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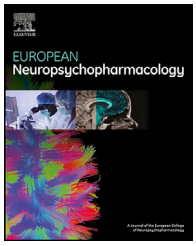

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The polygenic basis of relapse after a first episode of schizophrenia

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Abstract
Little is known about genetic predisposition to relapse. Previous studies have linked cognitive and psychopathological (mainly schizophrenia and bipolar disorder) polygenic risk scores (PRS) with clinical manifestations of the disease. This study aims to explore the potential role of PRS from major mental disorders and cognition on schizophrenia relapse. 114 patients recruited in the 2EPs Project were included (56 patients who had not experienced relapse after 3 years of enrollment and 58 patients who relapsed during the 3-year follow-up). PRS for schizophrenia (PRS-SZ), bipolar disorder (PRS-BD), education attainment (PRS-EA) and cognitive performance (PRS-CP) were used to assess the genetic risk of schizophrenia relapse.Patients with higher PRS-EA, showed both a lower risk (OR=0.29, 95% CI [0.11–0.73]) and a later onset of relapse (30.96± 1.74 vs. 23.12± 1.14 months, p=0.007. Our study provides evidence that the genetic burden of neurocognitive function is a potentially predictors of relapse that could be incorporated into future risk prediction models. Moreover, appropriate treatments for cognitive symptoms appear to be important for improving the long-term clinical outcome of relapse.

1. Introduction

Despite the efficacy of antipsychotic medication in the treatment of schizophrenia (SZ)-spectrum disorders, around 41–63% of patients will experience a relapse within the first three years after a first episode of psychosis (FEP) (Alvarez-Jimenez et al., 2012). Relapse is characterized by acute psychotic exacerbation. Its cumulative effect has been related to chronicity that entails clinical and functional deterioration (Wiersma et al., 1998), treatment resistance (Takeuchi et al., 2019), brain tissue loss (Andreasen et al., 2013), suicidal and violent behaviors (Hor and Taylor, 2010) and higher associated economic costs (Olesen et al., 2012).

Considering that relapse represents much of the personal and social burden of SZ, second episode predictors and relapse preventive interventions in the early stages of the disease have been considered crucial to achieve a better outcome (Alvarez-Jimenez et al., 2012; Bernardo et al., 2021).

Although the main predictive factor for relapse is non-adherence to antipsychotic medication (Kane et al., 2013; Pelayo-Terán et al., 2017), 20–30% of individuals who comply with treatment will develop subsequent relapses (Ceraso et al., 2020), which indicates that relapse is a multifactorial phenotype. While clinical and demographic variables appear to have modest effects on relapse, other factors such as persistent cannabis use (Bioque et al., 2022), caregivers' hypercriticism or poorer premorbid adjustment significantly increase the risk of developing a multiepisodic form of psychosis (Bowtell et al., 2018; Zipursky et al., 2014). Protective factors have been also identified, which are mainly psychosocial and psychological interventions such as family intervention, family psychoeducation, cognitive behavioral therapy and metacognitive therapy (Bighelli et al., 2021; Lecomte et al., 2019).

In this scenario, the search for biomarkers to stratify patients by their risk of relapse after clinical remission with antipsychotics is gaining attention (Rubio et al., 2021). Nevertheless, the lack of understanding about the pathophysiological mechanisms of relapse hinders research into potential biomarkers and the development of preventive and therapeutic interventions. Several potentially state-dependent biomarkers have been proposed such as inflammatory markers (Miller et al., 2013, 2011) or neurotrophins (Martinez-Cengotitabengoa et al., 2016; Martínez-Pinteño et al., 2022; Pillai et al., 2018). Recently, gene expression, as an intermediate measure between genetic and clinical variation, and epigenetics have been investigated to uncover relapse mechanisms and to identify potential biomarkers of relapse Martínez-Pinteño).

However, little is known about genetic predisposition to relapse. The advancement of genome-wide association studies (GWAS) in large, well-powered samples in psychiatry has allowed the estimation of genetic predisposition using genetic constructs such as polygenic risk scores (PRS). Previous studies have linked schizophrenia and bipolar disorder (BD) PRSs with symptom severity, comorbid conditions and cognitive functioning (Mistry et al., 2018a, 2018b), which further evidences the critical role of a common genetic background between mental disorders and their clinical manifestation. A recent study in a large sample of FEP demonstrated that cognitive rather than psychopathological PRS were associated with symptom recovery. This suggests that the underlying mechanisms mediating the emergence of a psychotic episode and its severity could be partially independent (Segura et al., 2022b).

Given the above, this study aims to explore the potential role of PRS from major mental disorders (SZ, BP) and cognition (educational attainment, cognitive performance) on SZ relapse evaluated over a 3-year follow-up period in a cohort of clinically stable first-episode SZ patients with less than 5 years of evolution.

2. Experimental procedures

2.1. Study design

This study is part of the project "Clinical and neurobiological determinants of second episodes of schizophrenia. Longitudinal study of first episode of psychosis" (PI11/00,325) (2EPs Project), the aim of which is to identify and characterize the clinical, environmental and biological factors that predict a relapse. The 2EPs is a naturalistic, multicenter, coordinated, multimodal study of patients with a first episode of schizophrenia (FES) with less than 5 years of evolution. It has a 3-year longitudinal-prospective follow-up design. The project includes six modules: general, neuroimaging, adherence, neurocognition, physical health and biological. Due to its main goals, the present study was framed within the general and biological modules. The general module aims to assess the presence or absence of relapses and includes clinical assessments. The aim of the biological module is to identify biomarkers that are potentially involved in second episodes (Gassó et al., 2021; Martínez-Pinteño et al., 2022; Rodríguez et al., 2022; Segura et al., 2022a). The 2EPs Project rationale and study design can be found elsewhere (Bernardo et al., 2021).

2.2. Subjects

The inclusion criteria for the 2EPs Project were a) age 16–40 years at the time of first assessment (baseline visit); b) meeting diagnostic criteria according to DSM-IV-TR for schizophrenia or schizophreniform disorder (American Psychiatric Association, 1994); c) being in remission from the first psychotic episode (which should have occurred within the last 5 years), according to Andreasen's criteria (Andreasen et al., 2005); d) not having relapsed after the first psychotic episode; e) speaking Spanish fluently, and f) signing the informed consent form. The exclusion criteria were a) having experienced a traumatic brain injury with loss of consciousness; b) presenting intellectual disability, with an intelligence quotient (IQ) <70 and presenting malfunctioning and problems with adaptive processes, and/or c) presenting somatic pathology with mental repercussion.

119 participants completed the 2EPs Project. A total of 114 (95.8%) of these participated in the biological module and provided a biological sample for DNA isolation at baseline.

The study was approved by the investigation ethics committees of all participating clinical centers. Informed consent was obtained from all participants. For children under the age of 18 years old, parents or legal guardians provided written informed consent before the study started, and patients assented to participate. When requested, participants in the study were given a report on the results of the tests. This study was conducted in accordance with the Declaration of Helsinki.

2.3. Clinical assessment

At baseline, demographic data and a complete personal and family history were collected in a systematic, self-devised interview. Diagnoses were determined according to the DSM-IV-TR criteria (American Psychiatric Association, 1994), using SCID-I (Williams et al., 1992) or the Kiddie-SADS (Kaufman et al., 1997), depending on age.

Clinical symptomatology was assessed using the Spanish validated version of the Positive and Negative Syndrome Scale (PANSS) (Peralta and Cuesta, 1994). It has been argued that some PANSS items described as negative symptoms may be better described as cognitive deficits. Given this controversy, prior to our analyses we decided to use the Marder PANSS Factor Scores (Marder et al., 1997), which have different, more restrictive criteria for assessing positive and negative symptomatology.

Pharmacological treatment was also recorded during all visits. The prescribed daily doses of antipsychotics were converted to chlorpromazine equivalent daily dose (CEED), following the method proposed by Leucht and colleagues (Leucht et al., 2016).

The Morisky Green Levine Medication Adherence Scale (MGLS) was used to measure the extent of medication non-adherence (Morisky et al., 1986).

2.4. Relapse definition

The main outcome variables were relapse rates. As inclusion criteria, patients fulfilled Andreasen's criteria of symptomatic remission to enter the study, as they were considered at risk of relapse over the 3-year period (Andreasen et al., 2005).

Relapse was defined as when participants stop fulfilling these remission criteria for at least one week of the follow-up, scoring 4 or more on any of the 8 items of the PANSS Scale used to define these criteria: delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect, social withdrawal and lack of spontaneity. Hospitalization was also reported in every follow-up visit and considered a relapse only when it was related to SZ symptoms (and not to other causes). Follow-up visits to detect relapses were scheduled every 3 months, at which information was collected from the entire period between visits, and the patients, family members or caregivers and clinical teams in charge of the clinical follow-up could notify the research team of the possible relapse of a participant.

2.5. Biological samples

Blood samples from each participant were collected at baseline in EDTA (BD Vacutainer K2EDTA tubes; Becton Dickinson, Franklin Lakes, New Jersey, USA). Genomic DNA was extracted using the MagNA Pure LC DNA Isolation Kit and a MagNA Pure LC 2.0 instrument (Roche Diagnostics GmbH, Mannheim, Germany) and DNA concentration and quality were measured using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Surrey, CA). A total of 2.5 μg of genomic DNA were sent for genotyping at the Spanish National Genotyping centre (CeGen) using the Axiom™ Spain Biobank Array (developed in the University of Santiago de Compostela, Spain).

2.6. PRS calculation

Genotyping data was submitted to the Michigan Imputation Server, following the standard pipeline and pre-imputation quality control required for Minimac4 software and setting a European population reference from build GRCh37/hg19, reference panel HRC 1.1 2016 and Eagle v2.4 phasing.

For the PRS calculation, GWAS summary results from two repositories (Psychiatric Genomics Consortium and the Social Science Genetic Association Consortium). The selected PRS were SZ (PRS-SZ; 69,369 cases and 236,642 controls)(Trubetskoy et al., 2022), BD (PRS-BD; 41,917 cases and 371,549 controls) (Mullins et al., 2021), education attainment and cognitive performance (PRS-EA and PRS-CP; 1131,881 and 257,841 individuals; respectively) (Lee et al., 2018a). Higher psychopathological PRS reflect a greater liability for the disorder and higher cognitive PRS a better cognitive performance. Duplicated and unknown strand GWAS summary single-nucleotide polymorphisms (SNPs) were excluded.

The aforementioned PRS were selected for this study according to multiple criteria. The psychopathological PRS (PRS-SZ, PRS-BD) were chosen for their clinical proximity to a FEP and the shared genetic background among the disorders (Lee et al., 2019). While PRS-CP captures more specific cognitive abilities, PRS-EA includes other personal and social abilities that reflect academic success (Lee et al., 2018b; Segura et al., 2022b).

Quality control was performed with PLINK v1.07 (Purcell et al., 2007). Inclusion criteria for SNPs were minor allele frequency >0.01, Hardy-Weinberg equilibrium $p > 10{-}6$, marker missingness $\langle 0.01$ and imputation INFO $\rangle$ 0.8. Pruning was done using a window/step size of 200/50 kb and r2 > 0.25. Sample quality control included individuals with heterozygosity values within three standard deviations (SD) from the mean, a missingness rate of <0.01, matching chromosomal and database-labeled sex and relatedness π-hat < 0.125.

Dosage-based PRS were constructed from imputed data using PRSice-2 v2.3.3 software (Choi and O'Reilly, 2019) with clumping parameters at 250 kb and r2 > 0.1, using the odds ratio (OR) or beta values of SNPs in the reference GWAS data using different p-value thresholds (1×10^{-8}, 1×10^{-7},1×10^{-6}, 1×10^{-5}, 1×10^{-4}, 1×10^{-3}, 1×10^{-2}, 5×10^{-2}, 1×10^{-1}, 1).

2.7. Statistical analysis

Data were analyzed using SPSS 20.0 (statistical analysis software, IBM, Chicago, IL, USA). Two-tailed p-values < 0.05 were considered to be of statistical significance.

A genetic principal component analysis (PCA) was performed to control population stratification by means of the SNPRelate package in R (Zheng et al., 2012). The first 10 components were used as covariates in the statistical analyses (Supplementary Fig. S1).

When indicated, PRS were dichotomized into high risk PRS (above the highest 75% score quartile) and mid-to-low risk PRS (below the highest 75% score quartiles) (Mas et al., 2020; Segura et al., 2022c).

Means and SD were computed for continuous variables. The normality of continuous variables was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests, and the equality of the variance between groups was assessed using Levene's test. The between-group difference in continuous variables was analyzed using a Student's *t*-test or Mann-Whitney *U* test. The relationship between continuous variables was analyzed using Pearson's correlation coefficient or Spearman's rank correlation coefficient, as appropriate.

The association of each PRS, constructed at each different threshold, with the relapse risk (dependent variable) was performed using binary logistic regression analysis, using the PRS as independent variable and sex, age, ethnicity and the first 10 components of the PCA as covariates.

To test the effect of selected PRS on the length of time taken to reach relapse (months from baseline), Kaplan Meier and Cox regression analysis were performed.

Post-hoc statistical power calculations of significant association were performed assuming a 5% level of significance, our sample

Table 1 Sociodemographic and clinical characteristics of the study participants at baseline classified as non-relapse or relapse.

	Non-Relapsed (3 years follow-up)	Relapsed	Between groups differences Statistic	p-value
N (%)	56 (49.1)	58 (50.9)		
Age, mean (SD)	26.46 (5.87)	25.41 (5.57)	t_{112}=0.980	$p = 0.329$
Age at onset, mean (SD)	24.38 (5.99)	23.44 (5.53)	t_{104}=0.839	$p = 0.403$
Gender, male, N (%)	43 (76.8)	39 (67.2)	X^2_1=1.285	$p = 0.257$
Family history, N (%)	19 (33.9)	20 (34.5)	X^2_1=0.191	$p = 0.909$
Ethnicity, Caucasian, N (%)	49 (87.5)	53 (91.4)	X^2_1=0.455	$p = 0.500$
DUP, mean (SD)	126.29 (189.05)	212.58 (388.201)	t_{108}=−1.482	$p = 0.141$
Marder Positive Symptoms, mean (SD)	11.38 (3.37)	11.60(3.82)	t_{112}=1.509	$p = 0.737$
Marder Negative Symptoms, mean (SD)	14.11 (4.87)	13.67 (5.48)	t_{112}=0.723	$p = 0.656$
CEDD, mean (SD)	250.18 (215.71)	317.25 (331.11)	t_{112}=7.310	$p = 0.202$
Morinsky Green, mean (SD)	0.70 (0.95)	0.60 (0.83)	t_{90}=0.545	$p = 0.587$
Adherence, yes, N (%)	26 (55.3)	25 (55.6)	X^2_1=0.001	$p = 0.982$

DUP, days if untreated psychosis.

size and the obtained odds-ratio. When the PRS were dichotomized using quartile distribution, its percentage in each group was also considered.

3. Results

Table 1 shows the sociodemographic and clinical characteristics of the 114 participants at study entry classified as non-relapse (patients who had not experienced relapse after 3 years of enrollment) ($N = 56$) or relapse (patients who relapsed during the 3-year follow-up) ($N = 58$). Non-significant differences in sociodemographic characteristics were observed between the two groups of patients.

Histogram of the distribution of the different PRSs in cases and controls is available in supplementary Fig. S2. The PRS-EA constructed with the 0.05 p-value threshold was significantly associated with the relapse risk (β=−0.42±0.21, OR=0.66, 95% CI [0.11-0.73], $p = 0.043$), explaining the highest percentage of the observed variance (R^2=2.1%) (Statistical power=65%) (Fig. 1). Patients in the highest quartile (High Risk PRS-EA) (non-relapsed 37.5% vs. relapsed 13.8%) showed lower risk of suffering a relapse (OR=0.29, 95% CI [0.11-0.73], X^2_1=6.87, $p = 0.009$; Statistical power=81%) (Fig. 2A) and relapse appeared later (30.96± 1.74 vs. 23.12± 1.14 months, $p = 0.009$) (Fig. 2B).

4. Discussion

The present study aimed to investigate the role of the genetic burden for psychopathological disorders and cognitive features in the risk of relapse after a first episode of SZ. The PRS-EA was significantly associated with the risk of relapse, whereas PRS for SZ or BD were not. Patients with higher PRS for educational attainment showed both a lower risk and a later onset of relapse.

Our results regarding the role of PRS-EA on relapse agreed with the recent results of our group carried out in a shorter-term follow-up design (Segura et al., 2022b). In a cohort of patients with FEP, we demonstrated that genetic predisposition to higher cognitive function was associated with better course of symptoms and better psychosocial functioning after one-year follow-up (Segura et al., 2022b).

Several authors have begun to explore the link between neurocognitive dysfunction and relapse in psychosis, as neurocognitive function is a potentially modifiable factor. There is now a growing focus on improving the outcome of psychosis by cognitive enhancement through remediation and other non-invasive approaches (Bighelli et al., 2021; Lecomte et al., 2019). The identification of neurocognitive function as a marker for a long-term clinical outcome such as relapse is important because neurocognitive markers are clearly defined, relatively easy to administer, reproducible, and can be measured objectively (Hui et al., 2019a). Different cognitive functions at early stages of the diseases have been identified as predictive of relapse in psychosis in short-term and long-term follow-ups (Chen et al., 2005; Hui et al., 2019b, 2016; Rund et al., 2016; Verdoux et al., 2000; Wölwer et al., 2008).

Interestingly, in our 2EPS cohort, no direct effect of baseline cognitive function on relapse risk was detected, however, relapse was significantly associated with poor performance of working memory, social cognition and global cognitive score at follow-up (Cuesta et al., 2022). It should be considered that patients in this cohort, at study entry, are in remission from the first psychotic episode, which should have occurred within the last 5 years. Therefore, cognitive measurements of the 2EPS study at baseline are not at early stages and could reflect the effects of medication or the effects of course of the disease on cognition. Instead, the polygenic architecture of cognition, captured by PRS-EA, has been related to cognitive function measured at the FEP and premorbid cognition measured as cognitive reserve (CR) (Segura et al., 2022b), which could explain its association with relapse in the present study. In fact, in our cohort, patients who relapsed and had higher personal CR showed less deterioration in attention, whereas those with higher CR who did not relapse showed better performance in processing speed and visual memory, adding evidence for the protective effect of CR over the course of the illness (Sánchez-Torres et al., 2022).

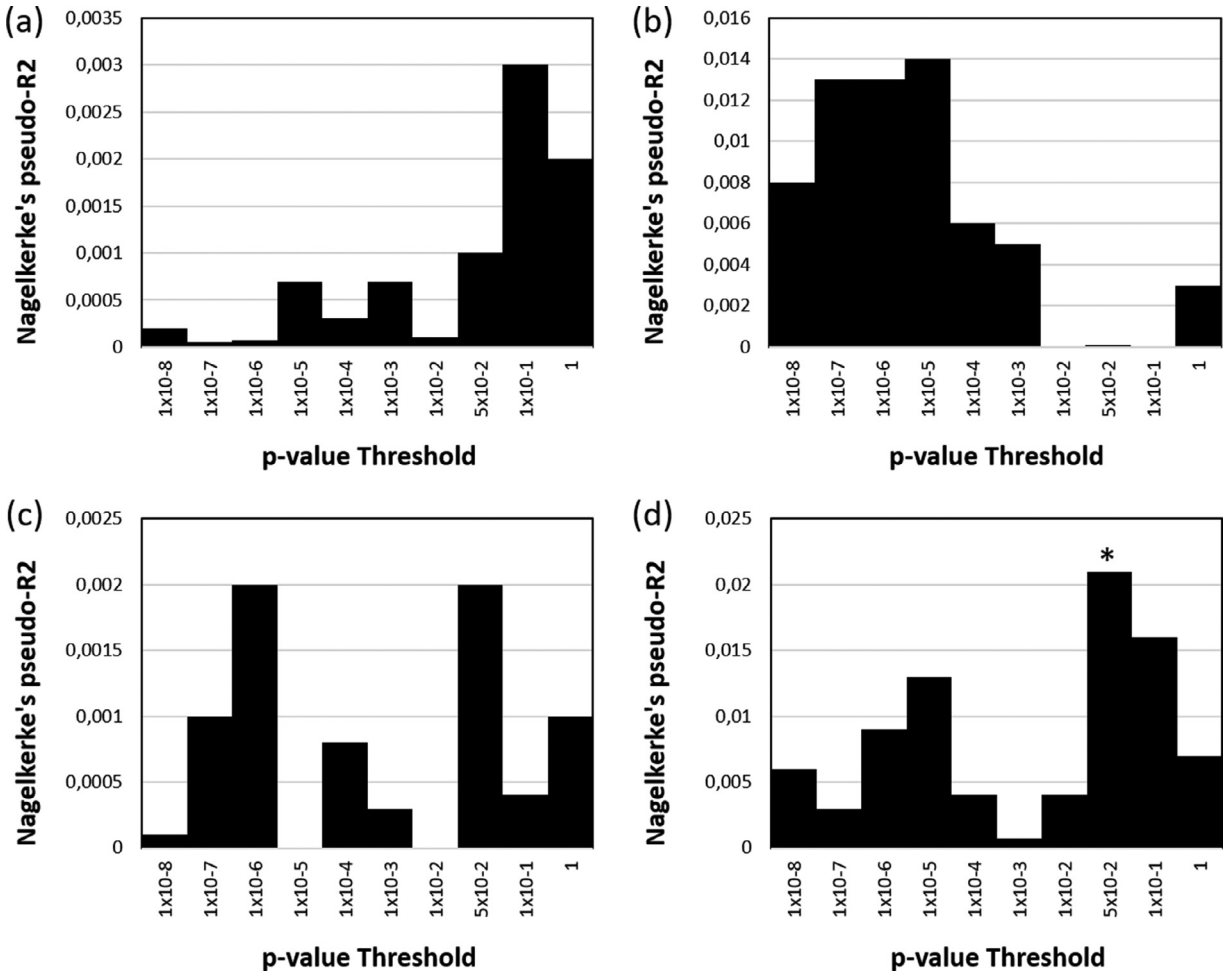

Figure 1 Association between the (a) PRS-SZ, (b) PRS-BD, (c) PRS-CP and (d) PRS-EZ and the relapse risk. The y-axis shows the variance explained (as the adjusted Nagelkerke's pseudo-R2) by the PRS at different p-value thresholds shown on the x-axis. $^{*}p<0.05$.

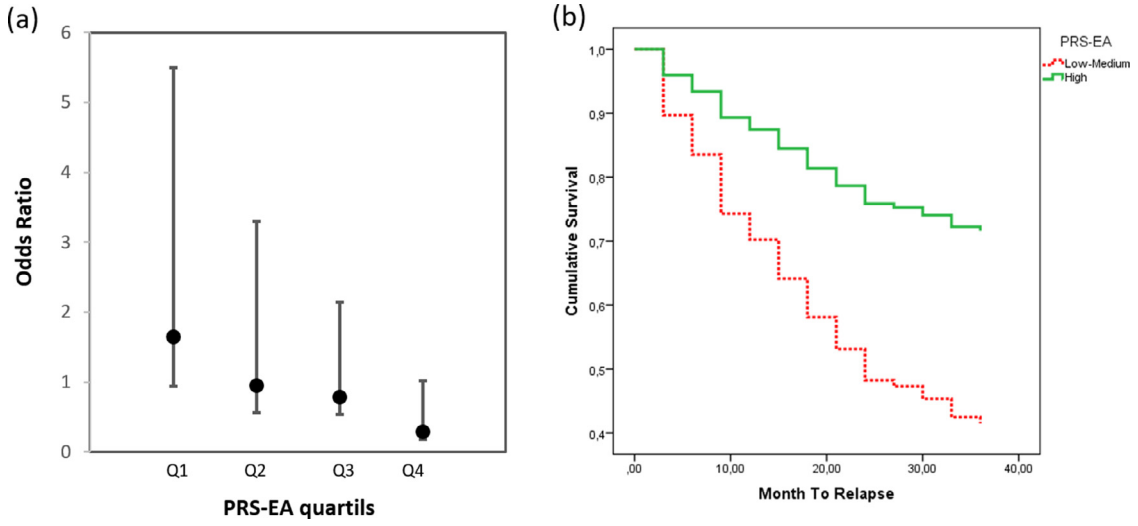

Figure 2 (a)Odds ratio for relapse PRS-EA. The threshold used for selecting risk alleles was 0.05. Based on PRSs, samples were allocated to quartile (quartile 1, lowest PRS; 4, highest PRS). Odds ratio and 95% CI were estimated using binary logistic regression including age, sex, ethnicity and the first 10 components of the PCA as covariates. The points represent the odds ratios. The bars represent the lower and upper CI of the odds ratios.(b) Cox regression analysis of the length of time (months from baseline) taken to reach relapse using dichotomized PRS-EA.

Some limitations of this study should be taken into consideration. Firstly, PRS-EA is a popular phenotype in genetics because it is easily measured and predicts a range of cognitive phenotypes among other health behaviors and outcomes. However, although we use it as a proxy of cognitive function, we have to bear in mind that this is a reductionist model that considers that genetic effects work directly through brain systems to cognitive performance to EA (Schork et al., 2022). A recent study shows that a large proportion (69%) of the total relationship between an individual's PRS-EA and their observed EA is due to indirect effects (i.e. parental behaviors, population stratification or assortative mating) (Okbay et al., 2022). Secondly, the 2EPs Project was a naturalistic study, so patients could have changed treatments during the follow-up period according to the clinician's decisions. Finally, the relatively high number of dropouts during the follow-up period could have limited the capability of detecting differences between groups (relapsed vs. non-relapsed) at the end of the follow-up period.

Our study provides evidence that the genetic burden of neurocognitive function is a potentially predictors of relapse in SZ, which would help with clinical decisions. More research is needed to replicate our findings before these markers can be used as a screening tool for relapse in clinical practice. However, appropriate approaches to new treatments for cognitive symptoms appear to be important for improving the long-term clinical outcome of relapse.

Role of funding source

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Author contributions

The results presented here are part of a broader project, the 2EPS study. MBe is the coordinator of the 2EPS study. AGS and LlP performed the statistical analysis and wrote the first draft of the manuscript, and both authors contributed equally to this work. PG and NF performed the sample isolation and preparation and participated in the statistical analysis. CGR participated in the coordination of the sample shipment, the maintenance of the 2EPS database and in the recruitment and assessment of the sample. EB is the coordinator of the Biological module of the 2EPS study. LMI, AAB, AM, RRJ, AR, SS, AI, JU, PAS, MJC, MP, AGP participated in the recruitment and assessment of the sample. SM designed, supervised and performed the statistical analysis, performed the interpretation of the results and wrote the first draft of the manuscript. All the authors, including the 2EPSs group authors listed in the acronym, contributed to the final draft of the manuscript.

Conflict of interest

A. Ibáñez has received research support from or served as speaker or advisor for Janssen-Cilag, Lundbeck and Otsuka. A. Gonzalez-Pinto has received grants and served as consultant, advisor or CME speaker for the following entities: Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Exeltis, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), and the Basque Government, J. Saiz-Ruiz has been as speaker for and on the advisory boards of Adamed, Lundbeck, Servier, Medtronic, Casen Recordati, Neurofarmagen, Otsuka, Indivior, Lilly, Schwabe, Janssen and Pfizer, outside the submitted work. M. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda, Pilar A. Saiz has been a consultant to and/or has received honoraria or grants from Adamed, CIBERSAM, European Comission, Government of the Principality of Asturias, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Plan Nacional Sobre Drogas and Servier. R. Rodriguez-Jimenez has been a consultant for, spoken in activities of, or received grants from: Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid Regional Government (S2010/ BMD-2422 AGES; S2017/BMD-3740), JanssenCilag, Lundbeck, Otsuka, Pfizer, Ferrer, Juste, Takeda, Exeltis, Casen-Recordati, Angelini. The rest of the authors reported no biomedical financial interests or potential conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2023.06.003.

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