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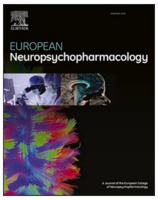

SHORT COMMUNICATION

Shared vulnerability and sex-dependent polygenic burden in psychotic disorders

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ABSTRACT

Evidence suggests a remarkable shared genetic susceptibility between psychiatric disorders. However, sex-dependent differences have been less studied. We explored the contribution of schizophrenia (SCZ), bipolar disorder (BD) and major depressive disorder (MDD) polygenic scores (PGSs) on the risk for psychotic disorders and whether sex-dependent differences exist (CIBERSAM sample: 1826 patients and 1372 controls). All PGSs were significantly associated with psychosis. Sex-stratified analyses showed that the variance explained in psychotic disorders risk was significantly higher in males than in females for all PGSs. Our results confirm the shared genetic architecture across psychotic disorders and demonstrate sex-dependent differences in the vulnerability to psychotic disorders.

1. Introduction

Psychotic disorders rank among the leading causes of disability worldwide affecting approximately 3 % of the general population (Perälä et al., 2007). Epidemiological and genetic studies show both high heritability and a complex genetic architecture, with a significant

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proportion of heritability contributed by common variants (Gratten et al., 2014).

Recent genome-wide association studies (GWAS) have identified a large number of risk loci that only convey modest increases in risk individually. The combination of these genetic variants into a polygenic score (PGS) constitutes a robust disease risk index. GWAS have also provided molecular evidence for a common genetic architecture among psychiatric disorders, clustering schizophrenia (SCZ), bipolar disorder (BD) and major depressive disorder (MDD) in the mood and psychotic disorders group, with the largest genetic correlation (rg) between SCZ and BD (rg=0.70) (Lee et al., 2021). Polygenic analyses in pilot studies within the psychotic disorder spectrum have already shown a substantial SCZ polygenic risk overlap between some of the diagnostic groups defined under this category (Smigielski et al., 2021).

The analysis of sex-dependent differential genomic load still represents an under-explored area in large-scale genomics of mental disorder. However, it has been long reported the existence of sex differences in psychotic disorders (Riecher-Rössler et al., 2018). To our knowledge, sex-stratified PGS analyses examining the genetic contribution to psychotic disorders risk among males and females have not been previously investigated.

The aim of this study was to evaluate whether PGSs for SCZ, BD and MDD are associated with psychotic disorders in a large sample of patients with broadly defined psychosis and healthy subjects. In addition, we also explored whether genetic sex differences exist in those associations.

2. Experimental procedures

2.1. Sample description

The sample consisted of 3198 unrelated individuals of European ancestry: 1826 patients (33.23 % females) with a range of psychotic disorders (Supplementary Table 1) and 1372 healthy controls (45.70 % females). Participants were recruited as part of the Spanish sample collection of CIBERSAM (Mental Health Networking Biomedical Research Centre) (Andreu-Bernabeu et al., 2022; Sada-Fuente et al., 2023). All patients met the DSM-IV diagnostic criteria for psychotic disorders. Healthy controls were recruited after being screened for psychiatric illness. All participants provided written informed consent, and the study was approved by the different ethical committees at the hospitals involved in the recruitment.

2.2. Genetic analysis

Samples were genotyped with the Infinium PsychArray from Illumina. Data quality control was done following standard quality control procedures (Trubetskoy et al., 2022). Imputation was conducted in the Michigan Imputation Server (www.imputationserver.sph.umich.edu) and only SNPs with an rsq > 0.3 and MAF > 0.01 were retained for subsequent analyses.

Ancestry principal components (PCs) on the 3198 individuals who passed QC were calculated using PLINK v.1.9 (Chang et al., 2015). For the sex-stratified and sensitivity analyses, PCs were recalculated in the respective groups.

PGSs were calculated from best-guess genotypes after imputation based on the following GWAS summary statistics: SCZ (Trubetskoy et al., 2022) (leave-one-out analyses excluding the CIBERSAM sample), BD (Mullins et al., 2021) and MDD (Wray et al., 2018). PRS continuous shrinkage (PRS-CS) tool was used to infer posterior SNP effect sizes under continuous shrinkage priors and to estimate the global shrinkage parameter (φ) using a fully Bayesian approach (Ge et al., 2019). The resulting corrected effect sizes after PRS-CS were then used to calculate individual risk scores using PLINK v.1.9 (Chang et al., 2015).

2.3. Statistical analysis

The statistical power of our sample was estimated with AVENGEME (Palla and Dudbridge, 2015).Our study had more than 90 % power ($\alpha = 0.05$) to detect effects of PGSs with an $R^2 \geq 2.21$ % (SCZ-PGS), $R^2 \geq 0.90$ % (BD-PGS), and $R^2 \geq 0.37$ % (MDD-PGS) on the risk of broadly defined psychosis.

Statistical analyses were performed with R program 4.1.3 (https://www.R-project.org/). Logistic regression models were used to associate psychotic disorder diagnosis with SCZ-PGS, BD-PGS and MDD-PGS, including sex, CIBERSAM group and the first ten PCs as covariates. For each PGS, two models were built: 1) baseline model including only covariates and 2) full model including PGS plus covariates. The proportion of variance explained by the PGS was calculated by the difference between the Nagelkerke's pseudo-R^2 values of the full model and the baseline model. Nagelkerke's pseudo-R^2 were converted to liability scale as proposed by Lee et al. (Lee et al., 2012) and assuming a prevalence of 1 % in the general population. Following the same aforementioned procedure, we assessed PGS contribution to psychotic disorders risk in males and females separately, including CIBERSAM group and the first ten PCs as covariates. In order to statistically compare the variances explained between males and females we performed bootstrap resampling (5000 permutations) of 400 psychotic disorder and 400 control subjects across males and females separately, and calculated explained variance predictions by logistic regression and R^2 estimations on the liability scale for all PGSs (SCZ, BD and MDD). For each PGS, we statistically compared the differences between the distribution of liability R^2 in males and females with two-sided *t*-tests.

In secondary analyses, subjects were ranked from lower to higher according to each PGS (SCZ, BD and MDD) adjusted for sex, CIBERSAM group and the first ten PCs (sex was excluded in sex-stratified analyses) and divided into quartiles. *Odds ratios* (ORs) were calculated based on the case-control ratio in each quartile using the lowest quartile as reference. Bonferroni correction was applied to correct for multiple testing. The criterion for significance was set at $p < 0.0056$ (0.05/9).

3. Results

We found an association between all PGSs and broadly defined psychosis in our sample. SCZ-PGS explained the highest percentage of the variance of psychotic disorders in the liability scale ($R^2 = 8.274$ %; $p < 2 \times 10^{-16}$), followed by BD-PGS ($R^2 = 2.414$ %; $p < 2 \times 10^{-16}$) and MDD-PGS ($R^2 = 0.268$ %; $p = 6.60 \times 10^{-04}$) (Fig. 1A and Supplementary Table 2). Sensitivity analyses showed that only using SCZ/schizoaffective samples (91.8 % of patients) yielded very similar results to those obtained with the whole sample (Supplementary Table 3). Despite the small sample size, the analyses of the remaining sample with other psychotic diagnoses (8.2 % of patients), also showed similar results to those observed for the full sample (Supplementary Table 3).

In the analyses of sex-specific genetic load in psychotic disorders, the variance explained was higher in males than in females for all PGS (Fig. 1A, Supplementary Table 2). When we statistically compared these sex-based differences, all PGS explained significantly more variance in psychotic disorders risk in males than in females (SCZ-PGS: $t = 96.704$, $df = 9458.4$, $p < 2.2 \times 10^{-16}$; BD-PGS: $t = 12.895$, $df = 9997.8$, $p < 2.2 \times 10^{-16}$; MDD-PGS: $t = 23.472$, $df = 9479.7$, $p < 2.2 \times 10^{-16}$) (Fig. 1B).

Lastly, quartile analyses (all, males, and females) based on SCZ-PGS, BD-PGS and MDD-PGS showed a significant progressive increase in the case-control ratio in all higher quartile categories for SCZ and BD-PGS, and, to a lesser extent, MDD-PGS (Fig. 1C and Supplementary Table 4). Compared with individuals in the first quartile, those at the highest quartile had an *OR* for psychotic disorder risk of 6.037 (95 % CI 4.847–7.518) for SCZ-PGS, 2.511 (95 % CI 2.048–3.078) for BD-PGS, and 1.302 (95 % CI 1.066–1.590) for MDD-PGS. Males and females showed the same pattern although this was less obvious in MDD-PGS sex-stratified analyses (Fig. 1C and Supplementary Table 4).

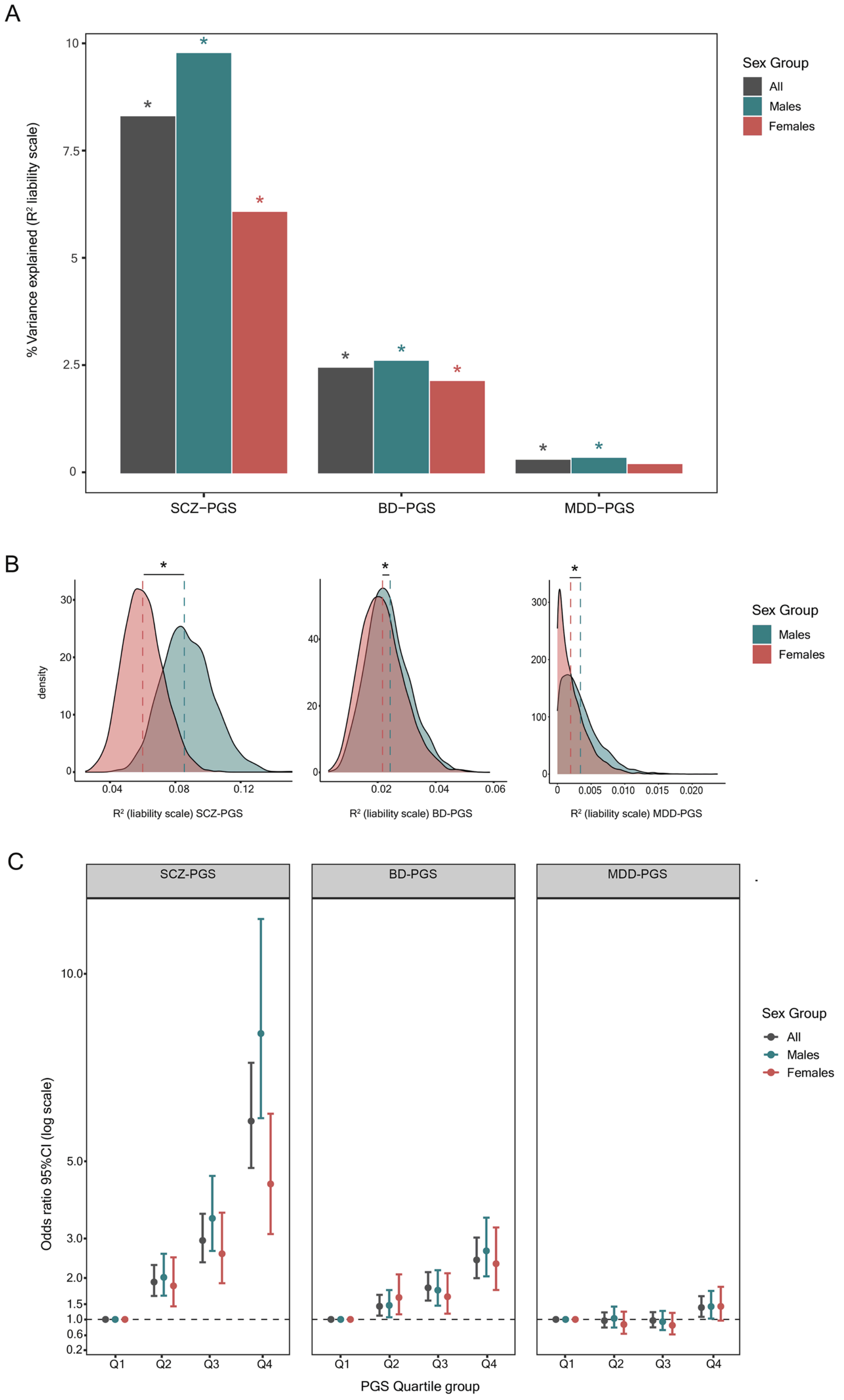

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Fig. 1. **A)** Percentage of the variance in psychotic disorder risk explained by SCZ-PGS (left), BD-PGS (middle) and MDD-PGS (right) in all patients with psychotic disorders and in males and females separately. Statistically significant p-values after Bonferroni correction are indicated by stars. **B)** PGS predictions in case-control subsamples after bootstrap resampling (5000 permutations) of 400 psychotic disorders patients and 400 healthy controls (selected from the overall CIBERSAM case-control sample) were performed in males and females, separately. Mean variance explained by SCZ-PGS (left panel), BD-PGS (middle panel) and MDD-PGS (right panel) on the liability scale (estimated prevalence of 0.01) in males and females. Variance explained in females and males was statistically compared with two-sided *t*-tests and is marked with an asterisk when it is significantly different ($p < 0.05$). **C)** ORs of psychotic disorders according to quartile distribution of SCZ (left), BD (middle) and MDD-PGS (right). Subjects were ranked according to each PGS adjusted for sex, CIBERSAM group and the first 10 principal components (PCs) (CIBERSAM group and 10 PCs in the sex-stratified analyses) from lower to higher and divided into quartiles. The y-axis corresponds to the observed OR (log scale), and the 95 % confidence intervals. Each quartile is compared with the 1st quartile (baseline). SCZ: Schizophrenia; BD: Bipolar Disorder; MDD: Major Depressive Disorder; PGS: Polygenic Score.

4. Discussion

In this study we show that PGSs for severe mental disorders (SCZ, BD and MDD) are associated with broadly defined psychosis in an independent Spanish sample, emphasizing the shared genetic architecture among these psychiatric disorders (Lee et al., 2021).

Our results replicate the ones reported in a previous study investigating the association of SCZ-PGS and BD-PGS with psychotic disorders in a smaller dataset (Calafato et al., 2018). Regarding the MDD-PGS analyses, as far as we know, this is the first study investigating its association with broadly defined psychosis.

Our sensitivity analyses show a similar SCZ / BD / MDD polygenic architecture across all broad psychotic diagnoses included in this study.

Although psychotic disorders present sex differences in age at onset, symptom profile, course and outcome, specific sex-dependent differences at the genetic level have been under-explored. To our knowledge, this is the first study that using PGS analyses captures sex-dependent differences in the shared genetic vulnerability between mood and psychotic disorders. Our results are in line with recent findings suggesting that sex differences in the genetic architecture of neuropsychiatric and behavioural traits exist but are small and polygenic (Martin et al., 2021). The largest genome-wide genotype-by-sex analysis of mood and psychotic disorders to date, reported significant sex-dependent effects across and within SCZ, BD, and MDD (Blokland et al., 2022). Moreover, sex-specific effects of SCZ-PGS have been reported on cognitive functioning across the lifespan (Koch et al., 2021). Although the clinical utility of PGS is very limited in the context of psychiatric disorders, our findings highlight the importance of considering women and men separately when transferring polygenic scores to clinical practice in the future. This will help to optimally inform sex-specific prevention, diagnosis and treatment strategies.

Our study was subject to some limitations. First, a slight lack of statistical power has to be acknowledged due to a limited sample size (De Prisco and Vieta, 2024), specifically in the sex-stratified analyses. Second, the small effect sizes detected suggest that environmental variables are likely to play a substantial role in these associations. Future PGS analyses may also incorporate environmental factors as well as gene–environment interactions, thereby improving the performance of PRSs. Third, ascertainment and participation bias may confound identification of true sex differences. Fourth, the dataset used in our analyses consisted exclusively of individuals of European ancestry, and thus the extrapolation of our findings to other ancestries should not be done straightforwardly.

Taken together, our results emphasize the use of transdiagnostic approaches which recognise the multidimensionality of psychopathology and enable the investigation of shared genetic risk factors. Moreover, understanding the genetic basis of sex differences in psychiatric disorders is crucial for developing sex-stratified diagnostics and therapeutics and for paving the way for precision medicine.

CRediT authorship contribution statement

Marina Mitjans: Conceptualization, Data curation, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Sergi Papiol:** Conceptualization, Data curation, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Mar Fatjó-Vilas:** Resources, Writing – review & editing. **Javier González-Peñas:** Methodology, Writing – review & editing. **Miriam Acosta-Díez:** Writing – review & editing. **Marina Zafrilla-López:** Writing – review & editing. **Javier Costas:** Writing – review & editing. **Celso Arango:** Resources, Writing – review & editing. **Elisabet Vilella:** Resources, Writing – review & editing. **Lourdes Martorell:** Resources, Writing – review & editing. **M Dolores Moltó:** Resources, Writing – review & editing. **Julio Bobes:** Resources, Writing – review & editing. **Benedicto Crespo-Facorro:** Resources, Writing – review & editing. **Ana González-Pinto:** Resources, Writing – review & editing. **Lourdes Fañanás:** Resources, Writing – review & editing. **Araceli Rosa:** Conceptualization, Supervision, Resources, Writing – review & editing. **Bárbara Arias:** Conceptualization, Supervision, Resources, Writing – review & editing.

Author disclosures

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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.2024.04.017.

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