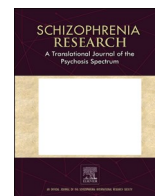


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## Metabolic polygenic risk scores effect on antipsychotic-induced metabolic dysregulation: A longitudinal study in a first episode psychosis cohort

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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.

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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-HT<sub>2A</sub> 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; Sifakis 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 certain 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 Squasina, 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<sub>SZ</sub>; 69,369 cases and 236,642 controls) (Ripke et al., 2020), bipolar disorder (PRS<sub>BD</sub>; 20,352 cases and 31,358 controls) (Stahl et al., 2019), depression (PRS<sub>DEP</sub>; 246,363 cases and 561,190 controls) (Howard et al., 2019), body mass index-adjusted waist-to-hip ratio (PRS<sub>WHR</sub>; 694,649 individuals) (Pulit et al., 2019), type II diabetes mellitus (PRS<sub>DM</sub>; 34,840 cases and 114,981 controls) (Morris et al., 2012), fasting glucose (PRS<sub>FG</sub>; 140,595 individuals) (Lagou et al., 2021), fasting insulin (PRS<sub>FI</sub>; 98,210 individuals) (Lagou et al., 2021) and serum TG, TC, HDL and LDL (PRS<sub>TG</sub>, PRS<sub>TC</sub>, PRS<sub>HDL</sub>, PRS<sub>LDL</sub>, 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  $\pi$ -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<sub>DEP</sub>, PRS<sub>TC</sub> and PRS<sub>LDL</sub> 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<sub>DEP</sub> 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%)         |
|   | Antiepileptic  | 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 <sup>2</sup> ) | 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).

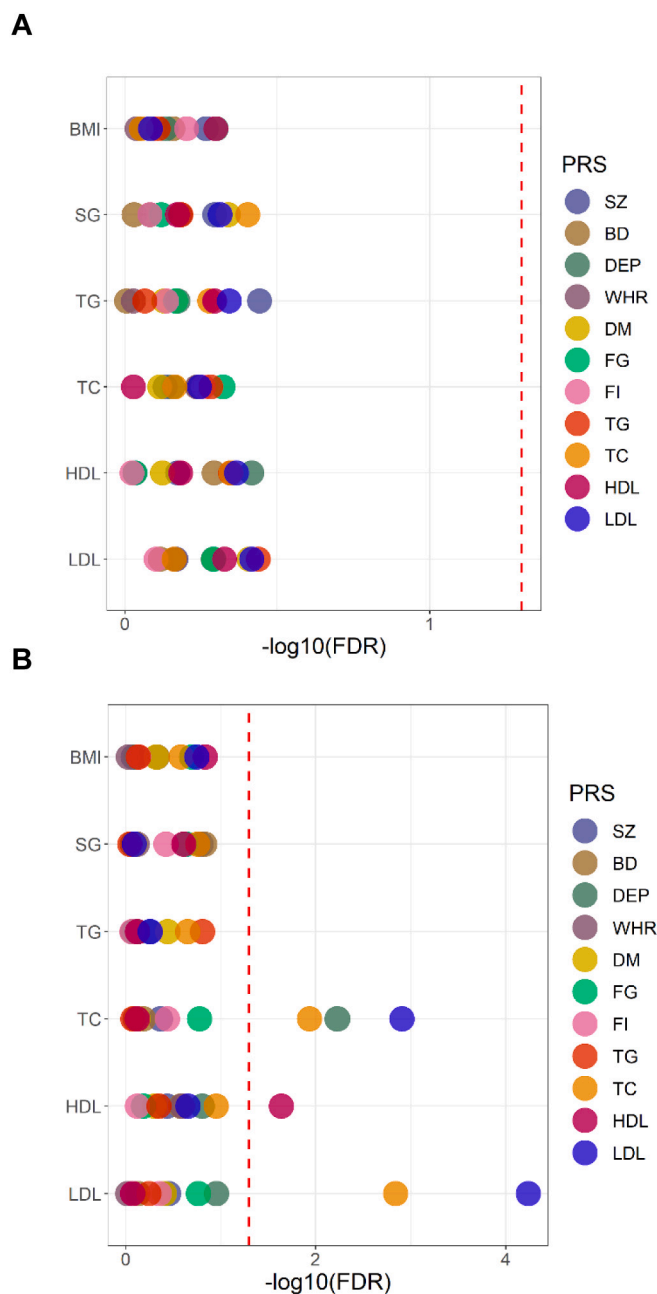
PR<sub>S<sub>LDL</sub></sub> at baseline, months 2 and 6 (FDR = 0.035, FDR = 0.009, FDR = 0.049; respectively). PR<sub>S<sub>HDL</sub></sub> was associated with HDL cholesterol trajectory (FDR = 0.023) with significant differences at month 6 (FDR = 0.036). Finally, PR<sub>S<sub>TC</sub></sub> and PR<sub>S<sub>LDL</sub></sub> were associated with LDL cholesterol (FDR = 0.001 and FDR = 5.82 × 10<sup>-5</sup>; respectively). Significantly different levels were found for PR<sub>S<sub>TC</sub></sub> at month 6 (FDR = 0.015) and for PR<sub>S<sub>LDL</sub></sub> 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 PR<sub>S<sub>DEP</sub></sub>, PR<sub>S<sub>TC</sub></sub>, PR<sub>S<sub>HDL</sub></sub> and PR<sub>S<sub>LDL</sub></sub> 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 PR<sub>S<sub>DEP</sub></sub> 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 × 10<sup>-5</sup>) (Table 3).

**4. Discussion**

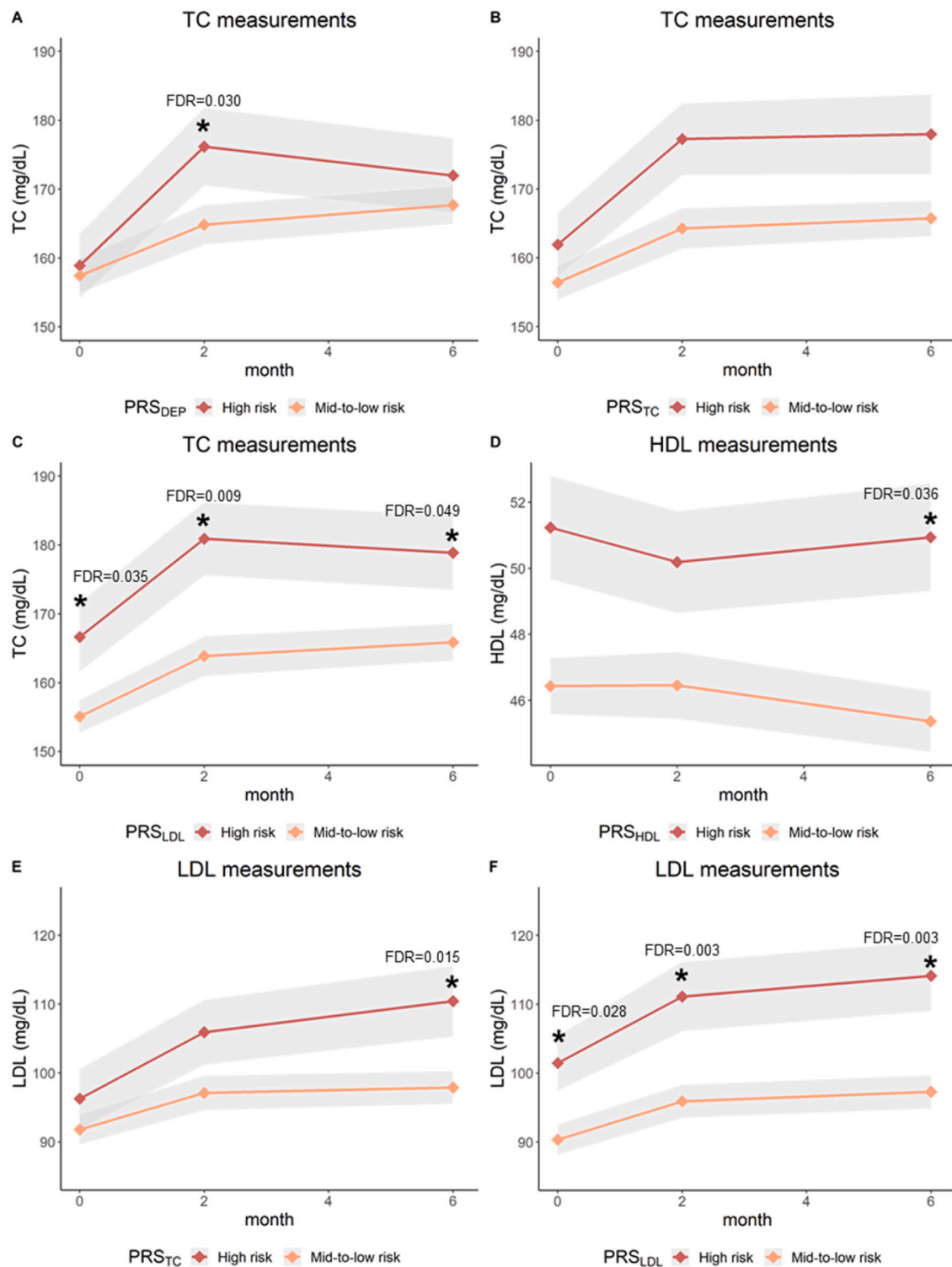
Traits associated with comorbid MetS such as abdominal obesity, hyperglycemia, dyslipidemia or lipoprotein imbalances have been widely acknowledged as side effects of SGA in schizophrenia patients. In this study, a battery of PRSs was constructed to assess the role of genetics in the metabolic changes 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 PR<sub>S<sub>DEP</sub></sub> showed significant associations. Regarding metabolic PRSs, those related to cholesterol levels (PR<sub>S<sub>TC</sub></sub>, PR<sub>S<sub>HDL</sub></sub> and PR<sub>S<sub>LDL</sub></sub>) 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<sub>DEP</sub>, B) TC stratified by PRS<sub>TC</sub>, C) TC stratified by PRS<sub>LDL</sub>, D) HDL stratified by PRS<sub>HDL</sub>, E) LDL stratified by PRS<sub>TC</sub> and F) LDL stratified by PRS<sub>LDL</sub>. 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<sub>DEP</sub> 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<sub>DEP</sub>, 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<sub>DEP</sub>, PRS<sub>TC</sub>, PRS<sub>HDL</sub> and PRS<sub>LDL</sub> with non-genetic risk factors for total, HDL and LDL cholesterol levels during the follow-up.

| Feature                  | PRS <sub>DEP</sub> |        |                |          | PRS <sub>TC</sub> |        |                |          | PRS <sub>HDL</sub> |        |                |          | PRS <sub>LDL</sub> |        |                |          |        |        |       |          |         |        |       |          |
|--------------------------|--------------------|--------|----------------|----------|-------------------|--------|----------------|----------|--------------------|--------|----------------|----------|--------------------|--------|----------------|----------|--------|--------|-------|----------|---------|--------|-------|----------|
|                          | TC                 |        | LDL            |          | HDL               |        | LDL            |          | HDL                |        | TC             |          | LDL                |        |                |          |        |        |       |          |         |        |       |          |
|                          | Estimate           | t      | R <sup>2</sup> | FDR      | Estimate          | t      | R <sup>2</sup> | FDR      | Estimate           | t      | R <sup>2</sup> | FDR      | Estimate           | t      | R <sup>2</sup> | 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/<br>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<br>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<sub>TC</sub>, PRS<sub>HDL</sub> and PRS<sub>LDL</sub> 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<sub>DEP</sub>, PRS<sub>TC</sub>, PRS<sub>HDL</sub> and PRS<sub>LDL</sub> 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.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2022.05.021>.

## Appendix A. PEPs group

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## References

- American Psychiatric Association, 1994. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association, Washington DC.
- Barton, B.B., Segger, F., Fischer, K., Obermeier, M., Musil, R., 2020. Update on weight-gain caused by antipsychotics: a systematic review and meta-analysis. *Expert Opin. Drug Saf.* 19, 295–314. <https://doi.org/10.1080/14740338.2020.1713091>.
- Bernardo, M., Bioque, M., Parellada, M., Saiz Ruiz, J., Cuesta, M.J., Llerena, A., Sanjuán, J., Castro-Fornieles, J., Arango, C., Cabrera, B., 2013. Assessing clinical and functional outcomes in a gene-environment interaction study in first episode of psychosis (PEPs). *Rev. Psiquiatr. Salud Ment.* 6, 4–16. <https://doi.org/10.1016/j.rpsmen.2012.11.001>.
- Bernardo, M., Bioque, M., Cabrera, B., Lobo, A., González-Pinto, A., Pina, L., Corripio, I., Sanjuán, J., Mané, A., Castro-Fornieles, J., Vieta, E., Arango, C., Mezquida, G., Gassó, P., Parellada, M., Saiz-Ruiz, J., Cuesta, M.J., Mas, S., 2017. Modelling gene-environment interaction in first episodes of psychosis. *Schizophr. Res.* 189, 181–189. <https://doi.org/10.1016/j.schres.2017.01.058>.
- Bioque, M., Llerena, A., Cabrera, B., Mezquida, G., Lobo, A., González-Pinto, A., Díaz-Caneja, C.M., Corripio, I., Aguilar, E.J., Bulbena, A., Castro-Fornieles, J., Vieta, E., Lafuente, A., Mas, S., Parellada, M., Saiz-Ruiz, J., Cuesta, M.J., Bernardo, M., Gassó, P., Amoretti, S., García Bernardo, E., Tapia-Casellas, C., Alonso-Solís, A., Grasa, E., Hernández, M., González, I., Ruiz, P., Modrego, F., Escartí, M.J., Mané, A., Torrent, C., Baeza, I., Contreras, F., Albacete, A., Bobes, J., García-Portilla, M.P., Zabala Rabadán, A., Segarra Echevarría, R., Rodríguez-Jimenez, R., Morales-Muñoz, I., Butjosa, A., Landín-Romero, R., Sarró, S., Ibáñez, A., Sánchez-Torres, A. M., Balanzá-Martínez, V., 2016. A pharmacovigilance study in first episode of psychosis: psychopharmacological interventions and safety profiles in the PEPs project. *Int. J. Neuropsychopharmacol.* 19, 1–10. <https://doi.org/10.1093/ijnp/pyv121>.
- Bioque, M., García-Portilla, M.P., García-Rizo, C., Cabrera, B., Lobo, A., González-Pinto, A., Díaz-Caneja, C.M., Corripio, I., Vieta, E., Castro-Fornieles, J., Bobes, J., Gutiérrez-Fraile, M., Rodríguez-Jimenez, R., Mezquida, G., Llerena, A., Saiz-Ruiz, J., Bernardo, M., Mesguer, A., Amoretti, S., Moreno, C., Parellada, M., Alonso-Solís, A., Rabella, M., Martínez-Cengotitabengoa, M., González-Ortega, I., Díaz, J.L., Barcones, M.F., Escartí, M.J., Cañete, C., Salgado, P., Cáceres, I., Torrent, C., Morilla, I., Baeza, I., de la Serna, E., Contreras, F., Albacete, A., García-Alvarez, L., de la Fuente, L., Eguiluz, J.I., Segarra, R., Morales-Muñoz, I., Torio, I., Usall, J., Butjosa, A., Sarró, S., Landín-Romero, R., Ibáñez, A., Cuesta, M.J., Balanzá-Martínez, V., 2018. Evolution of metabolic risk factors over a two-year period in a cohort of first episodes of psychosis. *Schizophr. Res.* 193, 188–196. <https://doi.org/10.1016/j.schres.2017.06.032>.
- Bulla, J., Hoffmann, K., Querengässer, J., Ross, T., 2017. Socioeconomic disadvantage and schizophrenia in migrants under mental health detention orders. *Int. J. Soc. Psychiatry* 63, 550–558. <https://doi.org/10.1177/0020764017716696>.
- Choi, S.W., O'Reilly, P.F., 2019. PRSice-2: polygenic risk score software for biobank-scale data. *Gigascience* 8. <https://doi.org/10.1093/gigascience/giz082>.
- Choi, S.W., Mak, T.S.H., O'Reilly, P.F., 2020. Tutorial: a guide to performing polygenic risk score analyses. *Nat. Protoc.* 15, 2759–2772. <https://doi.org/10.1038/s41596-020-0353-1>.
- Correll, C.U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P.B., Gaughran, F., Carvalho, A.F., Stubbs, B., 2017. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* 16, 163–180. <https://doi.org/10.1002/wps.20420>.
- Das, S., Forer, L., Schönherr, S., Sidore, C., Locke, A.E., Kwong, A., Vrieze, S.I., Chew, E. Y., Levy, S., McGue, M., Schlessinger, D., Stambolian, D., Loh, P.R., Iacono, W.G.,



- Swaroop, A., Scott, L.J., Cucca, F., Kronenberg, F., Boehnke, M., Abecasis, G.R., Fuchsberger, C., 2016. Next-generation genotype imputation service and methods. *Nat. Genet.* 48, 1284–1287. <https://doi.org/10.1038/ng.3656>.
- Delacortez, A., Lagares Santos, P., Saigi Morgui, N., Vandenberghe, F., Glatard, A., Gholam-Rezaee, M., Von Gunten, A., Conus, P., Eap, C.B., 2017. Influence of polygenic risk scores on lipid levels and dyslipidemia in a psychiatric population receiving weight gain-inducing psychotropic drugs. *Pharmacogenet. Genomics* 27, 464–472. <https://doi.org/10.1097/FPC.0000000000000313>.
- Eelink, E., van der Horst, M.Z., Zinkstok, J.R., Aalfs, C.M., Luyckx, J.J., 2021. Polygenic risk scores for genetic counseling in psychiatry: lessons learned from other fields of medicine. *Neurosci. Biobehav. Rev.* 121, 119–127. <https://doi.org/10.1016/j.neubiorev.2020.11.021>.
- Fernandez-Egea, E., Bernardo, M., Parellada, E., Justicia, A., Garcia-Rizo, C., Esmatjes, E., Conget, I., Kirkpatrick, B., 2008. Glucose abnormalities in the siblings of people with schizophrenia. *Schizophr. Res.* 103, 110–113. <https://doi.org/10.1016/j.schres.2008.04.017>.
- García-Rizo, C., Fernandez-Egea, E., Oliveira, C., Meseguer, A., Cabrera, B., Mezquida, G., Bioque, M., Penades, R., Parellada, E., Bernardo, M., Kirkpatrick, B., 2017. Metabolic syndrome or glucose challenge in first episode of psychosis? *Eur. Psychiatry* 41, 42–46. <https://doi.org/10.1016/j.eurpsy.2016.10.001>.
- Gardner, D.M., Murphy, A.L., O'Donnell, H., Centorrino, F., Baldessarini, R.J., 2010. International consensus study in psychiatry: lessons learned from other fields of medicine. *Neurosci. Biobehav. Rev.* 121, 119–127. <https://doi.org/10.1016/j.neubiorev.2020.11.021>.
- Gassó, P., Arnaiz, J.A., Mas, S., Lafuente, A., Bioque, M., Cuesta, M.J., Díaz-Caneja, C.M., García, C., Lobo, A., González-Pinto, A., Parellada, M., Corripio, I., Vieta, E., Castro-Fornieles, J., Mané, A., Rodríguez, N., Boloc, D., Saiz-Ruiz, J., Bernardo, M., 2020. Association study of candidate genes with obesity and metabolic traits in antipsychotic-treated patients with first-episode psychosis over a 2-year period. *J. Psychopharmacol.* 34, 514–523. <https://doi.org/10.1177/0269881120903462>.
- Habtwold, T.D., Islam, M.A., Liemburg, E.J., Bartels-Velthuis, A.A.A., van Beveren, N.J., Cahn, W., de Haan, L., Delespaul, P., Meijer, C.J., Myin-Germeys, I., Kahn, R.S., Schirmbeck, F., Simons, C.J.P., van Amelsvoort, T., van Haren, N.E., van Os, J., van Winkel, R., Bruggeman, R., Alizadeh, B.Z., 2020. Polygenic risk score for schizophrenia was not associated with glycemic level (HbA1c) in patients with non-affective psychosis: genetic risk and outcome of psychosis (GROUP) cohort study. *J. Psychosom. Res.* 132, 109968. <https://doi.org/10.1016/j.jpsychores.2020.109968>.
- Hiemstra, M., Nelemans, S.A., Branje, S., van Eijk, K.R., Hottenga, J.J., Vinkers, C.H., van Lier, P., Meeus, W., Boks, M.P., 2018. Genetic vulnerability to schizophrenia is associated with cannabis use patterns during adolescence. *Drug Alcohol Depend.* 190, 143–150. <https://doi.org/10.1016/j.drugalcdep.2018.05.024>.
- Howard, D.M., Adams, M.J., Clarke, T.K., Hafferty, J.D., Gibson, J., Shirali, M., Coleman, J.R.I., Hagenaars, S.P., Ward, J., Wigmore, E.M., Alloza, C., Shen, X., Barbu, M.C., Xu, E.Y., Whalley, H.C., Marioni, R.E., Porteous, D.J., Davies, G., Dearn, L.J., Hemani, G., Berger, K., Teismann, H., Rawal, R., Arolt, V., Baune, B.T., Dannewald, U., Domschke, K., Tian, C., Hinds, D.A., Trzaskowski, M., Byrne, E.M., Ripke, S., Smith, D.J., Sullivan, P.F., Wray, N.R., Breen, G., Lewis, C.M., McIntosh, A.M., 2019. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat. Neurosci.* 22, 343–352. <https://doi.org/10.1038/s41593-018-0326-7>.
- Janssens, A.C.J.W., 2019. Validity of polygenic risk scores: are we measuring what we think we are? *Hum. Mol. Genet.* 28, R143–R150. <https://doi.org/10.1093/hmg/ddz205>.
- Kember, R.L., Hou, L., Ji, X., Andersen, L.H., Ghorai, A., Estrella, L.N., Almasly, L., McMahon, F.J., Brown, C., Bućan, M., 2018. Genetic pleiotropy between mood disorders, metabolic, and endocrine traits in a multigenerational pedigree. *Transl. Psychiatry* 8, 218. <https://doi.org/10.1038/s41398-018-0226-3>.
- Lagou, V., Mägi, R., Hottenga, J.J., Grallert, H., Perry, J.R.B., Bouatia-Naji, N., Marullo, L., Rybin, D., Jansen, R., Min, J.L., Dimas, A.S., Ulrich, A., Zudina, L., Gädin, J.R., Jiang, L., Faggian, A., Bonnefond, A., Fadista, J., Stathopoulou, M.G., Isaacs, A., Willems, S.M., Navarro, P., Tanaka, T., Jackson, A.U., Montasser, M.E., O'Connell, J.R., Bielak, L.F., Webster, R.J., Saxena, R., Stafford, J.M., Pourcain, B.S., Timponi, N.J., Salo, P., Shin, S.Y., Amin, R., Smith, A.V., Li, G., Verweij, N., Goel, A., Ford, I., Johnson, P.C.D., Johnson, T., Kapur, K., Thorleifsson, G., Strawbridge, R.J., Rasmussen-Torvik, L.J., Esko, T., Mihailov, E., Fall, T., Fraser, R.M., Mahajan, A., Kanoni, S., Giedraitis, V., Kleber, M.E., Silbernagel, G., Meyer, J., Müller-Nurasyid, M., Ganna, A., Sarin, A.P., Yengo, L., Shungin, D., Luan, J., Horikoshi, M., An, P., Sanna, S., Boettcher, Y., Rayner, N.W., Nolte, I.M., Zemanek, T., van Iperen, E., Kovacs, P., Hastie, N.D., Wild, S.H., McLachlan, S., Campbell, S., Polasek, O., Carlson, O., Egan, J., Kiess, W., Willemsen, G., Kuusisto, J., Laakso, M., Dimitriou, M., Hicks, A.A., Rauramaa, R., Bandinelli, S., Thorand, B., Liu, Y., Miljkovic, I., Lind, L., Doney, A., Perola, M., Hingorani, A., Kivimäki, M., Kumari, M., Bennett, A.J., Groves, C.J., Herder, C., Koistinen, H.A., Kinnunen, L., de Faire, U., Bakker, S.J.L., Uusitupa, M., Palmer, C.N.A., Jukema, J.W., Sattar, N., Pouta, A., Snieder, H., Boerwinkle, E., Pankow, J.S., Magnusson, P.K., Krus, U., Scapoli, C., de Geus, E.J.C.N., Blüher, M., Wolfenbutter, B.H.R., Province, M.A., Abecasis, G.R., Meigs, J.B., Hovingh, G.K., Lindström, J., Wilson, J.F., Wright, A.F., Dedoussis, G.V., Bornstein, S.R., Schwarz, P.E.H., Tönjes, A., Winkelman, B.R., Boehm, B.O., März, W., Metspalu, A., Price, J.F., Deloukas, P., Körner, A., Lakka, T.A., Keinanen-Kiukkaanniemi, S.M., Saaristo, T.E., Bergman, R.N., Tuomilehto, J., Wareham, N.J., Langenberg, C., Männistö, S., Franks, P.W., Hayward, C., Vitart, V., Kaprio, J., Visvikis-Siest, S., Balkau, B., Althuler, D., Rudan, I., Stumvoll, M., Campbell, H., van Duijn, C.M., Gieger, C., Illig, T., Ferrucci, L., Pedersen, N.L., Pramstaller, P.P., Boehnke, M., Frayling, T.M., Shuldiner, A.R., Peyser, P.A., Kardia, S.L.R., Palmer, L.J., Penninx, B.W., Meneton, P., Harris, T.B., Navis, G., van der Harst, P., Smith, G.D., Forouhi, N.G., Loos, R.J.F., Salomaa, V., Soranzo, N., Boomsma, D.I., Groop, L., Tuomi, T., Hofman, A., Munroe, P.B., Gudnason, V., Siscovick, D.S., Watkins, H., Lecoeur, C., Vollenweider, P., Franco-Cereceda, A., Eriksson, P., Jarvelin, M.R., Stefansson, K., Hamsten, A., Nicholson, G., Karpe, F., Dermizakis, E.T., Lindgren, C.M., McCarthy, M.I., Froguel, P., Kaakinen, M.A., Lyssenko, V., Watanabe, R.M., Ingelsson, E., Florez, J.C., Dupuis, J., Barroso, I., Morris, A.P., Prokopenko, I., 2021. Sex-dimorphic genetic effects and novel loci for fasting glucose and insulin variability. *Nat. Commun.* 12. <https://doi.org/10.1038/s41467-020-19366-9>.
- Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R., Kissling, W., Stapf, M.P., Lässig, B., Salanti, G., Davis, J.M., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 382, 951–962. [https://doi.org/10.1016/S0140-6736\(13\)60733-3](https://doi.org/10.1016/S0140-6736(13)60733-3).
- Lin, Y.F., Chen, C.Y., Öngür, D., Betensky, R., Smoller, J.W., Blacker, D., Hall, M.H., 2018. Polygenic pleiotropy and potential causal relationships between educational attainment, neurobiological profile, and positive psychotic symptoms. *Transl. Psychiatry* 8. <https://doi.org/10.1038/s41398-018-0144-4>.
- Maj, C., Tosato, S., Zanardini, R., Lasalvia, A., Favaro, A., Leuci, E., De Girolamo, G., Ruggeri, M., Gennarelli, M., Bocchio-Chiavetto, L., 2020. Correlations between immune and metabolic serum markers and schizophrenia/bipolar disorder polygenic risk score in first-episode psychosis. *Early Interv. Psychiatry* 14, 507–511. <https://doi.org/10.1111/eip.12906>.
- Malan-Müller, S., Kilian, S., Van Den Heuvel, L.L., Bardien, S., Asmal, L., Warnich, L., Emsley, R.A., Hemmings, S.M.J., Seedat, S., 2016. A systematic review of genetic variants associated with metabolic syndrome in patients with schizophrenia. *Schizophr. Res.* 170, 1–17. <https://doi.org/10.1016/j.schres.2015.11.011>.
- Mas, S., Boloc, D., Rodríguez, N., Mezquida, G., Amoretti, S., Cuesta, M.J., González-Peñas, J., García-Alcón, A., Lobo, A., González-Pinto, A., Corripio, I., Vieta, E., Castro-Fornieles, J., Mané, A., Saiz-Ruiz, J., Gassó, P., Bioque, M., Bernardo, M., 2020. Examining gene-environment interactions using aggregate scores in a first-episode psychosis cohort. *Schizophr. Bull.* 46, 1019–1025. <https://doi.org/10.1093/schbul/sbaa012>.
- Mistry, S., Harrison, J.R., Smith, D.J., Escott-Price, V., Zammit, S., 2018a. The use of polygenic risk scores to identify phenotypes associated with genetic risk of bipolar disorder and depression: a systematic review. *J. Affect. Disord.* 234, 148–155. <https://doi.org/10.1016/j.jad.2018.02.005>.
- Mistry, S., Harrison, J.R., Smith, D.J., Escott-Price, V., Zammit, S., 2018b. The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: systematic review. *Schizophr. Res.* <https://doi.org/10.1016/j.schres.2017.10.037>.
- Mitchell, A.J., Vancampfort, D., De Herdt, A., Yu, W., De Hert, M., 2013. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophr. Bull.* 39, 295–305. <https://doi.org/10.1093/schbul/sbs082>.
- Morris, A.P., Voight, B.F., Teslovich, T.M., Ferreira, T., Segre, A.V., Steinthorsdottir, V., Strawbridge, R.J., Khan, H., Grallert, H., Mahajan, A., Prokopenko, I., Kang, H.M., Dina, C., Esko, T., Fraser, R.M., Kanoni, S., Kumar, A., Lagou, V., Langenberg, C., Luan, J., Lindgren, C.M., Müller-Nurasyid, M., Pechlivanis, S., Rayner, N.W., Scott, L.J., Wiltshire, S., Yengo, L., Kinnunen, L., Rossin, E.J., Raychaudhuri, S., Johnson, A.D., Dimas, A.S., Loos, R.J.F., Vedantam, S., Chen, H., Florez, J.C., Fox, C., Liu, C.T., Rybin, D., Couper, D.J., Kao, W.H.L., Li, M., Cornelis, M.C., Kraft, P., Sun, Q., Van Dam, R.M., Stringham, H.M., Chines, P.S., Fischer, K., Fontanillas, P., Holmen, O.L., Hunt, S.E., Jackson, A.U., Kong, A., Lawrence, R., Meyer, J., Perry, J.R.B., Platou, C.G.P., Potter, S., Rehnberg, E., Robertson, N., Sivapalanatnam, S., Stancáková, A., Stirrups, K., Thorleifsson, G., Tikkanen, E., Wood, A.R., Almgren, P., Atalay, M., Benediktsson, R., Bonnycastle, L.L., Burt, N., Carey, J., Charpentier, G., Crenshaw, A.T., Doney, A.S.F., Dorkhan, M., Edkins, S., Emilsson, V., Eury, E., Forsen, T., Gertow, K., Gigante, B., Grant, G.B., Groves, C.J., Guiducci, C., Herder, C., Hreidarsson, A.B., Hui, J., James, A., Jonsson, A., Rathmann, W., Klopp, N., Kravic, J., Krjutskov, K., Langford, C., Leander, K., Lindholm, E., Lobbens, S., Männistö, S., Mirza, G., Mühlhausen, T.W., Musk, B., Parkin, M., Rallidis, L., Saramies, J., Sennblad, B., Shah, S., Sigursson, G., Silveira, A., Steinbach, G., Thorand, B., Trakalo, J., Veglia, F., Wennyer, R., Winckler, W., Zabaneh, D., Campbell, H., Van Duijn, C., Uitterlinden, A.G., Hofman, A., Sijbrands, E., Abecasis, G.R., Owen, K.R., Zeggini, E., Trip, M.D., Forouhi, N.G., Syvänen, A.C., Eriksson, J.G., Peltonen, L., Nöthen, M.M., Balkau, B., Palmer, C.N.A., Lyssenko, V., Tuomi, T., Isomaa, B., Hunter, D.J., Qi, L., Shuldiner, A.R., Roden, M., Barroso, I., Wilsgaard, T., Beilby, J., Hovingh, K., Price, J.F., Wilson, J.F., Rauramaa, R., Lakka, T.A., Lind, L., Dedoussis, G., NjøLstad, I., Pedersen, N.L., Khaw, K.T., Wareham, N.J., Keinanen-Kiukkaanniemi, S.M., Saaristo, T.E., Korpi-HyöVälä, E., Saltevo, J., Laakso, M., Kuusisto, J., Metspalu, A., Collins, F.S., Mohlke, K.L., Bergman, R.N., Tuomilehto, J., Boehm, B.O., Gieger, C., Hveem, K., Cauchi, S., Froguel, P., Baldassarre, D., Tremoli, E., Humphries, S.E., Saleheen, D., Danesh, J., Ingelsson, E., Ripatti, S., Salomaa, V., Erbel, R., JöCkel, K.H., Moebus, S., Peters, A., Illig, T., Faire, U.De, Hamsten, A., Morris, A.D., Donnelly, P.J., Frayling, T.M., Hattersley, A.T., Boerwinkle, E., Melander, O., Kathiresan, S., Nilsson, P.M., Deloukas, P., Thorsteinsdottir, U., Groop, L.C., Stefansson, K., Hu, F., Pankow, J.S., Dupuis, J., Meigs, J.B., Althuler, D., Boehnke, M., McCarthy, M.I., 2012. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat. Genet.* 44, 981–990. <https://doi.org/10.1038/ng.2383>.
- Perkins, D.O., Olde Loohuis, L., Barbee, J., Ford, J., Jeffries, C.D., Addington, J., Bearden, C.E., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Mathalon, D.H., McGlashan, T.H., Seidman, L.J., Tsuang, M., Walker, E.F., Woods, S.W., 2020. Polygenic risk score contribution to psychosis prediction in a target population of persons at clinical high risk. *Am. J. Psychiatry* 177, 155–163. <https://doi.org/10.1176/appi.ajp.2019.18060721>.



- Perry, B.I., McIntosh, G., Weich, S., Singh, S., Rees, K., 2016. The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis. *Lancet Psychiatry* 3, 1049–1058. [https://doi.org/10.1016/S2215-0366\(16\)30262-0](https://doi.org/10.1016/S2215-0366(16)30262-0).
- Pillinger, T., McCutcheon, R.A., Vano, L., Mizuno, Y., Arumham, A., Hindley, G., Beck, K., Natesan, S., Efthimiou, O., Cipriani, A., Howes, O.D., 2020. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry* 7, 64–77. [https://doi.org/10.1016/S2215-0366\(19\)30416-X](https://doi.org/10.1016/S2215-0366(19)30416-X).
- Pina-Camacho, L., Del Rey-Mejías, Á., Janssen, J., Bioque, M., González-Pinto, A., Arango, C., Lobo, A., Sarró, S., Desco, M., Sanjuan, J., Lacalle-Auriales, M., Cuesta, P.M., Saiz-Ruiz, J., Bernardo, M., Parellada, M., 2016. Age at first episode modulates diagnosis-related structural brain abnormalities in psychosis. *Schizophr. Bull.* 42, 344–357. <https://doi.org/10.1093/schbul/sbv128>.
- Pisanu, C., Squassina, A., 2019. Treatment-resistant schizophrenia: insights from genetic studies and machine learning approaches. *Front. Pharmacol.* 10, 1–7. <https://doi.org/10.3389/fphar.2019.00617>.
- Pulit, S.L., Stoneman, C., Morris, A.P., Wood, A.R., Glastonbury, C.A., Tyrrell, J., Yengo, L., Ferreira, T., Marouli, E., Ji, Y., Yang, J., Jones, S., Beaumont, R., Croteau-Chonka, D.C., Winkler, T.W., Hattersley, A.T., Loos, R.J.F., Hirschhorn, J.N., Visscher, P.M., Frayling, T.M., Yaghoobkar, H., Lindgren, C.M., 2019. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Hum. Mol. Genet.* 28, 166–174. <https://doi.org/10.1093/hmg/ddy327>.
- Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A.R., Bender, D., Maller, J., Sklar, P., De Bakker, P.I.W., Daly, M.J., Sham, P.C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* 81, 559–575. <https://doi.org/10.1086/519795>.
- R Core Team [WWW Document], 2017. R a lang. *Environ. Stat. Comput. R Found. Stat. Comput. Vienna, Austria*. URL: <https://www.r-project.org/>.
- Radulescu, E., Jaffe, A.E., Straub, R.E., Chen, Q., Shin, J.H., Hyde, T.M., Kleinman, J.E., Weinberger, D.R., 2020. Identification and prioritization of gene sets associated with schizophrenia risk by co-expression network analysis in human brain. *Mol. Psychiatry* 25, 791–804. <https://doi.org/10.1038/s41380-018-0304-1>.
- Ripke, S., Walters, J.T.R., O'Donovan, M.C., 2020. Mapping Genomic Loci Prioritises Genes and Implicates Synaptic Biology in Schizophrenia. *medRxiv*. <https://doi.org/10.1101/2020.09.12.20192922>.
- Salagre, E., Arango, C., Artigas, F., Ayuso-Mateos, J.L., Bernardo, M., Castro-Fornieles, J., Bobes, J., Desco, M., Fañanás, L., González-Pinto, A., Haro, J.M., Leza, J.C., McKenna, P.J., Meana, J.J., Menchón, J.M., Micó, J.A., Palomo, T., Pazos, A., Pérez, V., Saiz-Ruiz, J., Sanjuán, J., Tabarés-Seisdedos, R., Crespo-Facorro, B., Casas, M., Vilella, E., Palao, D., Olivares, J.M., Rodríguez-Jimenez, R., Vieta, E., 2019. CIBERSAM: ten years of collaborative translational research in mental disorders. *Rev. Psiquiatr. Salud Ment.* 12, 1–8. <https://doi.org/10.1016/j.rpsm.2018.10.001>.
- Samson, S.L., Garber, A.J., 2014. Metabolic syndrome. *Endocrinol. Metab. Clin. N. Am.* 43, 1–23. <https://doi.org/10.1016/j.ecl.2013.09.009>.
- Santorio, M.L., Ota, V., de Jong, S., Noto, C., Spindola, L.M., Talarico, F., Gouvea, E., Lee, S.H., Moretti, P., Curtis, C., Patel, H., Newhouse, S., Carvalho, C.M., Gadelha, A., Cordeiro, Q., Bressan, R.A., Belangero, S.I., Breen, G., 2018. Polygenic risk score analyses of symptoms and treatment response in an antipsychotic-naïve first episode of psychosis cohort. *Transl. Psychiatry* 8, 174. <https://doi.org/10.1038/s41398-018-0230-7>.
- Siafis, S., Tzachanis, D., Samara, M., Papazisis, G., 2017. Antipsychotic drugs: from receptor-binding profiles to metabolic side effects. *Curr. Neuropharmacol.* 16, 1210–1223. <https://doi.org/10.2174/1570159x15666170630163616>.
- Smeland, O.B., Andreassen, O.A., 2021. Polygenic risk scores in psychiatry – large potential but still limited clinical utility. *Eur. Neuropsychopharmacol.* 51, 68–70. <https://doi.org/10.1016/j.euroneuro.2021.05.007>.
- Sneller, M.H., de Boer, N., Everaars, S., Schuurmans, M., Guloksuz, S., Cahn, W., Luyckx, J.J., 2021. Clinical, biochemical and genetic variables associated with metabolic syndrome in patients with schizophrenia Spectrum disorders using second-generation antipsychotics: a systematic review. *Front. Psychiatry* 12, 1–14. <https://doi.org/10.3389/fpsy.2021.625935>.
- Solmi, F., Mascarell, M.C., Zammit, S., Kirkbride, J.B., Lewis, G., 2019. Polygenic risk for schizophrenia, disordered eating behaviours and body mass index in adolescents. *Br. J. Psychiatry* 215, 428–433. <https://doi.org/10.1192/bjp.2019.39>.
- Stahl, E.A., Breen, G., Forstner, A.J., McQuillin, A., Ripke, S., Trubetskoy, V., Mattheisen, M., Wang, Y., Coleman, J.R.I., Gaspar, H.A., de Leeuw, C.A., Steinberg, S., Pavlides, J.M.W., Trzaskowski, M., Byrne, E.M., Pers, T.H., Holmans, P. A., Richards, A.L., Abbott, L., Agerbo, E., Akil, H., Albani, D., Alliey-Rodriguez, N., Als, T.D., Anjorin, A., Antilla, V., Awasthi, S., Badner, J.A., Bækvad-Hansen, M., Barchas, J.D., Bass, N., Bauer, M., Belliveau, R., Bergen, S.E., Pedersen, C.B., Boen, E., Boks, M.P., Boocock, J., Budde, W., Bunney, B., Burneister, M., Bybjerg-Grauholm, J., Byerley, W., Casas, M., Cerrato, F., Cervantes, P., Chambert, K., Charney, A.W., Chen, D., Churchhouse, C., Clarke, T.K., Coryell, W., Craig, D.W., Cruceanu, C., Curtis, D., Czerski, P.M., Dale, A.M., de Jong, S., Degenhardt, F., Del Favero, J., DePaulo, J.R., Djurovic, S., Dobbyn, A.L., Dumont, A., Elvsåshagen, T., Escott-Price, V., Fan, C.C., Fischer, S.B., Flickinger, M., Foroud, T.M., Forty, L., Frank, J., Fraser, C., Freimer, R.B., Frisén, L., Gade, K., Gage, D., Garnham, J., Giambartolomei, C., Pedersen, M.G., Goldstein, J., Gordon, S.D., Gordon-Smith, K., Green, E.K., Green, M.J., Greenwood, T.A., Grove, J., Guan, W., Guzman-Parra, J., Hamshere, M.L., Hautzinger, M., Heilbronner, U., Herms, S., Hipolito, M., Hoffmann, P., Holland, D., Huckins, L., Jamain, S., Johnson, J.S., Juréus, A., Kandaswamy, R., Karlsson, R., Kennedy, J.L., Kittel-Schneider, S., Knowles, J.A., Kogevinas, M., Koller, A.C., Kupka, R., Lavebratt, C., Lawrence, J., Lawson, W.B., Leber, M., Lee, P.H., Levy, S.E., Li, J.Z., Liu, C., Lucae, S., Maaser, A., MacIntyre, D. J., Mahon, P.B., Maier, W., Martinsson, L., McCarron, S., McGuffin, P., McInnis, M. G., McKay, J.D., Medeiros, H., Medland, S.E., Meng, F., Milani, L., Montgomery, G. W., Morris, D.W., Mühleisen, T.W., Mullins, N., Nguyen, H., Nievergelt, C.M., Adolfsson, A.N., Nwulia, E.A., O'Donovan, C., Loohuis, L.M.O., Ori, A.P.S., Oruc, L., Ösby, U., Perlis, R.H., Perry, A., Pfennig, A., Potash, J.B., Purcell, S.M., Regeer, E.J., Reif, A., Reinbold, C.S., Rice, J.P., Rivas, F., Rivera, M., Roussos, P., Ruderfer, D.M., Ryu, E., Sánchez-Mora, C., Schatzberg, A.F., Scheftner, W.A., Schork, N.J., Shannon Weickert, C., Shekhtman, T., Shilling, P.D., Sigurdsson, E., Slaney, C., Smeland, O.B., Sobell, J.L., Søholm Hansen, C., Spijker, A.T., St Clair, D., Steffens, M., Strauss, J.S., Streit, F., Strohmaier, J., Szelinger, S., Thompson, R.C., Thorgeirsson, T.E., Treutlein, J., Vedder, H., Wang, W., Watson, S.J., Weickert, T.W., Witt, S.H., Xi, S., Xu, W., Young, A.H., Zandi, P., Zhang, P., Zöllner, S., Adolfsson, R., Agartz, I., Alda, M., Backlund, L., Baune, B.T., Bellivier, F., Berrettini, W.H., Biernacka, J.M., Blackwood, D.H.R., Boehnke, M., Børglum, A.D., Corvin, A., Craddock, N., Daly, M. J., Danilowski, U., Esko, T., Etain, B., Frye, M., Fullerton, J.M., Gershon, E.S., Gill, M., Goes, F., Grigoriou-Serbanescu, M., Hauser, J., Hougaard, D.M., Hultman, C. M., Jones, I., Jones, L.A., Kahn, R.S., Kirov, G., Landén, M., Leboyer, M., Lewis, C.M., Li, Q.S., Lissowska, J., Martin, N.G., Mayoral, F., McElroy, S.L., McIntosh, A.M., McMahon, F.J., Melle, I., Metspalu, A., Mitchell, P.B., Morken, G., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Myers, R.M., Neale, B.M., Nimgaonkar, V., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Oedegaard, K.J., Owen, M.J., Paciga, S.A., Pato, C., Pato, M.T., Posthuma, D., Ramos-Quiroga, J.A., Ribases, M., Rietschel, M., Rouleau, G.A., Schalling, M., Schofield, P.R., Schulze, T.G., Serretti, A., Smoller, J.W., Stefansson, H., Stefansson, K., Stordal, E., Sullivan, P.F., Turecki, G., Vaaler, A.E., Vieta, E., Vincent, J.B., Werge, T., Nurnberger, J.I., Wray, N.R., Di Florio, A., Edenberg, H.J., Cichon, S., Ophoff, R.A., Scott, L.J., Andreassen, O.A., Kelsøe, J., Sklar, P., 2019. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat. Genet.* 51, 793–803. <https://doi.org/10.1038/s41588-019-0397-8>.
- Tomasik, J., Lago, S.G., Vázquez-Bourgon, J., Papiol, S., Suárez-Pinilla, P., Crespo-Facorro, B., Bahn, S., 2019. Association of Insulin Resistance with schizophrenia polygenic risk score and response to antipsychotic treatment. *JAMA Psychiatry*. <https://doi.org/10.1001/jamapsychiatry.2019.0304>.
- Torkamani, A., Wineinger, N.E., Topol, E.J., 2018. The personal and clinical utility of polygenic risk scores. *Nat. Rev. Genet.* 19, 581–590. <https://doi.org/10.1038/s41576-018-0018-x>.
- Vancampfort, D., Stubbs, B., Mitchell, A.J., De Hert, M., Wampers, M., Ward, P.B., Rosenbaum, S., Correll, C.U., 2015. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry* 14, 339–347. <https://doi.org/10.1002/wps.20252>.
- Vassos, E., Di Forti, M., Coleman, J., Iyegbe, C., Prata, D., Euesden, J., O'Reilly, P., Curtis, C., Koliakou, A., Patel, H., Newhouse, S., Traylor, M., Ajnakina, O., Mondelli, V., Marques, T.R., Gardner-Sood, P., Aitchison, K.J., Powell, J., Atakan, Z., Greenwood, K.E., Smith, S., Ismail, K., Pariante, C., Gaughran, F., Dazzan, P., Markus, H.S., David, A.S., Lewis, C.M., Murray, R.M., Breen, G., 2017. An examination of polygenic risk score prediction in individuals with first-episode psychosis. *Biol. Psychiatry* 81, 470–477. <https://doi.org/10.1016/j.biopsych.2016.06.028>.
- Vázquez-Bourgon, J., Ibáñez Alario, M., Mayoral-van Son, J., Gómez Revuelta, M., Ayesa Arriola, R., Juncal Ruiz, M., Ortiz-García de la Foz, V., Crespo Facorro, B., 2020. A 3-year prospective study on the metabolic effect of aripiprazole, quetiapine and ziprasidone: a pragmatic clinical trial in first episode psychosis patients. *Eur. Neuropsychopharmacol.* 39, 46–55. <https://doi.org/10.1016/j.euroneuro.2020.08.009>.
- Wang, S.H., Hsiao, P.C., Yeh, L.L., Liu, C.M., Liu, C.C., Hwang, T.J., Hsieh, M.H., Chien, Y.L., Lin, Y.T., Chandler, S.D., Faraone, S.V., Laird, N., Neale, B., McCarron, S. A., Glatt, S.J., Tsuang, M.T., Hwu, H.G., Chen, W.J., 2018. Polygenic risk for schizophrenia and neurocognitive performance in patients with schizophrenia. *Genes Brain Behav.* 17, 49–55. <https://doi.org/10.1111/gbb.12401>.
- Willer, C.J., Schmidt, E.M., Sengupta, S., Peloso, G.M., Gustafsson, S., Kanoni, S., Ganna, A., Chen, J., Buchkovich, M.L., Mora, S., Beckmann, J.S., Bragg-Gresham, J. L., Chang, H.Y., Demirkan, A., Den Hertog, H.M., Do, R., Donnelly, L.A., Ehret, G.B., Esko, T., Feitosa, M.F., Ferreira, T., Fischer, K., Fontanillas, P., Fraser, R.M., Freitag, D.F., Gurdasani, D., Heikkilä, K., Hyppönen, E., Isaacs, A., Jackson, A.U., Johansson, Å., Johnson, T., Kaakinen, M., Kettunen, J., Kleber, M.E., Li, X., Luan, J., Lyttikäinen, L.P., Magnusson, P.K.E., Mangino, M., Mihailov, E., Montasser, M.E., Müller-Nurasyid, M., Nolte, I.M., O'Connell, J.R., Palmer, C.D., Perola, M., Petersen, A.K., Sanna, S., Saxena, R., Service, S.K., Shah, S., Shungin, D., Sidore, C., Song, C., Strawbridge, R.J., Surakka, I., Tanaka, T., Teslovich, T.M., Thorleifsson, G., Van Den Herik, E.G., Voight, B.F., Volcik, K.A., Waite, L.L., Wong, A., Wu, Y., Zhang, W., Absher, D., Asiki, G., Barroso, I., Been, L.F., Bolton, J.L., Bonnycastle, L. L., Brambilla, P., Burnett, M.S., Cesana, G., D'Adamo, M., Doney, A.S.F., Döring, A., Elliott, P., Epstein, S.E., Eyjolfsson, G.I., Gigante, B., Goodarzi, M.O., Grallert, H., Gravitto, M.L., Groves, C.J., Hallmans, G., Hartikainen, A.L., Hayward, C., Hernandez, D., Hicks, A.A., Holm, H., Hung, Y.J., Illig, T., Jones, M.R., Kaleebu, P., Kastelein, J.J.P., Khaw, K.T., Kim, E., Klopp, N., Komulainen, P., Kumari, M., Langenberg, C., Lehtimäki, T., Lin, S.Y., Lindström, J., Loos, R.J.F., Mach, F., McArdle, W.L., Meisinger, C., Mitchell, B.D., Müller, G., Nagaraja, R., Narisu, N., Nieminen, T.V.M., Nsubuga, R.N., Olafsson, I., Ong, K.K., Palotie, A., Papamarkou, T., Pomilla, C., Pouta, A., Rader, D.J., Reilly, M.P., Ridker, P.M., Rivadeneira, F., Rudan, I., Ruukonen, A., Samani, N., Schrag, H., Seelye, J., Silander, K., Stancáková, A., Stirrups, K., Swift, A.J., Tiret, L., Uitterlinden, A.G., Van Pelt, L.J., Vedantam, S., Wainwright, N., Wijmenga, C., Wild, S.H., Willemsen, G.,

- Wilsgaard, T., Wilson, J.F., Young, E.H., Zhao, J.H., Adair, L.S., Arveiler, D., Assimes, T.L., Bandinelli, S., Bennett, F., Bochud, M., Boehm, B.O., Boomsma, D.I., Borecki, I.B., Bornstein, S.R., Bovet, P., Burnier, M., Campbell, H., Chakravarti, A., Chambers, J.C., Chen, Y.D.I., Collins, F.S., Cooper, R.S., Danesh, J., Dedoussis, G., De Faire, U., Feranil, A.B., Ferrières, J., Ferrucci, L., Freimer, N.B., Gieger, C., Groop, L. C., Gudnason, V., Gyllenstein, U., Hamsten, A., Harris, T.B., Hingorani, A., Hirschhorn, J.N., Hofman, A., Hovingh, G.K., Hsiung, C.A., Humphries, S.E., Hunt, S. C., Hveem, K., Iribarren, C., Järvelin, M.R., Jula, A., Kähönen, M., Kaprio, J., Kesäniemi, A., Kivimäki, M., Kooner, J.S., Koudstaal, P.J., Krauss, R.M., Kuh, D., Kuusisto, J., Kyvik, K.O., Laakso, M., Lakka, T.A., Lind, L., Lindgren, C.M., Martin, N. G., März, W., McCarthy, M.I., McKenzie, C.A., Meneton, P., Metspalu, A., Moilanen, L., Morris, A.D., Munroe, P.B., Njølstad, I., Pedersen, N.L., Power, C., Pramstaller, P.P., Price, J.F., Psaty, B.M., Quertermous, T., Rauramaa, R., Saleheen, D., Salomaa, V., Sanghera, D.K., Saramies, J., Schwarz, P.E.H., Sheu, W.H. H., Shuldiner, A.R., Siegbahn, A., Spector, T.D., Stefansson, K., Strachan, D.P., Tayo, B.O., Tremoli, E., Tuomilehto, J., Uusitupa, M., Van Duijn, C.M., Vollenweider, P., Wallentin, L., Wareham, N.J., Whitfield, J.B., Wolffenbuttel, B.H. R., Ordovas, J.M., Boerwinkle, E., Palmer, C.N.A., Thorsteinsdottir, U., Chasman, D. I., Rotter, J.I., Franks, P.W., Ripatti, S., Cupples, L.A., Sandhu, M.S., Rich, S.S., Boehnke, M., Deloukas, P., Kathiresan, S., Mohlke, K.L., Ingelsson, E., Abecasis, G.R., 2013. Discovery and refinement of loci associated with lipid levels. *Nat. Genet.* 45, 1274–1285. <https://doi.org/10.1038/ng.2797>.
- Zhang, J.P., Robinson, D., Yu, J., Gallego, J., Fleischhacker, W.W., Kahn, R.S., Crespo-Facorro, B., Vazquez-Bourgon, J., Kane, J.M., Malhotra, A.K., Lencz, T., 2019. Schizophrenia polygenic risk score as a predictor of antipsychotic efficacy in first-episode psychosis. *Am. J. Psychiatry* 176, 21–28. <https://doi.org/10.1176/appi.ajp.2018.17121363>.
- Zwicker, A., Fabbri, C., Rietschel, M., Hauser, J., Mors, O., Maier, W., Zobel, A., Farmer, A., Aitchison, K.J., McGuffin, P., Lewis, C.M., Uher, R., 2018. Genetic disposition to inflammation and response to antidepressants in major depressive disorder. *J. Psychiatr. Res.* 105, 17–22. <https://doi.org/10.1016/j.jpsychores.2018.08.011>.