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# Metabolic polygenic risk scores effect on antipsychotic-induced metabolic dysregulation: A longitudinal study in a first episode psychosis cohort

Àlex G. Segura [a], Albert Martínez-Pinteño [a], Patricia Gassó [a,b,c], Natalia Rodríguez [a], Miquel Bioque [b,c,d], Manuel J. Cuesta [e,f], Javier González-Peñas [b,g], Clemente García-Rizo [b,c,d], Antonio Lobo [b,h,i], Ana González-Pinto [b,j,k,l], Alicia García-Alcón [b,g], Alexandra Roldán [b,m], Eduard Vieta [b,c,n,o], Josefina Castro-Fornieles [b,c,p], Anna Mané [b,q], Jeronimo Saiz [b,r], Miguel Bernardo [b,c,d,o], Sergi Mas [a,b,c,*], PEPs Group [1]

[a] Department of Clinical Foundations, Pharmacology Unit, University of Barcelona, 08036 Barcelona, Spain
[b] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain
[c] Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 08036 Barcelona, Spain
[d] Hospital Clínic de Barcelona, Barcelona Clínic Schizophrenia Unit, Neuroscience Institute, 08036 Barcelona, Spain
[e] Department of Psychiatry, Complejo Hospitalario de Navarra, 31008 Pamplona, Spain
[f] Navarra Institute of Health Research (IdiSNA), Pamplona, Spain
[g] Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), 28007 Madrid, Spain
[h] Department of Medicine and Psychiatry, Universidad de Zaragoza, 50009 Zaragoza, Spain
[i] Instituto de Investigación Sanitaria Aragón (IIS Aragón), 50009 Zaragoza, Spain
[j] Hospital Universitario de Alava, 01009 Vitoria-Gasteiz, Spain
[k] Instituto de Investigación Sanitaria Bioaraba, 01009 Vitoria-Gasteiz, Spain
[l] University of the Basque Country, 48940 Vizcaya, Spain
[m] Psychiatry Department, Institut d'Investigació Biomèdica-Sant Pau (IIB-SANTPAU), Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona (UAB), 08041 Barcelona, Spain
[n] Hospital Clínic de Barcelona, 08036 Barcelona, Spain
[o] Department of Medicine, University of Barcelona, 08036 Barcelona, Spain
[p] Department of Child and Adolescent Psychiatry and Psychology, Clínic Institute of Neurosciences, Hospital Clínic de Barcelona, 08036 Barcelona, Spain
[q] Hospital del Mar Medical Research Institute (IMIM), Autonomous University of Barcelona (UAB), 08003 Barcelona, Spain
[r] University of Alcalá de Henares, Hospital Universitario Ramón y Cajal, IRYCIS, 28034 Madrid, Spain

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ABSTRACT

*Objective:* Metabolic syndrome is a health-threatening condition suffered by approximately one third of schizophrenia patients and largely attributed to antipsychotic medication. Previous evidence reports a common genetic background of psychotic and metabolic disorders. In this study, we aimed to assess the role of polygenic risk scores (PRSs) on the progression of the metabolic profile in a first-episode psychosis (FEP) cohort.
*Method:* Of the 231 FEP individuals included in the study, 192–220 participants were included in basal analysis and 118–179 in longitudinal 6-month models. Eleven psychopathologic and metabolic PRSs were constructed. Basal and longitudinal PRSs association with metabolic measurements was assessed by statistical analyses.
*Results:* No major association of psychopathological PRSs with the metabolic progression was found. However, high risk individuals for depression and cholesterol-related PRSs reported a higher increase of cholesterol levels during the follow-up (FDR $\leq$ 0.023 for all analyses). Their effect was comparable to other well-established pharmacological and environmental risk factors (explaining at least 1.2% of total variance).
*Conclusion:* Our findings provide new evidence of the effects of metabolic genetic risk on the development of metabolic dysregulation. The future establishment of genetic profiling tools in clinical procedures could enable practitioners to better personalize antipsychotic treatment selection and dosage.

* Corresponding author at: Dept. Clinical Foundations, University of Barcelona, IDIBAPS, CIBERSAM, Casanova 143, E-08036 Barcelona, Spain.
*E-mail address:* sergimash@ub.edu (S. Mas).
[1] Members are listed in Appendix A.

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## 1. Introduction

Premature mortality is significantly higher in people with severe mental disorders, partly due to preventable conditions such as metabolic syndrome (MetS) (Vancampfort et al., 2015). MetS is characterized by abdominal obesity, high fasting glucose, dyslipidemia and persistent high blood pressure that ultimately confer risk for life-threatening conditions such as cardiovascular disease and diabetes (Samson and Garber, 2014). Approximately one third of patients with schizophrenia suffer from MetS and its high prevalence is largely attributed to antipsychotic (AP) use, specially second-generation antipsychotics (SGA) (Correll et al., 2017; Mitchell et al., 2013; Perry et al., 2016). The relevance of the metabolic effects of AP may be particularly important in first-episode psychosis (FEP) patients (Vázquez-Bourgon et al., 2020).

The proposed mechanism of action for AP-induced MetS is based on 5-HT2A receptor antagonism that affects multiple brain regions and leads to greater food intake and metabolic disruption, detected promptly after first AP exposure (Barton et al., 2020; Siafis et al., 2017). However, higher AP-independent MetS risk has been found in drug-naïve patients with FEP and their relatives (Fernandez-Egea et al., 2008; Garcia-Rizo et al., 2017). This suggests a pleiotropic effect of schizophrenia genetic risk on metabolic dysregulation. Nonetheless, a previous study by Delacrétaz et al. showed that the lipid profile of a sample under psychotropic medication was associated with a polygenic risk score (PRS) of lipid levels (Delacrétaz et al., 2017), which provides evidence of an a priori schizophrenia-unrelated PRSs having an effect on MetS susceptibility in psychiatric populations. Further exploration of the genetic background and the effects of APs could help elucidate the underlying mechanisms of MetS.

Several genes and polymorphisms have been studied in relation to AP-induced MetS (Malan-Müller et al., 2016), although only the rs1414334 C allele of the *HTR2C* gene has been associated with MetS and replicated in multiple independent studies (Sneller et al., 2021). Nevertheless, considering that MetS and other comorbid traits are highly heritable conditions that have a great number of common genetic factors with small effects interacting with clinical and demographic factors, further studies are required to elaborate an algorithm for clinical practice.

The development of genotyping and computational tools has provided the opportunity to steer genetic studies towards new approaches designed to capture genetic susceptibility throughout the genome. The PRS of each individual is calculated with the number of risk alleles associated to a ceratin phenotype, weighted by the effect reported in genome-wide association studies (GWAS). Despite their limitations (Janssens, 2019), PRSs application in psychiatric pharmacogenetics might contribute to the development of new therapeutic targets, drug repurposing and treatment response prediction strategies to ultimately converge genetic profiling into personalized medicine (Eeltink et al., 2021). The few available studies on this topic provide inconsistent results on the association of PRSs and drug response (Pisanu and Squassina, 2019; Zwicker et al., 2018), which highlights the urgent need for further investigation.

In the advent of polygenic approaches, studies using sets of PRSs could be used to investigate the genetic architecture of schizophrenia comorbid conditions. In this study, we aim to assess the effect of genetic liability on metabolic parameters that lead to MetS with a battery of psychopathologic and metabolic PRSs, focusing on the longitudinal metabolic profile trajectory of FEP patients under AP treatment. We hypothesize that both psychopathologic and metabolic genetic liability will mediate the early metabolic imbalances preceding MetS.

## 2. Material and methods

This study is part of the multicentric project 'Phenotype–genotype interaction: application of a predictive model in first psychotic episodes, FIS PI080208' (known as the PEPs study, from the Spanish abbreviation for first psychotic episode), conducted by the Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) (Salagre et al., 2019). A complete description of the protocol for the PEPs study has been published previously (Bernardo et al., 2013). This longitudinal two-year prospective follow-up study presents clinical parameters from various assessments/visits: baseline, two-month, six-month, one-year and two-year follow-up. For the purpose of the present study, we focused on baseline, two-month and six-month data.

### 2.1. Sample

During the recruitment period (2009–2012), 335 subjects who presented a first psychotic episode were included in the PEPs Project. The inclusion criteria were age between 7 and 35 years at recruitment, presence of first psychotic symptoms (positive symptoms or disorganization) of at least one week's duration in the last 12 months, the ability to speak Spanish correctly, and providing written informed consent. The exclusion criteria were mental retardation according to DSM-IV criteria (American Psychiatric Association, 1994), history of head trauma with loss of consciousness, and presence of an organic disease with mental repercussions. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice and the Hospital Clinic Ethics and Research Board. All participants provided written informed consent prior to their inclusion in the study.

At baseline, a complete evaluation was performed by collecting demographic and environmental data, among others. Of the 335 FEP subjects, 231 (69.3%) provided blood samples for genetic analysis, passed the genetic quality control (see below), had European ancestry and were $\geq$16 years old.

As this was a naturalistic study, there were no specific guidelines for treatment, so patients received AP treatment based on the clinician's decision. Dosing, co-medication or treatment changes were based only on clinical necessity. Prior treatment with APs did not exceed 12 months at study entry (Bioque et al., 2016). The prescribed daily doses of SGA at baseline and at the two-month and six-month assessments were converted into an estimated equivalent amount of chlorpromazine following the current international consensus and expressed as chlorpromazine equivalent daily dose (CEDD) (Bioque et al., 2016; Gardner et al., 2010; Pina-Camacho et al., 2016). For this study, the dose of SGA was calculated as the mean of monthly CEDD. Moreover, clozapine and olanzapine were considered APs with high risk for metabolic disturbances (Leucht et al., 2013).

### 2.2. Metabolic and environmental data assessment

A complete medical history was taken at baseline. In medical visits at the beginning of the study and at 2, 6, 12 and 24 months, body weight and height were assessed to calculate body mass index (BMI) and serum glucose (SG), serum triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL) and low density lipoprotein cholesterol (LDL) were directly analyzed by enzymatic procedures with an automated chemical analyzer (Bioque et al., 2018; Gassó et al., 2020). The assessment of environmental data and the recording procedures are described in a previous study of the PEPs Project (Bernardo et al., 2017; Mas et al., 2020). Metabolic data at baseline were available for a range of 192–220 (57.3%–65.7%) and complete 6-month follow-up data for a range of 118–179 (35.2%–53.4%) individuals.

### 2.3. Blood samples and genotyping

Blood samples were collected in K2EDTA BD Vacutainer EDTA tubes (Becton Dickinson, Franklin Lakes, New Jersey), stored at −20 °C and sent to the central laboratory. DNA was extracted with the MagNA Pure LC DNA isolation Kit – Large volume and MagNA Pure LC 2.0 Instrument (Roche Diagnostics GmbH, Mannheim, Germany). DNA concentration was determined by absorbance (ND1000, NanoDrop, Wilmington,

Delaware). A total of 2.5 μg of genomic DNA was sent for genotyping at the Spanish National Genotyping Centre (CeGen) using Axiom™ Spain Biobank Array (developed in the University of Santiago de Compostela, Spain).

### 2.4. PRS calculation

Genotyping data was submitted to the Michigan Imputation Server (Das et al., 2016), following the standard pipeline for Minimac4 software and setting a European population reference from build GRCh37/hg19 and Eagle v2.4 phasing.

For the PRS calculation, GWAS summary results were used as reference data: schizophrenia ($PRS_{SZ}$; 69,369 cases and 236,642 controls) (Ripke et al., 2020), bipolar disorder ($PRS_{BD}$; 20,352 cases and 31,358 controls) (Stahl et al., 2019), depression ($PRS_{DEP}$; 246,363 cases and 561,190 controls) (Howard et al., 2019), body mass index-adjusted waist-to-hip ratio ($PRS_{WHR}$; 694,649 individuals) (Pulit et al., 2019), type II diabetes mellitus ($PRS_{DM}$; 34,840 cases and 114,981 controls) (Morris et al., 2012), fasting glucose ($PRS_{FG}$; 140,595 individuals) (Lagou et al., 2021), fasting insulin ($PRS_{FI}$; 98,210 individuals) (Lagou et al., 2021) and serum TG, TC, HDL and LDL ($PRS_{TG}$, $PRS_{TC}$, $PRS_{HDL}$, $PRS_{LDL}$, respectively; 188,577 individuals) (Willer et al., 2013). Reference data was obtained from multiple repositories (Broad Institute GWAShare center, Psychiatric Genomics Consortium, DIAGRAM Consortium, GIANT Consortium, MAGIC, Global Lipids Genetics Consortium). Duplicated and unknown strand GWAS summary SNPs were excluded.

The quality control was performed with PLINK v1.07 (Purcell et al., 2007). Inclusion criteria for SNPs were minor allele frequency (MAF) > 0.1, Hardy-Weinberg equilibrium $p > 10^{-6}$, marker missingness <0.01 and imputation INFO >0.8. Pruning was done using a window/step size of 200/50 kb and $r^2 > 0.25$. Sample quality control included individuals with heterozygosity values within three standard deviations (SD) from the mean, a missingness rate < 0.01, matching chromosomal and database-labelled sex, relatedness π-hat <0.125 and self-reported European ancestry. PRSs capacity to discriminate cases from controls and predictivity has been highly correlated with ancestry, since most reference GWAS participants are European (Perkins et al., 2020; Vassos et al., 2017).

PRS were constructed using PRSice-2 v2.3.3 software (Choi and O'Reilly, 2019), with clumping parameters at 250 kb and $r^2 > 0.1$ and using the odds ratio or beta values of SNPs in the reference GWAS data that had $p < 0.05$. This $p$ value was used as the default threshold for the 11 PRSs to avoid the genetic noise of weakly associated SNPs in the reference GWAS and model overfitting (Choi et al., 2020).

### 2.5. Statistical analysis

All the analyses were performed with R v4.1.2 ("R Core Team," 2017). Population stratification was controlled using the first 10 components of the genetic principal component analysis (PCA).

All PRSs were dichotomized into high risk PRS (above the highest 75% score quartile) and mid-to-low risk PRS (below the 75% score quartiles). This procedure was performed to better capture the effect of high genetic risk and avoid putative intermediate and low scores effect masking (Lin et al., 2018; Mas et al., 2020; Vassos et al., 2017; Wang et al., 2018).

Basal PRS association with metabolic variables was evaluated with generalized linear models corrected by sex, age and previous AP treatment days. Linear mixed-effects modelling was used for longitudinal analyses, considering the month of assessment as a random effect and the PRS as the fixed effect, corrected by sex, age, previous AP days and SGA CEDD. For models with a significant PRS effect, post-hoc analyses were performed. Differential SGA CEDD for the significant PRSs was assessed with linear mixed-effects models. To assess the variation explained by PRS, pharmacological and environmental risk variables (sex, age, socioeconomic status, and smoking) Nakagawa's $R^2$ was calculated.

To avoid false positive results, the false discovery rate (FDR) method was applied for all analyses and the significance threshold was set at FDR < 0.05. Specifically, multiple testing correction was applied for all metabolic measurements at baseline, their progression, the differential SGA CEDD, the models including environmental risk factors and post hoc analyses.

## 3. Results

### 3.1. Descriptive statistics

Demographic, clinical and pharmacological variables of the sample at study entry are reported in Table 1 and the metabolic measurements for the assessments during the 6-month follow-up in Table 2. Further information of the 11 constructed PRSs is shown in Supplementary Fig. 1.

### 3.2. Basal metabolic status

Fig. 1A shows the association of the constructed psychopathologic and metabolic PRSs with the initial metabolic status. No PRS was significantly associated to any metabolic measurement at basal point. Complete analysis information is reported in Supplementary Table 1.

### 3.3. Longitudinal analyses

Four PRSs reported significant associations with the metabolic changes during the follow-up (Fig. 1B, Supplementary Table 2). $PRS_{DEP}$, $PRS_{TC}$ and $PRS_{LDL}$ were associated with total cholesterol levels (FDR = 0.006, FDR = 0.012, FDR = 0.001; respectively) and significant post-hoc differences were found for $PRS_{DEP}$ at month 2 (FDR = 0.030) and for

**Table 1**
Demographic, clinical and pharmacological data at baseline and monthly SGA dose of the study participants ($n$ = 231).

| Feature | | Mean (SD) or n (%) |
|---|---|---|
| Sex | Female | 71 (30.7%) |
| | Male | 160 (68.9%) |
| Sociodemographic status | High | 90 (39.6%) |
| | Medium-low | 137 (60.6%) |
| Tobacco use | Yes | 144 (63.2%) |
| | No | 84 (36.8%) |
| Age at FEP | | 24.54 (5.7) |
| Psychosis type | Non-affective | 195 (84.4%) |
| | Affective | 36 (15.6%) |
| Antipsychotic medication at basal point | Olanzapine | 96 (41.6%) |
| | Risperidone | 87 (37.7%) |
| | Aripiprazole | 37 (16.0%) |
| | Paliperidone | 31 (9.1%) |
| | Quetiapine | 27 (11.7%) |
| | Amisulpride | 12 (5.2%) |
| | Haloperidol | 5 (2.2%) |
| | Clozapine | 7 (3.0%) |
| | Perphenazine | 2 (0.9%) |
| | Clotiapine | 1 (0.4%) |
| | Pimozide | 1 (0.4%) |
| | Ziprasidone | 1 (0.4%) |
| | Zuclopenthixol | 1 (0.4%) |
| Other medication at basal point | Anxiolytic | 99 (43.8%) |
| | Antidepressive | 29 (12.9%) |
| | Antiepileptict | 21 (9.3%) |
| | Lithium | 14 (6.2%) |
| SGA CEDD (mg) | | 146.7 (77.4) |
| Previous days of AP treatment | | 56.4 (76.6) |
| Exposition to clozapine/olanzapine | Exposed | 107 (46.3%) |
| | Non-exposed | 124 (53.7%) |

First-episode psychosis (FEP); second-generation antipsychotic (SGA); chlorpromazine equivalent daily dose (CEDD); antipsychotic (AP).

**Table 2**
Metabolic measurements mean values for the basal, 2-month and 6-month assessments of the follow-up.

| Metabolic measurement | Basal | | 2-month | | 6-month | |
|---|---|---|---|---|---|---|
| | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| BMI (kg/m$^2$) | 221 | 23.1 (3.1) | 189 | 24.1 (3.1) | 183 | 25.0 (3.4) |
| SG (mg/dL) | 183 | 83.3 (6.7) | 144 | 85.6 (6.5) | 146 | 84.2 (7.6) |
| TG (mg/dL) | 176 | 75.0 (26.9) | 143 | 82.9 (32.10) | 153 | 89.3 (34.5) |
| TC (mg/dL) | 201 | 158.0 (30.5) | 160 | 168.0 (32.5) | 167 | 169.0 (31.2) |
| HDL (mg/dL) | 174 | 47.5 (9.9) | 153 | 47.3 (10.6) | 163 | 46.8 (10.4) |
| LDL (mg/dL) | 174 | 93.0 (25.5) | 149 | 99.6 (27.1) | 159 | 101.0 (28.2) |

Body mass Index (BMI); serum glucose (SG); triglycerides (TG); total cholesterol (TC); high-density lipoprotein cholesterol (HDL); low-density lipoprotein cholesterol (LDL).

$PRS_{LDL}$ at baseline, months 2 and 6 (FDR = 0.035, FDR = 0.009, FDR = 0.049; respectively). $PRS_{HDL}$ was associated with HDL cholesterol trajectory (FDR = 0.023) with significant differences at month 6 (FDR = 0.036). Finally, $PRS_{TC}$ and $PRS_{LDL}$ were associated with LDL cholesterol (FDR = 0.001 and FDR = $5.82 \times 10^{-5}$; respectively). Significantly different levels were found for $PRS_{TC}$ at month 6 (FDR = 0.015) and for $PRS_{LDL}$ groups at baseline, months 2 and 6 (FDR = 0.028, FDR = 0.003, FDR = 0.003; respectively) (Fig. 2). These associations were also found when introducing the continuous rather than the dichotomic PRSs in the longitudinal models (see Supplementary Table 3).

Linear mixed-effect models were performed to ensure that the reported significant associations were not caused by unequal administration of SGA in the high and mid-to-low $PRS_{DEP}$, $PRS_{TC}$, $PRS_{HDL}$ and $PRS_{LDL}$ groups. All analyses were not significant (FDR > 0.05 for all) (Supplementary Table 4).

The effect of the PRSs was assessed with multiple well-established pharmacological (AP dosage, AP-induced MetS potency) and environmental risk factors (sex, age, socioeconomic status and smoking). All PRSs remained significant (FDR ≤ 0.031) in each model, except $PRS_{DEP}$ and its association with TC. Significant PRSs explained a considerable proportion of the observed variability of each model, ranging from 1.2%–4.3%. Moreover, as could be expected, well known risk factors for MetS such as sex, age and/or clozapine/olanzapine exposition were significantly associated in most models (FDR ≤ $9.22 \times 10^{-5}$) (Table 3).

## 4. Discussion

Traits associated with comorbid MetS such as abdominal obesity, hyperglycemia, dyslipidemia or lipoprotein imbalances have been widely acknowledged as side effects of SGA in schizophrenia patients. In this study, a battery of PRSs was constructed to assess the role of genetics in the metabolic changes following a first psychotic episode. We selected PRSs that comprise the genetic risk for three highly correlated mental conditions (schizophrenia, bipolar disorder and depression) (Mistry et al., 2018a) and eight metabolic risk scores that aimed to cover the diagnostic criteria for MetS. Of the metabolic traits assessed, only those related to any form of cholesterol seemed to be affected by the computed PRSs. Among psychopathologic PRSs, only $PRS_{DEP}$ showed significant associations. Regarding metabolic PRSs, those related to cholesterol levels ($PRS_{TC}$, $PRS_{HDL}$ and $PRS_{LDL}$) showed significant effects on its corresponding metabolic parameter (TC, HDL or LDL). Our findings suggest that metabolic dysregulation after a first psychotic episode is chiefly driven by the genetic risk of metabolic phenotypes rather than psychopathologic genetic liability, thus conjecturing that the mechanisms mediating SGA side effects are – at least – partially independent of the psychotic symptomatology.

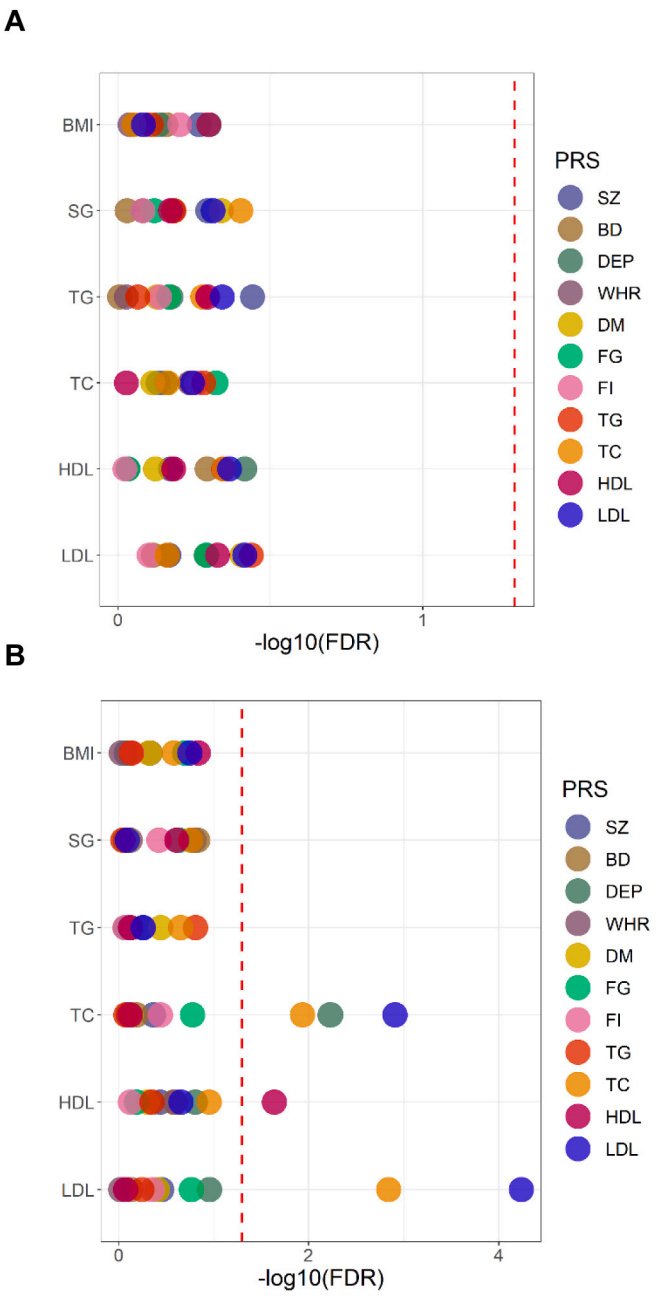


**Fig. 1.** Association of psychopathological and metabolic PRSs with metabolic measurements A) at baseline and B) during the 6-month follow-up.
Body mass index (BMI); serum glucose (SG); triglycerides (TG); total cholesterol (TC); high-density lipoprotein cholesterol (HDL); low-density lipoprotein cholesterol (LDL); schizophrenia (SZ); bipolar disorder (BD); depression (DEP); waist-to-hip ratio (WHR); type-II diabetes mellitus (DM); fasting glucose (FG); fasting insulin (FI).

The estimation of genetic risk in complex traits such as schizophrenia through PRS constructs has become a common approach since it considers the additive effect of multiple genetic variants and overcomes multiple limitations of single-candidate gene studies. In this sense, psychopathologic PRSs have been associated with psychiatric disorders, symptomatology and related phenotypes (Hiemstra et al., 2018; Mistry et al., 2018b, 2018a; Santoro et al., 2018; Zhang et al., 2019) and with expression modules acknowledged as potential drug targets (Radulescu et al., 2020). As for metabolic effects, previous studies have found the effect of schizophrenia PRSs on lower BMI and binge eating in adolescents (Solmi et al., 2019), on ghrelin serum levels and insulin resistance

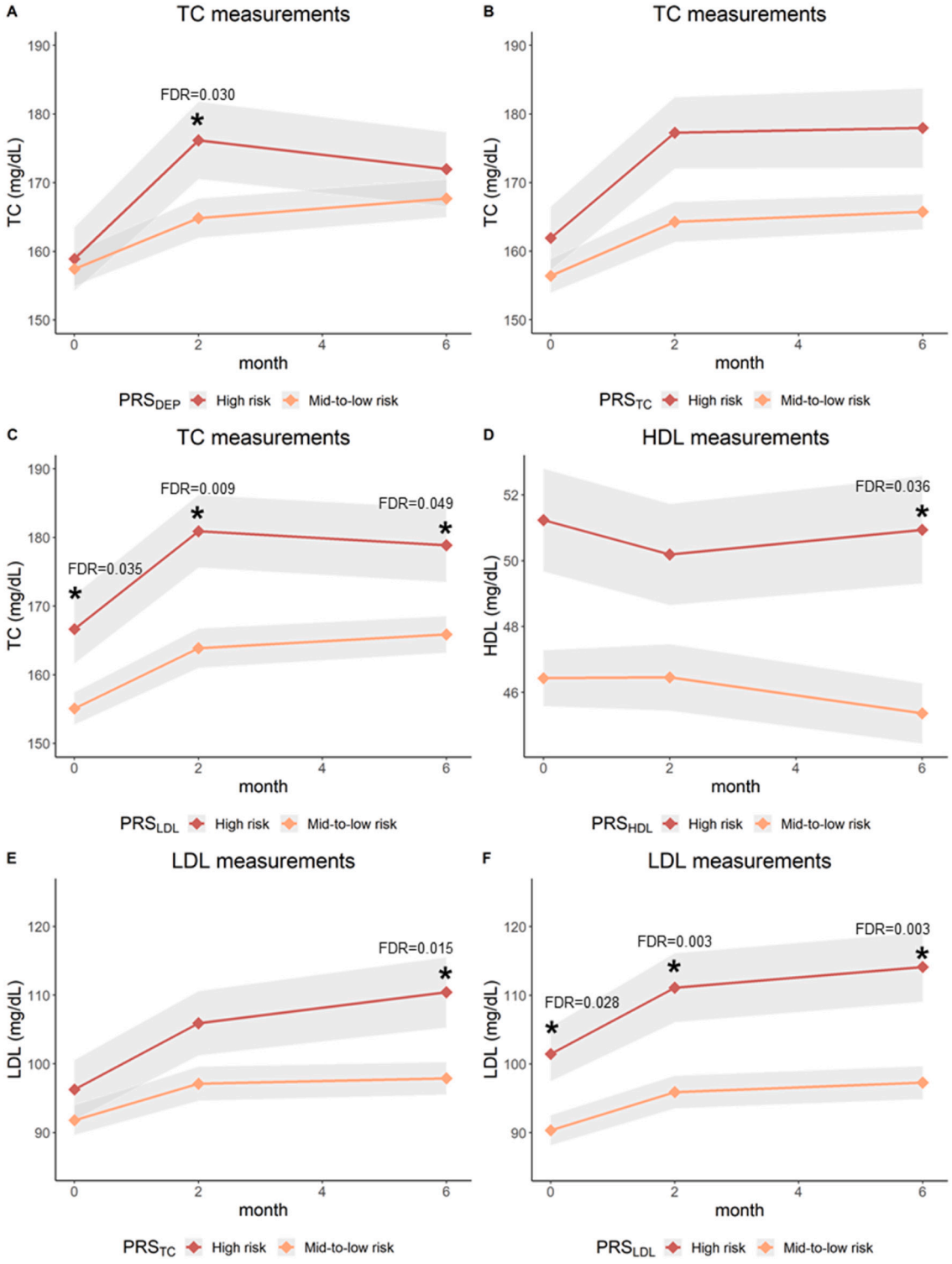


**Fig. 2.** Summary of the progression of metabolic measures during the 6-month follow-up stratified by PRS category. Figures show the mean of each metabolic measurement and standard error range for each month of assessment. A) TC stratified by $PRS_{DEP}$, B) TC stratified by $PRS_{TC}$, C) TC stratified by $PRS_{LDL}$, D) HDL stratified by $PRS_{HDL}$, E) LDL stratified by $PRS_{TC}$ and F) LDL stratified by $PRS_{LDL}$. Significant post hoc analyses are marked with an asterisk.
Total cholesterol (TC); high-density lipoprotein cholesterol (HDL); low-density lipoprotein cholesterol (LDL); depression (DEP).

in FEP individuals (Maj et al., 2020; Tomasik et al., 2019) but not on glycated hemoglobin in schizophrenia patients (Habtewold et al., 2020) and the correlation of a bipolar disorder PRS with diabetes, TG, TC, HDL and LDL cholesterol (Kember et al., 2018). In our study no effect of these PRSs was observed, except for the influence of $PRS_{DEP}$ on TC progression. These findings could be explained by the larger sample size and therefore greater power of the reference GWAS used to calculate $PRS_{DEP}$, that can ultimately have more power to detect differences in the metabolic progression. Yet, this association did not persist in the longitudinal modelling including other risk factors.

To the best of our knowledge this is the first time that PRSs for metabolic traits derived from large population studies have been applied

**Table 3**
Longitudinal modelling of $PRS_{DEP}$, $PRS_{TC}$, $PRS_{HDL}$ and $PRS_{LDL}$ with non-genetic risk factors for total, HDL and LDL cholesterol levels during the follow-up.

| Feature | $PRS_{DEP}$ | | | $PRS_{TC}$ | | | | | | $PRS_{HDL}$ | | | | | | $PRS_{LDL}$ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TC | | | TC | | | LDL | | | HDL | | | LDL | | | TC | | | LDL | | |
| | Estimate | t | $R^2$ | FDR | Estimate | t | $R^2$ | FDR | Estimate | t | $R^2$ | FDR | Estimate | t | $R^2$ | FDR | Estimate | t | $R^2$ | FDR | Estimate | t | $R^2$ | FDR |
| PRS | −7.516 | −2.403 | 0.009 | 0.082 | −8.669 | −2.796 | 0.012 | 0.031 | −13.116 | −4.261 | 0.028 | 2.02E-04 | −3.921 | −3.779 | 0.024 | 0.001 | −8.988 | −3.230 | 0.019 | 0.008 | −13.644 | −4.959 | 0.043 | 9.78E-06 |
| Sex | 0.366 | 0.124 | 2.33E-05 | 0.945 | 1.314 | 0.440 | 3.03E-04 | 0.792 | −0.174 | −0.059 | 4.74E-06 | 0.953 | −6.524 | −6.444 | 0.069 | 5.18E-09 | 4.326 | 1.617 | 0.005 | 0.320 | 2.888 | 1.100 | 0.002 | 0.554 |
| Age | 1.932 | 8.010 | 0.101 | 4.26E-13 | 1.862 | 7.733 | 0.093 | 1.54E-12 | 1.902 | 7.991 | 0.098 | 3.26E-13 | 0.140 | 1.701 | 0.005 | 0.293 | 1.265 | 5.699 | 0.058 | 2.32E-07 | 1.321 | 6.045 | 0.063 | 4.16E-08 |
| Clozapine/ olanzapine | −4.751 | −1.704 | 0.005 | 0.300 | −5.345 | −1.927 | 0.006 | 0.218 | −5.579 | −2.031 | 0.006 | 0.192 | −4.136 | −4.460 | 0.033 | 9.22E-05 | −3.816 | −1.515 | 0.004 | 0.371 | −3.605 | −1.453 | 0.004 | 0.396 |
| Socioeconomic status | −3.301 | −0.316 | 0.004 | 0.846 | −3.341 | −0.322 | 0.004 | 0.850 | −7.147 | −0.698 | 0.006 | 0.699 | −2.589 | −0.729 | 0.001 | 0.709 | −4.847 | −0.501 | 0.002 | 0.748 | −9.040 | −0.956 | 0.003 | 0.601 |
| Tobacco use | 16.602 | 1.192 | 0.003 | 0.495 | 12.636 | 0.905 | 0.002 | 0.628 | 13.191 | 0.957 | 0.002 | 0.610 | 1.809 | 0.364 | 3.15E-04 | 0.822 | 7.125 | 0.531 | 0.002 | 0.748 | 6.969 | 0.528 | 0.002 | 0.742 |

Total cholesterol (TC); high-density lipoprotein cholesterol (HDL); low-density lipoprotein cholesterol (LDL); depression (DEP).

to assess the genetic risk to develop AP-induced metabolic disturbances. The PRSs related to cholesterol showed significant associations, but not those related to obesity, diabetes or triglycerides. The longitudinal analyses showed an association of $PRS_{TC}$, $PRS_{HDL}$ and $PRS_{LDL}$ with cholesterol changes during the 6 months. Individuals with higher TC, HDL and LDL cholesterol-related PRSs showed increased levels of TC, HDL and LDL cholesterol levels during the follow-up and the trajectories pointed towards a persistent increase. In contrast, patients at lower risk showed a moderate increase of cholesterol levels after two months of study entry followed by a slight decrease after six months.

No baseline metabolic measurement was different for any PRS group. The young age of the FEP sample could explain the lack of metabolic differences at study entry. A continuous exposition to environmental insults might subsequently trigger the metabolic imbalances in high risk individuals found in the longitudinal analyses. Thus, we hypothesize that the action mechanisms of SGA interact not only with the psychopathologic pathways that affect the psychotic symptomatology but also with the metabolic genetic liability that ultimately leads to a comorbid MetS.

We assessed the effect of $PRS_{DEP}$, $PRS_{TC}$, $PRS_{HDL}$ and $PRS_{LDL}$ along with previously described pharmacological and environmental risk factors (Bulla et al., 2017; Pillinger et al., 2020; Sneller et al., 2021). The analyses showed that the significant PRSs explained a considerable proportion of the cholesterol variance – similar to clozapine/olanzapine intake in some cases – and thus worth to be considered for cholesterol imbalances after AP exposition in our sample. In the long run, the validation and establishment of PRSs could be used in personalized medicine, as a complementary source of clinical information for early screening, to guide therapeutic decisions and for counseling high-risk healthy individuals (Torkamani et al., 2018).

The findings of this study should be interpreted in the context of its limitations. Firstly, the individuals of our cohort had their FEP within the last 12 months and therefore most of them were not AP-naïve at basal point, so all analyses were corrected by previous treatment days. Moreover, specific data about non-AP drugs with metabolic effects were not available. Nonetheless, it is unlikely that a relevant number of FEP patients – all of them of young age – were prescribed with pharmacological treatment for metabolic disorders during the study. Secondly, the lack of an untreated FEP group meant that the specific effect of SGA exposition on the longitudinal progression of the metabolic profile could not be elucidated. Thirdly, although the sample is one of the largest cohorts of FEP patients with longitudinal data in the literature, its size limits its statistical power and did not allow the study of subgroups stratified by AP treatment. Fourthly, the association of the PRSs with cardiometabolic conditions could not be analyzed due to the low number of individuals reporting a diagnostic, greatly explained by the young age of the sample. Finally, the clinical relevance of the findings, as with most studies using this methodology, is still limited as of today (Smeland and Andreassen, 2021).

## 5. Conclusion

Despite the abovementioned limitations, the present study provides new and strong evidence of the role of genetic risk to the development of metabolic dysregulation after AP treatment and therefore new insights into the genetic architecture of comorbid MetS. Our results suggest that metabolic imbalances, specially dyslipoproteinemia, are predominantly mediated by metabolic rather than psychopathologic genetic risk, evidencing the existence of independent mechanisms mediating AP side effects. Further exploration is required to better characterize the pathophysiological mechanisms underlying AP response and ultimately provide new tools to transfer genetic profiling to clinical practice, thus contributing to the development of personalized medicine in psychiatry.

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## Appendix A. PEPs group

Mezquida, Gisela and Amoretti, Silvia (Barcelona Clínic Schizophrenia Unit, Neuroscience Institute Hospital Clínic de Barcelona, 08036 Barcelona, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain. Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 08036 Barcelona, Spain); Pina- Camacho, Laura and Parellada, Mara (Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), School of Medicine, Universidad Complutense, 28007 Madrid, Spain; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain); Corripio, Iluminada and Alonso-Solís, Anna (Psychiatry Department, Institut d'Investigació Biomèdica-SantPau (IIB-SANTPAU), Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona (UAB), 08041 Barcelona, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain); Zorrilla, Iñaki and García-Corres, Edurne (Hospital Universitario de Alava, Instituto de Investigación Sanitaria Bioaraba, 01009 Vitoria-Gasteiz, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain. University of the Basque Country (UPV/EHU), 48940 Vizcaya, Spain); De-la-Cámara, Concepción (Hospital Clínico Universitario and Instituto de Investigación Sanitaria (IIS) Aragón, 50009 Zaragoza, Spain. Department of Medicine and Psychiatry. Universidad de Zaragoza, 50009 Zaragoza, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain); Saz, Pedro (Department of Medicine and Psychiatry. Zaragoza University. Instituto de Investigación Sanitaria Aragón (IISAragón), 50009 Zaragoza, Spain.); Rivero, Olga (Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain. Biomedical Research Institute INCLIVA, Fundación Investigación Hospital Clínico de Valencia, 46010 Valencia, Spain. Departament of Genetics, University de Valencia, 46010 Valencia, Spain); Escartí-Fabra, Mª José (Department of Psychiatry, Hospital Clínico Universitario de Valencia, 46010 Valencia, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain. Biomedical Contributors Research Institute INCLIVA, 46010 Valencia, Spain); Legido, Teresa and Trabsa, Amira (Hospital del Mar Medical Research Institute. (IMIM), 08003 Barcelona, Spain); Sagué-Vilavella, Maria and Verdolini, Norma (Hospital Clínic de Barcelona, 08036 Barcelona, Spain; Department of Medicine, University of Barcelona; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain; Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 08036 Barcelona, Spain); Baeza, Imma and de la Serna, Elena (Department of Child and Adolescent Psychiatry and Psychology, Clinic Institute of Neurosciences, Hospital Clínic de Barcelona, 08036 Barcelona, Spain. University of Barcelona, 08036Barcelona, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain. Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 08036 Barcelona, Spain); Contreras-Fernandez, Fernando (Psychiatric Service, Bellvitge Universitary Hospital, IDIBELL, University of Barcelona, 08908 Barcelona, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain); Bobes, Julio and García-Portilla, María Paz (Área de Psiquiatría, Universidad de Oviedo, Hospital Universitario Central de Asturias (HUCA), 33011 Oviedo, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain; Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), 33011 Oviedo, Spain); Gutiérrez-Fraile, Miguel (Araba University Hospital, Bioaraba Research Institute, 01009 Vitoria-Gasteiz, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain); Segarra-Echevarría, Rafael (Cruces University Hospital, BioCruces Health Research Institute, University of the Basque Country (UPV/EHU), 48940 Vizcaya, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain); Sanchez-Pastor, Luis (Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), 28041 Madrid, Spain); Rodriguez-Jimenez, Roberto (Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), 28041 Madrid, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain. CogPsy Group, Universidad Complutense de Madrid (UCM), 28040 Madrid, Spain.); Usall, Judith (Parc Sanitari Sant Joan de Déu. Institut de Recerca Sant Joan de Déu, 08950 Barcelona, Spain); Butjosa, Anna (Parc Sanitari Sant Joan de Déu, Institut de Recerca Sant Joan de Déu Hospital Sant Joan de Déu, 08950 Barcelona, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain); Sarró, Salvador and Pomarol-Clotet, Edith (FIDMAG Germanes Hospitalàries Research Foundation, 08035 Barcelona, Spain. Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain); Ibáñez, Ángela (Department of Psychiatry, Hospital Universitario Ramón y Cajal, IRYCIS, Universidad de Alcalá, 28034 Madrid, Spain; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), 28029 Madrid, Spain); Ilundain, Jose L. (Department of Psychiatry, Complejo Hospitalario de Navarra, 31008 Pamplona, Spain. Navarra Institute of Health Research (IdiSNA), 31008 Pamplona, Spain).

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