooling [OR = 2.5 (95%CI 1.2–5.1)], and weight gain of at least 7% at three months [OR = 3.1 (95%CI 1.4–6.6)]. Following univariate analyses, only variables showing significant associations with weight gain were included in the multivariable logistic regression model, and the associations described here correspond to the adjusted results presented in Table 3.

Multicollinearity was assessed using variance inflation factors (VIFs), and all predictors showed VIF values below 2.0, indicating no evidence of problematic collinearity.

### 3.4. MC4R methylation changes in patients treated with SGAs

EP patients on SGAs treatment for few weeks (median = 23.4 weeks) showed hypermethylation within the *MC4R* promoter at CpG1 ($p = 0.006$) and CpG2 ($p = 0.010$) compared with individuals exposed for a few weeks to haloperidol (median = 18.6 weeks). No significant differences in DNA methylation were observed for the three other genes evaluated [*ADRA2A* (CpG1, $p = 0.283$; CpG2, $p = 0.845$; CpG3, $p = 0.829$; CpG4, $p = 0.728$; CpG5, $p = 0.866$; CpG6, $p = 0.502$), *INSIG2* (CpG1, $p = 0.493$; CpG2, $p = 0.229$; CpG3, $p = 0.699$; CpG4, $p = 0.726$), and *LEP* (CpG1, $p = 0.328$; CpG2, $p = 0.875$; CpG3, $p = 0.171$; CpG4, $p = 0.535$; CpG5, $p = 0.844$; CpG6, $p = 0.993$)] (Figs. 2A-D).

Detailed results for all CpG sites, including non-significant findings and adjusted *p*-values, are provided in Supplementary Table S3.

### 3.5. DNA methylation markers did not predict the percentage of weight gain during follow-up

No significant differences among the groups in relation to weight gain were found in baseline DNA methylation with respect to the CpG sites and the mean of CpGs investigated, even after controlling for demographic variables or interaction between the groups of weight gain (<7% or ≥ 7%) and type of AP treatment at baseline (Table 4).

In the epigenetic sample, 25.4% of patients were prescribed antidepressants with AP use and 39.0% were prescribed concomitant with mood stabilizers (Supplemental Material, Table S4).

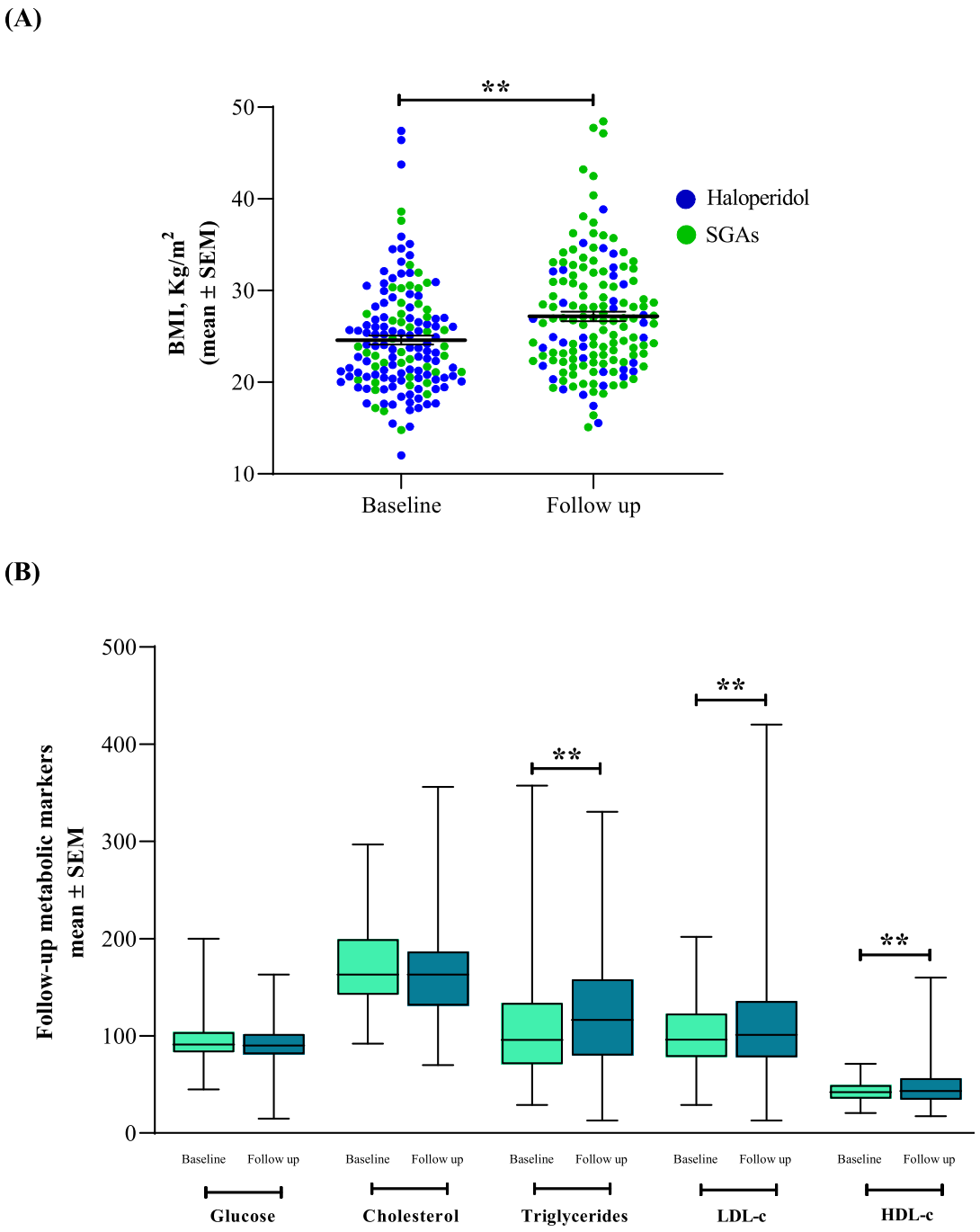


**Fig. 1.** Longitudinal changes of BMI and metabolic markers in EP patients, independent of AP type (clinical sample): (A) EP patients exhibited a significant increase in BMI during follow-up, independent of the AP type (haloperidol or SGAs). Blue circles represent patients receiving haloperidol, and green circles illustrates those treated with SGAs. Data are expressed as mean and dispersion. The black line represents the mean values, and error bars refer to SEM of BMI (SEM, calculated as SD/$\sqrt{n}$). (B) EP patients presented increased triglycerides, HDL-c, and LDL-c on the 12 months follow-up. No significant changes were observed in relation to glucose and total cholesterol. Boxplots illustrate the median, interquartile range, and overall distribution of metabolic marker values over the follow-up period. Analyses were performed using GLM with repeated-measures, comparing mean changes from baseline to 12 months. $^{**}p < 0.001$. Abbreviations: BMI: Body Mass Index; HDL-c: High-Density Lipoprotein cholesterol; LDL-c: Low-Density Lipoprotein cholesterol; SEM: Standard Error Mean; SGAs: Second-generation antipsychotics. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

### *3.6. Associations between baseline MC4R methylation and duration of SGA treatment*

Positive correlations were observed between baseline *MC4R* methylation and the duration of prior SGA treatment, both at individual CpG sites (CpG1: $r = 0.49$, $p = 0.048$; CpG2: $r = 0.53$, $p = 0.028$) and for the mean methylation level across CpGs ($r = 0.54$, $p = 0.024$). No significant correlations were found for FGA treatment or with metabolic variables (Table 5).

## 4. Discussion

### *4.1. Clinical and sociodemographic effects on metabolic changes*

In this cohort, AP treatment was associated with significant changes in metabolic parameters over the 12-month follow-up. At follow-up,

**Table 2**
Differences in clinical variables between EP patients according to AP treatment at 12-months follow-up.

| | Clinical sample (n = 147) | | | Epigenetic sample (n = 59) | | |
|---|---|---|---|---|---|---|
| Sociodemographic and clinical variables | Exclusively or predominantly haloperidol (*n* = 46) | Exclusively or predominantly SGAs[a] (n = 101) | p-value | Exclusively or predominantly haloperidol (n = 17) | Exclusively or predominantly SGAs[b] (n = 42) | p-value |
| Sex at birth (male), n (%)[1] | 30 (65.2) | 63 (62.4) | 0.854 | 12 (70.6) | 26 (61.9) | 0.567 |
| Self-reported ethnicity (non-white), n (%)[1] | 14 (60.4) | 28 (27.7) | 0.844 | 10 (58.8) | 14 (33.3) | 0.086 |
| Marital status (living without partner), n (%)[1] | 35 (76.1) | 86 (85.1) | 0.243 | 12 (70.6) | 30 (71.4) | 1.000 |
| Years of education (≤9), n (%)[1] | 20 (44.4) | 51 (51.0) | 0.479 | 5 (29.4) | 20 (47.6) | 0.252 |
| Age, mean (SD)[2] | 29.2 (12.5) | 27.8 (15.9) | 0.610 | 32.1 (15.6) | 31.8 (14.6) | 0.947 |
| Age of psychosis, mean (SD)[2] | 28.3 (10.8) | 28.2 (14.4) | 0.967 | 31.0 (15.6) | 31.1 (14.2) | 0.994 |
| DUP (weeks), median (min-max)[3] | 6.9 (0–256) | 6.1 (0–257) | 0.511 | 6.4 (0–256) | 7.0 (0–223) | 0.598 |
| Duration of psychosis (weeks), median (min-max)[3] | 16.6 (3–260) | 14.6 (0–261) | 0.537 | 36.1 (4–322) | 47.9 (0–310) | 0.491 |
| Primary diagnosis (non-affective psychosis), n (%)[1] | 46 (100.0) | 101 (100.0) | | 9 (52.9) | 17 (40.5) | 0.403 |
| Metabolic markers | | | | | | |
| Body weight (Kg), mean (SD)[2] | 81.1 (19.0) | 76.8 (18.6) | 0.196 | 79.1 (27.3) | 77.6 (16.9) | 0.803 |
| BMI (kg/m$^2$), mean (SD)[2] | 27.4 (6.9) | 27.1 (6.1) | 0.765 | 27.9 (10.9) | 26.7 (6.0) | 0.608 |
| Glucose (mg/dl), mean (SD)[2] | 91.2 (25.5) | 92.4 (16.6) | 0.787 | 89.5 (9.5) | 92.0 (10.0) | 0.376 |
| Cholesterol (mmol/L), mean (SD)[2] | 165.1 (51.1) | 163.0 (48.9) | 0.807 | 178.8 (26.9) | 186.1 (36.3) | 0.458 |
| Triglycerides (mmol/L), mean (SD)[2] | 137.7 (57.6) | 116.6 (63.7) | 0.057 | 130.6 (49,9) | 145.3 (82.0) | 0.495 |
| LDL-c (mmol/L), mean (SD)[2] | 110.4 (64.7) | 110.1 (41.9) | 0.973 | 107.9 (20,9) | 116.6 (30.8) | 0.290 |
| HDL-c (mmol/L), mean (SD)[2] | 53.9 (27.4) | 48.4 (21.6) | 0.189 | 44.9 (14.5) | 43.1 (11.5) | 0.629 |

Abbreviations: AP: Antipsychotic; BMI: Body Mass Index; DUP: Duration of Untreated Psychosis; EP: Early psychosis; HDL-c: High-Density Lipoprotein Cholesterol; LDL-c: Low-Density Lipoprotein Cholesterol; SGAs: Second-generation antipsychotics; SD: Standard Deviation. *Years of education, n = 2 missing; *Age of psychNosis, n = 4 missing. ** We considered them regarding the use for the longest period during the follow-up.

[a] SGAs, clinical sample: n = 2 aripiprazole; n = 3 ziprasidone; n = 10 clozapine; *n* = 16 quetiapine; *n* = 26 olanzapine; and *n* = 44 risperidone.

[b] SGAs, epigenetic sample: n = 1 aripiprazole; n = 6 clozapine; n = 11 quetiapine; *n* = 12 olanzapine; and n = 12 risperidone.

[1] Fisher's Exact Test.

[2] T-test.

[3] Mann-Whitney. Significant results are depicted in bold ($p < 0.05$).

around 60% of patients of both cohorts had gained at least 7% of weight and increased in blood parameters related to lipid metabolism. More specifically, EP patients who were treated exclusively or predominantly with SGAs during the 12-month follow-up had an almost three times as high chance of weight gain than those using haloperidol, a FGA.

Besides the confirmation that SGAs are associated with an increased weight gain risk in psychosis (Rognoni et al., 2021), we showed that sociodemographic factors were also associated with weight gain; particularly, self-reported non-white skin colour – which in Brazil is highly correlated with worse socioeconomic indicators (Brazilian Census 2022, IBGE) – and fewer years of schooling. Similar to our findings, previous evidence has shown that educational attainment is associated with obesity in the general population (Cohen et al., 2013; López-Gil et al., 2024). Additionally, a cohort involving Brazilian women in their 40s revealed that obesity was notably associated with lower socioeconomic background, highlighting the influence of these factors (Damaso et al., 2023). Besides, these social inequalities indicators may have an even greater impact in LMICs reinforcing the contribution of the findings of this study.

We also showed that initial weight gain (first three months) was a strong predictor of weight gain over 12 months. A previous study demonstrated stabilization in the weight gain with the use of APs between six and nine months of treatment, with the greatest proportion of weight gain occurring in the first six months (Mustafa et al., 2019). Taken together, these data reinforce the importance of continuous and intensive monitoring of metabolic parameters and early intervention to prevent weight gain, as recommended in recent guidelines (Fitzgerald et al., 2022; Ostuzzi et al., 2022), emphasizing the importance of comprehensive baseline metabolic screening and individualized AP to minimize metabolic adverse effects (American Diabetes Association et al., 2004; Lopez-Morinigo et al., 2022; NICE's guideline, 2015; Strube et al., 2024).

### 4.2. Epigenetic alterations associated with weight gain

To our knowledge this is the first study reporting changes in DNA methylation of the *MC4R* gene in psychotic patients receiving AP treatment. We found that EP patients under SGAs showed hypermethylation of the *MC4R* promoter region at CpG1 and CpG2 when compared to patients under haloperidol.

The *MC4R* is implicated in the weight gain associated with SGA medications, with some evidence suggesting a role for genetic variants near the *MC4R* locus (Czerwensky et al., 2013; Malhotra et al., 2012). Moreover, the SGAs can induce weight gain through alterations in appetite regulation, potentially involving *MC4R* signalling in the hypothalamus, an essential regulator of food intake (Li et al., 2021).

There are two activator transcriptional regulators with a known role in adipogenesis, lipid metabolism and metabolic pathways binding at CpG1: upstream stimulatory factor (USF1) (Coon et al., 2005; Wu et al., 2009), and E2F transcription factor 2 (E2F2) (Blanchet et al., 2011). CpG2 is a site for a hormone-activated transcription factor named GATA1, which regulates gene expression and also plays a key role in adipogenesis (Lentjes et al., 2016). These factors could bind to exert transcriptional promoter activity, resulting in downregulation of the *MC4R* gene expression.

Given that the majority of patients presented eutrophic BMI and

**Table 3**
Univariate and multivariate regression models for weight gain at 12-months follow-up (clinical sample).

| Sociodemographic and clinical variables[≠] | 12 months follow-up | | Crude | p | Model 1 | p |
|---|---|---|---|---|---|---|
| | <7% (n = 61) | ≥7% (n = 86) | Exp (B)[1] (95% CI) | | Exp (B)[2] (95% CI) | |
| Sex at birth, n (%) | | | | | | |
| Female | 25 (41.0) | 29 (33.7) | 1 | | | |
| Male | 36 (59.0) | 57 (66.3) | 1.3 (0.7–2.6) | 0.391 | | |
| Skin colour, n (%) | | | | | | |
| White | 50 (82.0)[a] | 55 (64.0)[b] | 1 | | 1 | |
| Non-white | 11 (18.0)[a] | 31 (36.0)[b] | **2.5 (1.1–5.3)** | **0.023** | **2.6 (1.1–5.8)** | **0.025** |
| Years of school, n (%)* | | | | | | |
| >9 | 38 (62.3)[a] | 36 (42.9)[b] | 1 | | 1 | |
| ≤9 | 23 (37.7)[a] | 48 (57.1)[b] | **2.2 (1.1–4.3)** | **0.023** | **2.5 (1.2–5.1)** | **0.013** |
| Age of onset psychosis, n (%)* | | | | | | |
| 35 years or more | 18 (30.0) | 14 (16.9) | 1 | | 1 | |
| 25 to 34 years | 14 (23.3) | 19 (22.9) | 2.0 (0.7–5.4) | 0.170 | 1.6 (0.6–4.2) | 0.364 |
| 15 to 24 years | 28 (46.7) | 50 (60.2) | **3.0 (1.3–7.0)** | **0.012** | 1.8 (0.6–5.0) | 0.279 |
| Smoking on baseline. n (%) | | | | | | |
| No | 43 (70.5) | 57 (66.3) | 1 | | | |
| Yes | 18 (29.5) | 29 (33.7) | 1.1 (0.5–2.1) | 0.869 | | |
| DUP, n (%) | | | | | | |
| <49th percentil | 29 (45.3) | 44 (53.0) | 1 | | | |
| ≥50th percentil | 35 (54.7) | 39 (47.0) | 0.7 (0.4–1.4) | 0.449 | | |
| Duration of AP treatment at baseline, n (%) | | | | | | |
| <49th percentil | 32 (50.0) | 39 (47.0) | 1 | | | |
| ≥50th percentil | 32 (50.0) | 44 (53.0) | 1.1 (0.6–2.2) | 0.780 | | |
| Weight gain on 3 months, n (%) | | | | | | |
| <7% | 47 (77.0)[a] | 40 (46.5)[b] | 1 | | 1 | |
| ≥7% | 14 (23.0)[a] | 46 (53.5)[b] | **3.9 (1.9–8.0)** | **<0.001** | **3.1 (1.4–6.6)** | **0.004** |
| Type of AP during follow-up, n (%) | | | | | | |
| Exclusively or predominantly haloperidol | 24 (39.3) | 22 (25.6) | 1 | | 1 | |
| Exclusively or predominantly SGAs | 37 (60.7) | 64 (74.4) | **2.2 (1.1–4.4)** | **0.034** | **2.9 (1.2–6.9)** | **0.017** |
| Other psychotropic medications at baseline, n (%) | | | | | | |
| Exclusively AP | 51 (83.6) | 64 (74.4) | 1 | | | |
| AP and antidepressants[a] | 8 (13.1) | 15 (17.4) | 1.5 (0.6–3.8) | 0.399 | | |
| AP and mood stabilisers[b] | 2 (3.3) | 7 (8.1) | 2.8 (0.6–14.0) | 0.213 | | |

Abbreviations: AP: Antipsychotic; CI: Confidence interval; DUP: Duration of untreated psychosis; Exp(B): Odds ratio; SGAs: Second-generation antipsychotics.
* Years of education, n = 2 missing; *Age of psychosis, n = 4 missing. ≠ Fisher's Exact Test (different subscript letter means significance difference).
[a] Antidepressants: n = 1 bupropion; n = 3 fluoxetine; n = 1 imipramine; n = 1 mirtazapine; and n = 17 sertraline.
[b] Mood stabilizers: n = 1 carbamazepine; n = 1 lithium; and *n* = 7 valproic acid.
[1] Unadjusted: binary logistic regression model including the binary outcome (percentage of weight gain at 12 months, <7% and ≥7%).
[2] Model 1: variables statistically significant in crude model, adjusted for sext at birth and baseline BMI. Significant results are depicted in bold ($p < 0.05$).

metabolic markers within normal limits at baseline, the observed *MC4R* promoter hypermethylation in patients exposed to SGAs is more consistent with an early drug-induced epigenetic modulation rather than a pre-existing metabolic susceptibility. This interpretation aligns with recent epigenome-wide evidence that psychotropic treatment rapidly induces global DNA methylation changes after only one month, even before overt metabolic alterations (Dubath et al., 2024).

Moreover, the lack of methylation changes in other metabolic genes and our gene-specific findings in *MC4R* suggest that early pharmacologically driven methylation may provide pathway-specific epigenetic signatures underlying AP-related metabolic dysregulation. Given that *MC4R* plays a key role in hypothalamic regulation of appetite and energy expenditure, early hypermethylation at this locus may represent an adaptive or compensatory response to AP-induced metabolic stress, potentially contributing to later weight gain and glucose dysregulation observed in treated patients. Thus, in this study, the association of increased methylation of an *MC4R* promoter region with SGA treatment was observed, suggesting the consequences of *MC4R* promoter methylation may account for the weight gain in psychosis patients after receiving AP drugs.

Although the concomitant use of psychotropic medications such as antidepressants or mood stabilizers could theoretically influence DNA methylation (Alladi et al., 2018; Webb et al., 2020) and metabolic outcomes (Bezerra et al., 2023; Correll et al., 2015; Mazereel et al., 2020), our analyses did not reveal any significant associations with these co-medications. Therefore, the observed *MC4R* epigenetic changes and metabolic findings are unlikely to be confounded by the effects of concomitant antidepressant or mood stabilizer use.

Our initial hypotheses regarding the association between DNA methylation of metabolism-related genes, short-term exposure to AP, and weight gain over a 12-month period were not confirmed for other genes, as *ADRA2A*, *INSIG2* and *LEP*. The absence of these significant associations in psychosis patients may be explained by some methodological and clinical factors.

Methodologically, other epigenetic regulators, such as histone modifications or non-coding RNAs, may play a more prominent influence in those occurring in brain regions directly involved in antipsychotic response and metabolic regulation than DNA methylation measured in peripheral blood. Supporting this, Brocos-Mosquera et al., 2021 reported increased histone posttranslational modifications at the *ADRA2A* promoter region in brain tissues of AP-treated schizophrenia patients with upregulation of *ADRA2A* mRNA expression.

One could speculate that our negative finding of *LEP* methylation is related to another CpG island which was not part of our current investigation. A recent study showed altered blood *LEP* methylation in schizophrenia patients when compared to controls, with some CpG sites showing differences in methylation in opposite directions. However, no associations were investigated regarding weight changes or AP treatment (Song et al., 2022).

Clinical and environmental complexity, including gene-environment interactions and differences between patient populations (age, sex, BMI, ethnicity, and other modifiable lifestyles, including smoking), may further contribute to inconsistent findings (Lisoway et al., 2021). Another possible explanation for our negative finding could be that *LEP*

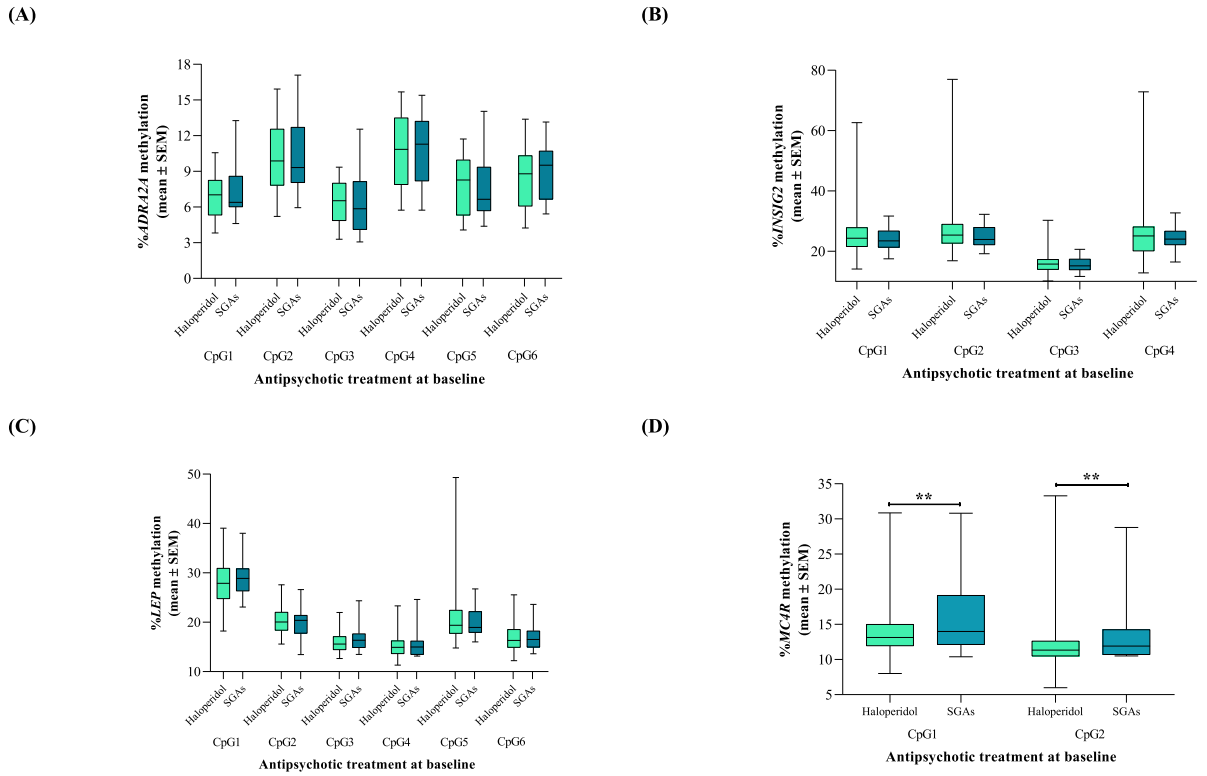


**Fig. 2.** Effect of AP treatment at baseline on DNA methylation markers (epigenetic sample): (A-C) No significant differences were found in three genes methylation (*ADRA2A*, *INSIG2* and *LEP*); (D) EP patients on SGAs treatment at baseline showed hypermethylation within the *MC4R* promoter at CpG1 and CpG2. Boxplots illustrate the median, interquartile range, and variability of each gene methylation and its CpGs regarding the two groups based on the type of AP: haloperidol or SGAs. Data were tested using GzLM, adjusted for sex at birth, age of onset psychosis, skin colour, years of school, duration of AP treatment until blood collection, concomitant other psychotropic medications and BMI baseline. For multiple test errors, the Bonferroni's test was used and considered an adjusted *p*-value (0.05/number of DNA methylation at CpG sites) statistically significant. **p < 0.001. Abbreviations: SEM: Standard Error Mean; SGAs: Second-generation antipsychotics.

**Table 4**
Association of baseline DNA methylation with weight gain on EP patients at 12 months follow-up (epigenetic sample).

| DNA methylation Mean (SEM) | 12 months follow-up | | Crude[1] | p | Adjusted[2] | p |
|---|---|---|---|---|---|---|
| | <7% ($n$ = 19) | ≥7% ($n$ = 40) | Wald Chi-Square (95% CI) | | Wald Chi-Square (95% CI) | |
| *ADRA2A* (mean CpGs1-6) | 8.2 (0.5) | 8.5 (0.4) | 0.6 (−1.5–1.0) | 0.713 | 0.6 (−1.7–0.7) | 0.450 |
| CpG1 | 6.7 (0.4) | 7.1 (0.3) | 0.5 (−1.4–0.7) | 0.521 | 1.9 (−1.7–0.3) | 0.167 |
| CpG2 | 9.7 (0.6) | 10.3 (0.5) | 0.8 (−2.1–0.9) | 0.437 | 0.8 (−2.4–0.7) | 0.271 |
| CpG3 | 6.3 (0.4) | 6.4 (0.3) | 0.6 (−1.2–1.0) | 0.860 | 0.6 (−1.4–0.8) | 0.588 |
| CpG4 | 10.5 (0.7) | 10.7 (0.5) | 0.9 (−1.9–1.4) | 0.796 | 0.2 (−1.9–1.2) | 0.687 |
| CpG5 | 7.6 (0.6) | 7.8 (0.4) | 0.7 (−1.6–1.1) | 0.748 | 0.4 (−1.8–0.9) | 0.534 |
| CpG6 | 8.6 (0.6) | 8.5 (0.4) | 0.7 (−1.3–1.4) | 0.924 | 0.1 (−1.5–1.0) | 0.751 |
| *INSIG2* (mean CpGs1-4) | 24.6 (2.1) | 23.3 (0.7) | 1.8 (−2.3–4.9) | 0.460 | 1.7 (−1.2–6.2) | 0.186 |
| CpG1 | 26.6 (2.3) | 24.3 (0.6) | 1.8 (−1.4–5.9) | 0.230 | 4.4 (−0.3–7.5) | 0.035* |
| CpG2 | 28.3 (3.0) | 27.7 (2.0) | 3.5 (−6.5–7.7) | 0.860 | 0.3 (−5.9–9.1) | 0.598 |
| CpG3 | 16.4 (1.0) | 15.8 (0.4) | 0.9 (−1.2–2.5) | 0.475 | 1.7 (−0.6–3.1) | 0.187 |
| CpG4 | 27.0 (2.9) | 24.7 (0.8) | 2.3 (−2.3–6.9) | 0.321 | 2.4 (−0.9–8.3) | 0.116 |
| *LEP* (mean CpGs1-6) | 19.8 (0.7) | 19.5 (0.4) | 0.7 (−1.2–1.8) | 0.654 | 0.1 (−1.6–1.4) | 0.862 |
| CpG1 | 29.2 (1.0) | 27.8 (0.7) | 1.2 (−1.1–3.7) | 0.271 | 0.1 (−2.0–2.7) | 0.767 |
| CpG2 | 20.3 (0.8) | 20.4 (0.5) | 0.9 (−1.8–1.6) | 0.912 | 1.3 (−2.6–0.7) | 0.256 |
| CpG3 | 16.6 (0.8) | 16.1 (0.3) | 0.7 (−0.9–2.0) | 0.427 | 0.4 (−1.0–1.9) | 0.546 |
| CpG4 | 15.5 (0.8) | 15.2 (0.3) | 0.7 (−1.1–1.7) | 0.687 | 0.3 (−1.8–1.0) | 0.592 |
| CpG5 | 20.5 (0.9) | 20.3 (0.8) | 1.4 (−2.6–2.9) | 0.931 | 0.1 (−2.5–3.0) | 0.882 |
| CpG6 | 16.8 (0.7) | 17.0 (0.4) | 0.8 (−1.8–1.4) | 0.825 | 0.3 (−2.1–1.2) | 0.564 |
| *MC4R* (mean CpGs1-2) | 12.7 (0.4) | 14.2 (0.8) | 1.7 (−4.0–0.9) | 0.096 | 2.3 (−4.2–0.5) | 0.128 |
| CpG1 | 13.6 (0.5) | 15.3 (0.8) | 1.3 (−4.2–0.9) | 0.097 | 2.6 (−4.4–0.4) | 0.109 |
| CpG2 | 11.7 (0.4) | 13.1 (0.8) | 1.3 (−3.9–1.1) | 0.128 | 1.7 (−4.1–0.8) | 0.192 |

Abbreviations: CI: Confidence interval; EP: Early psychosis; SEM: Standard error of the mean. [1] Unadjusted: GzLM considering only differences groups in relation to percentage of weight gain at 12 months (<7% and ≥ 7%). [2] Adjusted: GzLM considering weight gain at 12 months adjusted for sex at birth, skin colour, years of school, age of onset psychosis, type of AP treatment and other psychotropic medications such as antidepressants or mood stabilizers at baseline and baseline BMI.

* No statistically significant after Bonferroni's test for multiple comparisons and adjusted p-value (*INSIG2*: 0.05/4 CpGs ≤ 0.012).

**Table 5**
Correlations of baseline *MC4R* methylation and metabolic variables with period of prior AP treatment at baseline (epigenetic sample).

| | Variables | Haloperidol (n = 42) | | SGAs (*n* = 17) | |
|---|---|---|---|---|---|
| | | r | p | r | p |
| *MC4R* methylation | CpG1 | 0.12 | 0.448 | **0.49*** | **0.048** |
| | CpG2 | 0.16 | 0.309 | **0.53*** | **0.028** |
| | mean | 0.14 | 0.364 | **0.54*** | **0.024** |
| Metabolic variables | Baseline body weight (Kg) | −0.17 | 0.275 | −0.30 | 0.246 |
| | Baseline BMI (kg/m$^2$) | −0.11 | 0.496 | −0.25 | 0.339 |
| | Glucose (mg/dl) | −0.27 | 0.083 | −0.22 | 0.391 |
| | Cholesterol (mmol/L) | −0.04 | 0.795 | −0.04 | 0.877 |
| | Triglycerides (mmol/L) | −0.14 | 0.396 | −0.27 | 0.298 |
| | LDL-c (mmol/L) | 0.10 | 0.544 | 0.41 | 0.105 |
| | HDL-c (mmol/L) | −0.15 | 0.349 | 0.20 | 0.444 |

Abbreviations: SGAs: Second-generation antipsychotics. The values represent the Pearson's correlation (*r*) and *p* values without Bonferroni correction; Significant results are depicted in bold ($p < 0.05$).

gene is more sensitive to psychotropic treatment (Endomba et al., 2020; Stubbs et al., 2016). The principles of *LEP* methylation in humans may be influenced by multiple factors and have not been entirely established (Valleau and Sullivan, 2014).

Regarding to *INSIG2,* the average of DNA methylation also was not significantly associated with dyslipidemia (Liu et al., 2022). However, no previous findings were demonstrated about *INSIG2* methylation in psychosis and AP-related to weight gain.

Some limitations should be considered when interpreting the negative findings for the other genes. First, the small size of the epigenetic sample may have limited the statistical power to detect subtle methylation differences, particularly after correction for multiple testing. Future studies with larger cohorts are warranted to replicate and extend these findings. Second, the cross-sectional assessment of methylation at baseline prevents definitive conclusions regarding the directionality of the observed associations. Despite these constraints, prospective longitudinal studies incorporating drug-naïve patients and simultaneous evaluations of metabolic parameters are required to determine whether *MC4R* methylation primarily reflects AP exposure or contributes mechanistically to metabolic dysregulation.

Third, we did not include a control group in the present study, limiting our ability to separate the effects of AP treatment, weight changes, and the natural progression of psychosis. The absence of a control group limits causal inference and generalizability of the epigenetic findings. To address these questions, future research should include control groups of psychotic patients with and without weight gain and assess differences in methylation changes over longitudinal follow-ups. Additionally, our epigenetic cohort included a heterogeneous group of patients – half diagnosed with affective psychosis – treated with a range of psychotropic medications, including mood stabilizers and antidepressants, which may also influence weight gain, metabolic outcomes, and epigenetic profile of these target genes. Consequently, while our findings likely reflect shared mechanisms underlying metabolic side effects, they may not capture individual drug-specific effects. *Finally, we defined the predominant AP use as exposure to the same drug class at ≥ 3 of 5 assessment time points to quantify sustained pharmacological exposure in EP.* Although not a standardized criterion, this approach is consistent *with previous longitudinal studies investigating metabolic and epigenetic effects of AP treatment, providing a reliable proxy for cumulative drug effects* (Dubath et al., 2024; Pillinger et al., 2018).

Understanding the role of epigenetic changes in the development and progression of weight gain in psychosis is essential, particularly in determining how these changes influence specific genes across different stages of the disorder and how AP treatment may modulate these alterations. Epigenetic profiling has the potential to identify individuals at greatest risk for weight gain during the early stages of psychosis. However, distinguishing the direct effects of medication on DNA methylation from changes driven by weight gain remains challenging.

Despite these limitations, this study provides valuable insight into AP-related mechanisms contributing to weight gain and metabolic changes, with implications for preventing cardiovascular and metabolic complications in psychosis. Hypothesis-driven epigenetic research may further elucidate how gene modulation leads to metabolic side effects and highlights additional candidate regions or mechanisms. Ultimately, these findings could inform more personalized approaches to AP prescribing in early intervention services, offering opportunities to reduce adverse outcomes, optimize treatment adherence, and improve long-term clinical outcomes.

## 5. Conclusion

Weight gain is a common adverse effect among patients in the early stages of psychosis, influenced not only by the particular AP prescribed but also by indicators of increased social vulnerability. Although the association between epigenetic alterations in some relevant genes and weight gain during the initial weeks of treatment was not confirmed, we identified a possible association of *MC4R* methylation with liability to AP drug-induced weight gain, suggesting the underlying mechanisms and provide *MC4R* as an epigenetic marker for early identification of individuals at risk of AP-induced metabolic dysregulation.

## CRediT authorship contribution statement

**C.M. Loureiro:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **H.A. Fachim:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **G.C. Bissoli:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **F. Corsi-Zuelli:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **R. Shuhama:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Data curation. **P.R. Menezes:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **P. Louzada-Junior:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Formal analysis. **C.F. Dalton:** Writing – review & editing, Writing – original draft, Supervision, Methodology. **G.P. Reynolds:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **C.M. Del-Ben:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis.

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## Declaration of competing interest

The authors report no financial interests or potential conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2026.02.011.

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