Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis

Running title: Gene–Environment Interactions in a FEP cohort

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ABSTRACT

Background: Consistent evidence supports the involvement of genetic and environmental factors, and their interactions, in the etiology of psychosis. First-episode psychosis (FEP) comprises a group of disorders that show great clinical and long-term outcome heterogeneity, and the extent to which genetic, familial and environmental factors account for predicting the long-term outcome in FEP patients remains scarcely known.

Methods: The SEGPEPs is an inception cohort study of 243 first-admission patients with FEP who were followed-up for a mean of 20.9 years. FEP patients were thoroughly evaluated by standardized instruments, with 164 patients providing DNA. Aggregate scores estimated in large populations for polygenic risk score (PRS-Sz), exposome risk score (ERS-Sz) and familial load score for schizophrenia (FLS-Sz) were ascertained. Long-term functioning was assessed by means of the Social and Occupational Functioning Assessment Scale (SOFAS). The relative excess risk due to interaction (RERI) was used as a standard method to estimate the effect of interaction of risk factors.

Results: Our results showed that a high FLS-Sz gave greater explanatory capacity for long-term outcome, followed by the ERS-Sz and then the PRS-Sz. The PRS-Sz did not discriminate significantly between recovered and non-recovered FEP patients in the long term. No significant interaction between the PRS-Sz, ERS-Sz or FLS-Sz regarding the long-term functioning of FEP patients was found.

Conclusions: Our results support an additive model of familial antecedents of schizophrenia, environmental risk factors and polygenic risk factors as contributors to a poor long-term functional outcome for FEP patients.

Keywords: schizophrenia, polygenic risk score (PRS), first episode psychosis, outcome, exposome risk score (ERS), gene-environment interaction

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INTRODUCTION

Clinical outcomes in psychotic disorders appear to have improved over recent years after initiating early intervention services for at-risk states of psychosis and first-episode psychosis (FEP) (Fusar-Poli, McGorry and Kane, 2017). However, FEP patients show marked heterogeneity of outcome and systematic evidence on the long-term outcomes of FEP patients is very limited (Heilbronner, Samara, Leucht, Falkai and Schulze, 2016; Johnstone, Frith, Lang and Owens, 1995). Genetic and environmental factors, and their interactions, seem to be essential not only in the development of schizophrenia and FEP but also in their long-term outcome (van Os, Kenis and Rutten, 2010).

It is well established that psychotic disorders share substantial polygenic components by means of rare and common genetic risk factors for disease that converge on common neurobiological mechanisms (Iyegbe & O'Reilly, 2022). Consistent advances in genomics allow for calculations of individual polygenic risk scores for schizophrenia (PRS-Sz) on the basis of the risk alleles identified in the most recent genome-wide association study (GWAS) of the Psychiatric Genomics Consortium (Trubetskoy et al., 2022). PRSs provide a cumulative estimation of genome-wide effects of common variants, and consistent evidence has demonstrated their capacity to differentiate between cases and controls (Calafato et al., 2018; Vassos et al., 2017). However, the amount of variance explained by the PRS-Sz for differentiation between schizophrenia cases and controls (7.3%) does not allow for its implementation in clinical practice and its discriminative ability between psychosis subtypes is still very limited (Rodriguez et al., 2022).

One of the main challenges of personalized psychiatry in FEP is the search for improving the prognostic accuracy of illness course. Research on environmental factors has been scarcely addressed despite substantial evidence supporting environmental factors and exposures in the etiology of psychosis (Guloksuz et al., 2019; Radua et al., 2018; Stilo & Murray, 2019). In this regard, the combination of empirically-validated genome screening data with environmental risk factors having a high level of evidence for association with psychotic disorders may help in predicting the illness course at an individual level.

A recent population-based study found that the PRS-Sz, family psychiatric history and socioeconomic status were significantly associated with poor long-term outcome in schizophrenia patients (Agerbo et al., 2015). Despite their interdependencies, only modest fractions of variance in liability (7%) by the other predictors were explained (Agerbo et al., 2015). Taken together, the development and course of psychosis seem to be related to a combination of environmental and genetic effects because the latter by itself cannot explain the etiology of the illness (Stepniak et al., 2014; van Os et al., 2010). However, the extent to which the interplay between genetic, familial and environmental factors allows for predicting the long-term outcome in FEP patients is still unknown.

Epidemiological methods for ascertaining the strength of the direct effects of two risk factors on their own and regarding their interaction have been applied to gene–environment issues in psychosis (Kendler & Gardner, 2010). These studies aimed at disentangling whether two risk factors have additive or multiplicative effects on a disease and whether these effects are more than their individual contribution (Mas et al., 2020; Pries et al., 2020). In most situations in psychiatry, the use of additive models has been recommended (Kendler & Gardner, 2010). The standard method used to

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estimate the effect of interaction of two risk factors in case–control studies is the relative excess risk due to interaction (RERI). The RERI provides a useful metric of departure from the additivity of effects on a relative risk scale (Hosmer & Lemeshow, 1992; Knol & VanderWeele, 2012).

Aims

Our primary aim was to determine whether an additive gene–environment (G × E) interaction based on polygenic and environmental risk scores influences the long-term outcome of FEP. Our secondary hypothesis was that familial antecedents would provide complementary information to the PRS-Sz in predicting the long-term outcomes of FEP.

MATERIALS AND METHODS

Sample

The SEGPEPs cohort included a large dataset of FEP patients who had their first admission for psychosis between January 1990 and December 2008 in a defined catchment area (Navarra, Spain) covering approximately 200,000 inhabitants in the public health system. A complete description of the SEGPEPs study has been published previously (Peralta et al., 2021). The inclusion criteria for this longitudinal and naturalistic study were: a diagnosis of FEP fulfilling the DSM-III-R or DSM-IV criteria; age between 15 and 65 years; residing in the catchment area of the hospital; completing the inpatient treatment period and a six-month assessment after discharge; having close relatives available to provide broad background information; and providing written informed consent. Exclusion criteria were: previous antipsychotic treatment for more than 2 months; suspected or confirmed diagnosis of drug-induced psychosis; history of serious medical or neurological disease; and intellectual disability defined by an IQ of < 70.

The SEGPEPs cohort comprised 510 FEP patients at baseline but the final sample after a mean follow-up of 20.9 years (SD = 5.21) was 243 subjects. There were no significant differences in baseline demographic and clinical characteristics between subjects who were followed up and those who were not, except for age, which was significantly lower in the sample that was followed up ($p < 0.001$)(Peralta et al., 2022).

Assessment methodology and raters

FEP patients were assessed by senior researchers (VP or MJC) at the time of inception in the study. Patients were traced and those who consented to be re-evaluated at 10–22 years of follow-up were blindly evaluated by means of direct interviews with themselves and a close significant other or relative by two trained and expert psychiatrists (LMI and EGJ).

Baseline assessments

All patients were evaluated by means of the Comprehensive Assessment of Symptoms and History (Andreasen, Flaum and Arndt, 1992)(CASH), supplemented by specific assessment instruments to account for relevant variables not included in the CASH. All information collected was used to diagnose patients according to the DSM-5 criteria (APA, 2013).

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Outcome measure

Psychosocial functioning was rated by means of the Social and Occupational Functioning Assessment Scale (SOFAS)(Goldman, Skodol and Lave, 1992) at the long-term follow-up assessment. A cut-off score of ≥ 61 sustained over the last year was used to differentiate between functional recovered and non-recovered patients. A SOFAS score between 61 and 100 points reflects a gradient of recovery from a range of "some difficulty in social, occupational, or school functioning" to "superior functioning in a wide range of activities.

Polygenic risk score

Genome-wide genotyping was performed in a sample of 173 subjects using the Illumina Global Screening Array (730,059 genetic variants). Single nucleotide polymorphisms (SNPs) and individuals were excluded if their call rate was below 97%. One sample was removed due to such a call-rate threshold. Likewise, SNPs with minor allele frequency (MAF) < 0.05% were removed. No sex-mismatch was observed between genetic sex and clinical data sex. A first-degree relative was identified and then removed after computing their pairwise identity-by-descent values using PLINK 1.9 (Chang et al., 2015). To account for possible population stratification, we computed multi-dimensional scaling components using PLINK 1.9 (Chang et al., 2015) based on a pruned genetic dataset of 93,177 LD-independent SNPs. 5 non-European ancestry samples were removed. Subjects with heterozygosity > 3.61 $\times$ SD in absolute value were also removed (3 samples). At this step of quality control, those SNPs with a Hardy-Weinberg Equilibrium (HWE) p value of < 1×10^{-4} or MAF < 1% were excluded. Subsequently, palindromic SNPs and SNPs with a MAF deviation of > 10% with respect to European reference populations were also excluded. The final quality-controlled dataset ready for imputation consisted of 164 subjects (94.8% of the initial sample) and 489,135 genetic markers (67.0% of the initial sample). Prephasing and imputation were performed using, respectively, Eagle(Durbin, 2014) and Minimac4(Das et al., 2016) and the Haplotype Reference Consortium dataset (HRC version r1.1)(McCarthy et al., 2016) hosted on the Michigan Imputation Server (Das et al., 2016). A MAF value of > 1% and an imputation quality of R^2 > 0.3 were required for inclusion of the variants into further analyses.

The schizophrenia PRS (PRS-Sz) was calculated using the imputation dosage for each risk allele based on the summary statistics of the latest schizophrenia GWAS (Trubetskoy et al., 2022). The 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 (auto settings)(Ge, Chen, Ni, Feng and Smoller, 2019).

Exposome risk score

We applied the Maudsley environmental risk score (MERS) partly modified to compute our exposome risk score for schizophrenia (ERS-Sz). We used four out of the six original variables of the MERS, after eliminating both paternal age (not available in this study) and ethnic origin (at the time of the study there was no migrant population in Spain and all participants were natives of Spain). Place of birth (urbanicity) was stratified as low (rural populations and towns with < 10,000 inhabitants), medium (towns and cities with < 100,000 inhabitants) and high (born in Pamplona, which has > 100,000 inhabitants). Obstetric complications (OCs) were evaluated by means of the

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Lewis-Murray scale (LMS) (Lewis, Owen and Murray, 1989) and classified as probable or definitive. We used the LMS total score to account for the significant heterogeneity in studies using only low birth weight (2500g), which might be attributable to 'population shifts' across studies (Cannon, Jones and Murray, 2002). Moreover, the effect sizes of the relationships between OCs and schizophrenia are generally small with odds ratios less than 2 (Cannon et al., 2002; Etchecopar-Etchart, Mignon, Boyer and Fond, 2022). And evidence from the last two decades provided updated consistency and magnitude of association of numerous OCs contributing to increase the risk for psychotic disorders (Davies et al., 2020).

Cannabis use at inception of the study was evaluated by means of the European version of the Addiction Severity Index (Kokkevi & Hartgers, 1995; McLellan et al., 1992). The intensity of abuse of cannabis before FEP was dichothomized as follows: no exposure (EuropAsi severity profile= 0-1) and little/moderate to high exposure (EuropAsi severity profile= 2-9).

Childhood adversity was evaluated by means of the Global Family Environment Scale (GFES) (Rey et al., 1997), which indexes the global quality of the environment in which the child was raised. Raters use a hypothetical continuum from 1 (e.g., severe abuse and deprivation) to 90 (e.g., stable and secure nurturing) and formulate a single score reflecting the lowest quality of family environment to which the child has been exposed. We used the cut-off score of ≤60 sustained during childhood to account for scoring poor childhood adversity. As the GFES followed a similar metric that Global Assessment of Functioning (GAF) (Pedersen, Urnes, Hummelen, Wilberg and Kvarstein, 2018), scores below 60 are indicative of moderate/severe impairment in the quality of the family environment (Rey, Walter, Plapp and Denshire, 2000).

Familial load score for schizophrenia

Familial load for schizophrenia disorders was assessed in the first-degree relatives of the participants by means of the Family History Research Diagnostic Criteria (Andreasen, Endicott, Spitzer and Winokur, 1977)(FH-RDC) administered at baseline and follow-up interviews. The combined information from the two interviews was used to rate the family history. The familial load score for schizophrenia (FLS-Sz) should be regarded as a simple extension of the family history positive–negative dichotomy to take account of family size and age structure (Verdoux et al., 1996)**.**

The FLS-Sz is a continuous measure of liability log-transformed to characterize the level of psychiatric illness. A FLS-Sz score of 0 indicates that there is an equal chance that the illness will be familial or sporadic; a positive score indicates a higher chance that it will be familial, and a negative value suggests a higher chance that it will be sporadic (Cuesta et al., 2015). The FLS-Sz was dichotomized using the highest quartile to consider a high familial load for schizophrenia (FLS-Sz_{75}).

Statistical analysis

Sociodemographic and genetic variables were summarized using descriptive statistics (mean and standard deviation; frequency and percentage) for the whole sample and by group according to the outcome (recovered/not recovered). The PRS-Sz,

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ERS-Sz and FLS-Sz variables were categorized using the 75th quantile of the original continuous variables, with the highest quartiles (> 75%) considered as genetic and exposure risk states. Correlation between individual environmental, genetic and family load exposures was also assessed using linear regression, both crude and adjusted by age and gender, and with the categorized version using logistic regression. Logistic regression models were fitted to test univariate associations between these categorical variables and evolution. Models were additionally adjusted by age and gender, and when the PRS-Sz was included, two ancestry components (PC1 and PC2) were added as covariates to control for potential hidden population substructure issues despite the European descent of all samples included. To test the joint effect of environmental and genetic scores, they were included additively and the RERI was estimated. The same procedure was used to test the joint effect of the family–environment interaction. A RERI value of more than zero indicates a positive deviation from additivity and was considered significant when the 95% confidence interval (CI) did not contain zero. The RERI was estimated using the epiR library in R (version 4.1.3). To estimate the impact of each term of the fitted models, the caret library was used, which calculate the variable importance and scales it to have a maximum value of 100. Additionally, a sensitivity analysis was conducted using the original continuous version of the three scores (PRS-Sz, ERS-Sz and FLS-Sz) and bootstrapping for estimation of 95%CI, as in Knol, van der Tweel, Grobbee, Numans and Geerlings (2007).

Ethics

The SEGPePs study was examined and approved by the clinical research ethical committee of Navarra (2016/71). All clinical and research procedures of this study fulfilled the ethical standards of the relevant national and institutional committees on human experimentation and of the Helsinki Declaration of 1975, as revised in 2008.

RESULTS

The final long-term follow-up SEGPEPs cohort comprised 243 patients (a 47.6% retention percentage from the initial baseline sample of 510 patients). For the present analysis, we included the whole follow-up sample for the ERS-Sz and FLS-Sz (*n* = 243; 137 males, 106 females; mean age = 48.52 ± 10.45) but only 164 patients (95 males, 69 females; mean age = 48.46 ± 10.89) had the genotype available and were included in the present analysis. There were no significant differences in baseline demographic and clinical characteristics between patients with and without a PRS (Table 1). After a 21-year FEP follow-up, 128 (52.7%) patients showed functioning recovery, as seen by a SOFAS score of ≥ 61. Variables related to poor long-term outcome were FLS>Sz_{75} (X^2=0.01, p = 0.005) and ERS>Sz_{75} (X^2 = 3.86, p= 0.049), specifically the obstetric complications (X^2=10.69, p = 0.001) and childhood adversity (X^2=17.42, p = 0.001) components (see Table 2).

The association assessment between exposures showed that PRS-Sz_{75} and ERS-Sz_{75} were not associated either when adjusted for age and gender (OR: 0.78; 95%CI: 0.32, 1.88; p = 0.580) or when using the continuous scores (adjusted b = −0.022; 95%CI: −0.062, 0.017; p = 0.269). Similarly, PRS-Sz_{75} and FLS-Sz_{75} were not associated, either when adjusted for age and gender (OR: 0.74; 95%CI: 0.31, 1.75; p = 0.493) or when using the continuous score (adjusted b = −0.018; 95%CI: −0.051, 0.015; p = 0.283). The association between FLS-Sz_{75} and ERS-Sz_{75} was close to the limit of statistical significance

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(age and gender adjusted OR: 1.69; 95%CI: 0.88, 3.22; p = 0.112), but not when using the continuous scores (adjusted b = 0.010; 95%CI: −0.114, 0.134; p = 0.876).

PRS-Sz_{75} does not discriminate between long-term recovered and not recovered cases using age and gender adjusted logistic regression analysis (OR: 1.17; 95%CI: 0.57, 2.41) (see Supplementary Table S1). ERS-Sz_{75} discriminates between these two groups (age and gender adjusted: OR: 1.98; 95%CI: 1.09; 3.59; p = 0.026; Nagelkerke R^2 = 0.031). FLS-Sz_{75} also discriminates between these two groups (age and gender adjusted: OR: 2.50; 95%CI: 1.36, 4.58; p = 0.003; Nagelkerke R^2 = 0.057) (see Supplementary Table S1). That is, to have high environmental risk (ERS-Sz>Sz_{75}) duplicates the risk of not recovering at follow-up, which is a similar effect to having a high familial load score (FLS-Sz>FLS-Sz_{75}); however, a high PRS-Sz did not have a significant impact on this recovery.

There was no evidence of a positive additive interaction between PRS-Sz_{75} and ERS-Sz_{75} after (age and gender adjusted RERI = 1.06; 95%CI: −3.72, 5.84; see Table 3 and Figure 1A for adjusted data and Supplementary Table 2 for unadjusted analyses). Similarly, there was no evidence of a positive additive interaction between FLS-Sz_{75} and ERS-Sz_{75} (age and gender adjusted RERI = −0.24; 95%CI: −4.22, 3.72) (see Table 3, Supplementary Tables S2 and Figure 1B). Sensitivity analyses using continuous PRS-Sz and ES-Sz variables confirmed the absence of interaction (see Supplementary Table S3).

In short, our best-fitting model could be considered the additive model that includes FLS-Sz, PRS-Sz and ERS-Sz adjusted for age and gender, and whenever PRS-Sz was included, two ancestry variables PC1 and PC2 were added as covariates. PRS-Sz, ERS-Sz and FLS-Sz additively increment the risk of poor long-term outcome. And when the risk factors are considered together, they provide age-gender adjusted ORs of 1.30 (95% CI: 0.62, 2.73) for PRS-Sz_{75}, 2.06 (95%CI: 0.94, 4.50) for ERS-Sz_{75} and 1.96 (95%CI: 0.93, 4.15; R^2 = 0.081) for FLS-Sz_{75} (see Supplementary Table S1). The variable importance for PRS-Sz75 is 0.70, for ERS-Sz75 is 1.81 and for FLS-Sz75 is 1.76.

Results of the additional analyses examining the effects and interactions between the specific dimensions of ERS-Sz with PRS-Sz_{75} and FLS-Sz_{75} on the course of the disease are given in Supplementary Table S4. The results confirm the absence of interaction terms between the different exposure scores when assessing the effect on poor long-term outcome and the importance of both obstetric complications and childhood adversity, together with the FLS-Sz, on this endpoint. A model including all variables without interactions identified that PRS-Sz_{75} was not significant (OR: 1.35; 95%CI: 0.64, 2.85; p = 0.429). Hence, the final multivariate logistic regression model fitted included age and gender for adjustment, obstetric complications (OR: 2.28; 95%CI: 1.03, 5.05; p = 0.042), childhood adversity (OR: 2.31; 95%CI: 1.23, 4.34; p = 0.009) and FLS-Sz_{75} (OR: 2.02; 95%CI: 1.07, 3.81; p = 0.029; Nagelkerke R^2 = 0.141). The variance importance for the exposure dimensions were 2.03 for obstetric complications, 2.61 for childhood adversity and 2.18 for FLS-Sz75.

DISCUSSION

Three main findings were found in this study. First, the FLS-Sz for schizophrenia showed a higher predictive power of poor long-term functioning of FEP patients than the ERS-Sz and PRS-Sz; and the ERS-Sz was higher than the PRS-Sz. Second, the PRS-Sz did not discriminate significantly between recovered and non-recovered FEP patients in the long term. Third, there were no significant interactions between PRS-Sz and ERS-Sz

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or between FLS-Sz and ERS-Sz regarding the long-term functioning of FEP patients. Therefore, the three risk factors seem to be better understood within additive models.

Long-term outcome studies in schizophrenia revealed great heterogeneity due to differences in populations, assessment methods and designs. However, there is strong evidence that full recovery in schizophrenia is relatively rare (13.5%) (Jaaskelainen et al., 2013) and nearly half of patients experience only moderate recovery (Morgan et al., 2021). Less evidence has been reported in FEP patients although remission and recovery rates are more favorable than in schizophrenia patients (Alvarez-Jimenez et al., 2012; Lally et al., 2017; Santesteban-Echarri et al., 2017). These findings are in agreement with the fact that 53% of our patients showed moderate functional recovery after 21 years of follow-up.

Our findings regarding FLS-Sz are in agreement with consistent evidence demonstrating that a first-degree relative with schizophrenia is the strongest risk factor for developing the same illness (relative risk: 9.9)(Lichtenstein et al., 2009). Likewise, a positive family history of schizophrenia seems to be a moderate predictor of poor outcome in the long-term follow-up cohorts of schizophrenia (Esterberg, Trotman, Holtzman, Compton and Walker, 2010; Kakela et al., 2014) and FEP patients (Bromet, Naz, Fochtmann, Carlson and Tanenberg-Karant, 2005). Nevertheless, a Chinese-based study reported that the predictive value of family history over poor long-term functioning was stronger in the early stages of illness (Ran et al., 2018). The presence of first-degree relatives affected by schizophrenia is a complex risk factor implying a strong genetic effect, but it seems necessary also to consider strong shared influences due to the deviance of nurturing, culture and family environment that the psychotic illness caused in affected parents (Niemi, Suvisaari, Haukka and Lonnqvist, 2005). Moreover, this association is not specific because almost any psychiatric disorder in first-degree relatives is associated with an increased risk of schizophrenia (van Os et al., 2010).

There are several studies addressing aggregate scores resulting from a cumulative measure of environmental liability for schizophrenia, namely the MERS (Mas et al., 2020; Vassos et al., 2020), ERS (Pries et al., 2019), polyenviromic risk score (Padmanabhan, Shah, Tandon and Keshavan, 2017) and psychosis polyrisk score (Oliver et al., 2020). All these measures displayed consistent differences in case–control studies of schizophrenia, high correlations with conversion to psychosis in familial high-risk FEP subjects (Padmanabhan et al., 2017), showing that the accumulation of environmental factors leads to more severe disease (Stepniak et al., 2014) and reporting good risk stratification properties of ERS-Sz in the general population (Pries et al., 2021). Moreover, an accumulation of environmental factors was associated with a proportional lowering of the age at onset of schizophrenia, which is a factor with demonstrated evidence of an association with poor long-term outcome in a cross-sectional study that comprehensively examined a large dataset of schizophrenia patients (Stepniak et al., 2014). In addition, poor functioning in FEP patients was significantly associated with the cumulative environmental load for schizophrenia in a large data set of FEP patients, unaffected siblings and healthy controls from the EUGEI study (Erzin et al., 2021b). And these cross-sectional associations were replicated in a relatively short follow-up duration study from the Athens FEP Research Study (Erzin et al., 2021a). Both studies emphasized the clinical utility of exposome score for the stratification of potential poor outcome in in FEP.

Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351

Despite no previous studies examining the influence of the ERS-Sz over the long-term course of FEP patients, our longitudinal study verifies that the ERS-Sz is a strong predictor of poor long-term outcome in FEP patients. Moreover, we examined the effect of the specific components of the ERS-Sz and found that childhood adversity and obstetric complications contributed negative and significantly to poor long-term outcome in our FEP sample.

The utility in real-world healthcare settings of the PRS-Sz resulting from the GWAS has increased since the OR for being diagnosed with schizophrenia has risen to 2.3, with an OR of 4.6 between the top and bottom 10% of polygenic risk (Zheutlin et al., 2019). However, this effect is not specific because it conveys important pleiotropic effects on related psychiatric disorders (Zheutlin et al., 2019), and thus cannot provide useful information on the interactions of individual genes with the environment (Vassos et al., 2022).

Three recent studies used the RERI in schizophrenia spectrum disorders. Two studies (Mas et al., 2020; Pries et al., 2020) reported a positive additive interaction between the PRS-Sz and the ERS-Sz. These findings show that the combined effect of both risk factors contributes more than the simple sum of each individual factor for differentiating between FEP patients and healthy controls (Mas et al., 2020), and this positive additive interaction also seems to contribute across the extended psychosis phenotype (Pries et al., 2020) . In addition, another study found a significant additive interaction between the PRS-Sz and antecedents of childhood adversity (van Os et al., 2020). However, no direct comparison was possible with our results because our study design was not focused on the differentiation between patients and healthy subjects, but comprised a dichotomized FEP sample in terms of long-term poor and good outcome.

The PRS-Sz, family psychiatric history and socioeconomic status were consistently related to schizophrenia in a population-based study (Agerbo et al., 2015) and a family history of schizophrenia or psychoses was found to be partly mediated through the individual's genetic liability. However, the extent to which the PRS-Sz for schizophrenia might predict the course of the disorder is still uncertain (Binder, 2019). Our findings were not in agreement with results from the 20-year follow-up Suffolk County study, which found the PRS-Sz to be significantly predictive of illness severity and significantly associated with higher scores on negative symptoms (avolition) and higher cognitive deficits (Jonas et al., 2019). The different outcome measures for both studies might account for these differences because they used the Global Assessment Functioning (GAF) scale as a measure of outcome and we used the SOFAS. The SOFAS seems to be more focused than the GAF scale on social and occupational functioning independent of the overall severity of the individual's psychopathological symptoms (Aas, 2014).

In addition, we found suggestive but not nominally statistically significant evidence of an additive interaction between the PRS-Sz and the ERS-Sz. It seems that in FEP patients with a high ERS-Sz, the PRS-Sz increased the odds of non-recovery at long-term follow-up, as seen by inspection of the RERI confidence intervals.

While heritability reflects the proportion of overall variability in a population trait that results from additive genetic effects, the presence of familial antecedents of psychosis encompasses a wider context, named transmissibility or familiality, because it also involves the sharing of environmental factors (Kendler & Neale, 2009).

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Taken together, our results support an additive model of familial antecedents of schizophrenia, environmental risk factors and polygenic risk factors as contributors to a poor long-term functional outcome for FEP patients.

Limitations

Our results should be considered while noting several methodological limitations. First, caution is warranted because the size of the sample might not be sufficient to detect genetic and environmental influences and interactions affecting the long-term course of FEP patients. This lack of power is particularly important for PRS-Sz, expected to have modest contributions to the overall explained variability. Second, the three prognostic domains (PRS-Sz, ERS-Sz and FLS-Sz) were derived from their highest quartiles of the whole sample because no healthy control subjects were included in the study. Third, in the ERS-Sz we included the presence of definitive obstetric complications instead of only the birthweight item as in the original MERS. However, most studies used a global score of obstetric complications (Cannon et al., 2002; Radua et al., 2018). Moreover, aggregate scores resulting from a cumulative measure of environmental liability have been proposed mainly for schizophrenia but not for FEP patients, although these risk scores have started to be used in other populations, such as individuals at potential risk for psychosis (Oliver et al., 2020). Fourth, we used a single cut-off point in the SOFAS (≥ 61) to define poor functioning in the final outcome of the 21-year follow-up of our FEP patients. However, the SOFAS is the most employed scale in the long-term follow-up studies of psychosis. Our sample was entirely made up of patients with European ancestry because at the time of the study in Spain there was no migration. Cross-validation of these results in non-European individuals should therefore be undertaken. Finally, the size of our genotyped sample (n=164) and the use of dichotomized risk scores might have reduced the power for even detecting its main effects and future studies will be needed to replicate our findings in larger samples.

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Conflicts of interest

The authors reported no conflicts of interest.

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Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351

Table 1: Demographic, clinical and diagnostic characteristics of SEGPEPs sample at the long-term follow-up (n= 243) and those with PRS available (N= 164)

	Full SEGPEPs follow-up sample (n=243)	**SEGPEPs follow-up sample with PRS (n=164)**	**SEGPEPs follow-up sample without PRS (n=79)**	**X^2 or $F_{(df)}$**	**p**
Age at intake, y	27.6 ± 9.8	27.3 ± 9.4	27.9 ± 10.3	$0.648_{(241)}$	0.616
Age, y	48.9 ± 10.7	48.9 ± 9.6	48.8 ± 11.2	$0.003_{(241)}$	0.954
Socioeconomic score (1-5)	3.07 ± 0.7	3.06 ± 0.6	3.07 ± 0.7	$0.001_{(241)}$	0.970
Education, years	11.2 ± 3.3	11.1 ± 3.2	11.2 ± 3.4	$0.110_{(241)}$	0.740
Follow-up, y	20.9 ± 5.5	21.1 ± 5.1	20.5 ± 5.6	$2.799_{(241)}$	0.096
SAPS, global ratings score	2.86 ± 3.6	3.25 ± 4.2	2.68 ± 3.3	$1.203_{(241)}$	0.257
SANS, global ratings score	5.89 ± 4.9	6.06 ± 5.8	5.81 ± 4.4	$0.137_{(241)}$	0.711
SOFAS (total score	62.8 ± 21.4	61.8 ± 26.4	63.3 ± 18.6	$0.276_{(241)}$	0.600
Current CPZ doses	330.48± 424.1	301.61± 462.6	344.39± 405.0	$0.541_{(241)}$	0.463
WAT_IQ	98.53 ± 12.5	97.5 ± 12.4	98.9 ± 12.5	$0.676_{(240)}$	0.412
Gender, n (male/female)	137/106	75/53	62/35	$0.518_{(1)}$	0.545
Single status, n (yes/no)	74/169	53/111	21/58	$0.828_{(1)}$	0.363
Diagnosis, n (%):				$7.805_{(7)}$	0.350
Schizophrenia	113 (46.5%)	72 (43.9%)	41 (51.9%)		
Schizophreniform disorder	6 (2.5%)	3 (1.8%)	3 (3.8%)		
Brief psychotic disorder	20 (8.2%)	14 (8.5%)	6 (7.5%)		
Delusional disorder	4 (1.6%)	1 (0.6%)	3 (3.8%)		
Schizoaffective disorder	39 (16.0%)	31 (18.9%)	8 (10.1%)		
Mania/bipolar disorder	42 (17.3%)	30 (18.3%)	12 (15.1%)		
Major depressive disorder	10 (4.1%)	7 (4.3%)	3 (3.7%)		
Psychotic disorder NOS	9 (3.7%)	6 (3.7%)	3 (3.7%)		
Polygenic risk score	0.74 ± 0.4	0.74 ± 0.4		NA	NA
Exposome risk score	1.48 ± 2.1	1.42 ± 2.1	1.61 ±2.1	$0.418_{(1)}$	0.518
Familial load score	12.1 ± 74.0	12.9 ± 84.5	10.3 ± 45.5	$0.069_{(1)}$	0.793
Functioning recovery, %*	52.7%	53.0%	51.8%	$0.028_{(1)}$	0.866

CPZ = Chlorpromazine equivalent doses; SAPS= Scale for the Assessment of Positive Symptoms; SANS= Scale for the Assessment of Negative Symptoms; SOFAS= Social and Occupational Functioning Assessment Scale; WAT= Word Accentuation Test.
*: Functioning recovery= SOFAS sustained over the last year ≥61. NA: Non applicable.

Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351

Table 2: Differences of polygenic risk score, exposome risk score and family load of schizophrenia between good- and poor long-term outcome patients

Variable	N	Category	Total (n=243)	Good long-term outcome (n=128)	Poor long-term outcome (n=115)	X^2 or $t_{(df)}$	p
$Age_{baseline}$	243	Mean(SD)	27.60(9.82)	27.30(9.43)	27.94(10.27)	t_{232}=-0.50	0.618
Sex	243	Men	137 (56.38)	75 (58.59)	62 (53.91)	X^2_1=0.37	0.545
		Women	106 (43.62)	53 (41.41)	53 (46.09)		
PRS-Sz	164	Mean(SD)	0.00(1.00)	-0.09 (1.10)	0.10 (0.87)	t_{160}=-1.17	0.242
PC1	164	Mean(SD)	0.00(0.08)	0.00 (0.08)	0.00 (0.08)	t_{157}=-0.55	0.582
PC2	164	Mean(SD)	0.00(0.08)	-0.01 (0.07)	0.01 (0.08)	t_{152}=-1.00	0.320
$PRS\text{-}Sz_{75}$	164	$\leq SCZ_{75}$	123 (75.0)	66 (75.9)	57 (74.0)	X^2_1=0.01	0.928
		$>SCZ_{75}$	41 (25.0)	21 (24.1)	20 (26.0)		
FLS-Sz	243	Mean(SD)	0.00(1.00)	-0.07 (0.54)	0.08 (1.34)	t_{146}=-1.10	0.272
$FLS\text{-}Sz_{75}$	237	$\leq Sz_{75}$	175 (73.8)	103 (81.7)	72 (64.9)	X^2_1=7.85	0.005
		$>Sz_{75}$	62 (26.2)	23 (18.3)	39 (35.1)		
ERS-Sz	243	Mean(SD)	0.00(1.00)	-0.11 (0.99)	0.12 (1.01)	t_{237}=-1.75	0.080
ERS_{75}	243	$\leq Sz_{75}$	182 (74.9)	103 (80.5)	79 (68.7)	X^2_1=3.86	0.049
		$> Sz_{75}$	61 (25.1)	25 (19.5)	36 (31.3)		
ERS components							
Urbanicity[2]	243	Rural	90 (37.04)	44 (34.38)	46 (40.00)	X^2_1=0.60	0.439
		Urban	153 (62.96)	84 (65.62)	69 (60.00)		
Cannabis use[2]	243	Absent	166 (68.31)	81 (63.28)	85 (73.91)	X^2_1=2.69	0.101
		Present	77 (31.69)	47 (36.72)	30 (26.09)		
Obstetric complications	243	No	201 (82.72)	116 (90.62)	85 (73.91)	X^2_1=10.69	0.001
		Yes	42 (17.28)	12 (9.38)	30 (26.09)		
Childhood Adversity[3]	243	No	168 (69.14)	104 (81.25)	64 (55.65)	X^2_1=17.42	0.001
		Yes	75 (30.86)	24 (18.75)	51 (44.35)		

PRS: Polygenic risk score. ERS: Exposome risk score, FLS: Family load score

[1] Urbanicity was stratified as low (including rural population and towns of less than 10.000 inhabitants) and medium to high cities.

[2] Cannabis use was stratified as no exposure and moderate to high exposure.

[3] Childhood adversity was stratified as a cut-off score of ≤60 sustained during childhood in the Global Family Environment Scale (GFES) [31].

Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351

Table 3: Gene-environment interaction and family-environment interaction on poor long-term outcome based on logistic regression models

	Interaction PRS-Sz and ERS-Sz		Interaction FLS-Sz and ERS-Sz	
	PRS ≤ Sz_{75} OR (95%CI)	PRS>Sz_{75} OR(95%CI)	FLS≤ Sz_{75} OR (95%CI)	FLS>Sz_{75} OR(95%CI)
ERS ≤ Sz_{75}	1	1.12 [0.49; 2.57]	1	2.74 [1.32; 5.67]
ERS > Sz_{75}	2.01 [0.84;4.81]	3.19 [0.73; 13.99]	2.11 [1.02; 4.40]	3.61 [1.35; 9.67]
RERI	1.06 (-3.72, 5.84)		-0.24 (-4.22, 3.72)	
R^2 Nagelkerke	0.059		0.080	
Variable Importance				
ERS	1.56		2.00	
PRS or FLS	PRS: 0.27		FLS: 2.71	
Interaction	PRS*ERS: 0.38		FLS*ERS: 0.70	

CI: Confidence interval; ERS: Exposome risk score; PRS: polygenic risk score; FLS: Family load score; RERI: Relative excess risk due to interaction. Adjusted for sex and age, and if PRS was included, adjusted additionally for two PCs; Variable Importance: Importance of the variable estimated with caret package

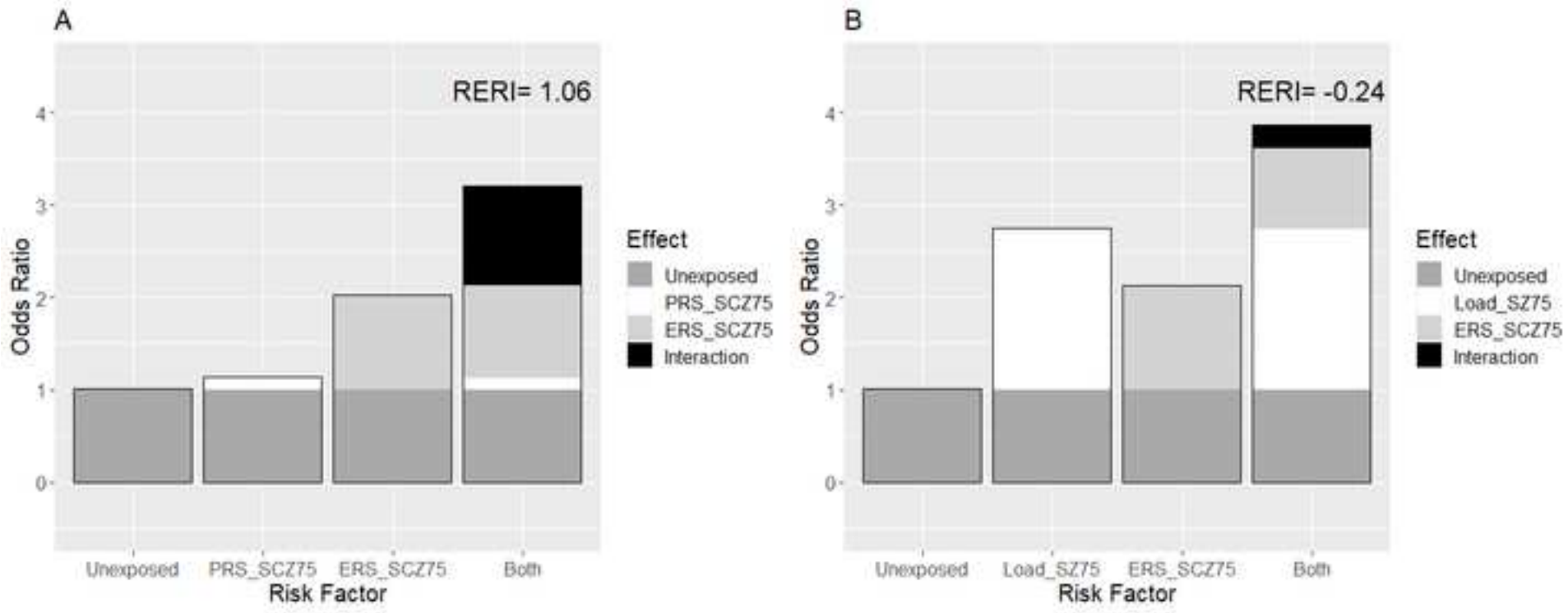
Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351

Figure 1A) Additive effect of ERS-ExpoZ75 and PRS-SCZ75 on poor long-term outcome.

Figure 1B) Additive effect of ERS-ExpoZ75 and Load-SZ75 on poor long-term outcome.

RERI: relative excess risk due to interaction; ERS-ExpoZ75: Exposome risk score (75% cut-point); PRS-SCZ75: polygenic risk score (75% cut-point); Load-SZ75 : Family Load (75% cut-point).

Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351



Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351

Supplementary Table 1: Univariate and additive models of the influence of polygenic risk score, exposome risk score and family risk score of schizophrenia on poor long-term outcome in FEP patients based on logistic regression models

		Row data				Age-gender adjusted[Ω]			
Variable	Category	OR (95%CI)	P value	R^2 Nagel	Variable importance	OR (95%CI)	P Value	R^2 Nagel	Variable importance
Univariate models									
PRS	≤Sz_{75}	Reference				Reference			
	>Sz_{75}	1.10[0.54;2.24]	0.787	0.001	0.27	1.17[0.57,2.41]	0.674	0.026	0.42
ERS	≤Sz_{75}					Reference			
	>Sz_{75}	1.88[1.04;3.38]	0.034	0.024	2.10	1.98[1.09;3.59]	0.026	0.031	2.23
FLS	≤ Sz_{75}	Reference				Reference			
	> Sz_{75}	2.43[1.34;4.41]	0.004	0.048	2.91	2.50[1.36;4.58]	0.003	0.057	2.97
Additive model PRS & ERS									
PRS	≤Sz_{75}	Reference				Reference			
	>Sz_{75}	1.12[0.55;2.29]	0.759		0.30	1.21[0.58;2.52]	0.610		0.51
ERS	≤Sz_{75}	Reference				Reference			
	>Sz_{75}	2.05[0.98;4.30]	0.057	0.030	1.90	2.18[1.01;4.70]	0.047	0.058	1.99
Additive model FLS & ERS									
FLS	≤Sz_{75}	Reference				Reference			
	>Sz_{75}	2.31[1.26;4.21]	0.007		2.72	2.39[1.29;4.40]	0.005		2.79
ERS	≤Sz_{75}	Reference				Reference			
	>Sz_{75}	1.72[0.94;3.15]	0.079	0.065	1.77	1.84[0.99;3.40]	0.053	0.078	1.94
Additive model PRS, ERS and FLS									
PRS	≤Sz_{75}	Reference				Reference			
	>Sz_{75}	1.20 [0.58;2.48]	0.620		0.50	1.30 [0.62;2.73]	0.482		0.70
ERS	≤Sz_{75}	Reference				Reference			
	>Sz_{75}	1.93 [0.90;4.10]	0.089		1.70	2.06 [0.94;4.50]	0.070		1.81
FLS	≤ Sz_{75}	Reference				Reference			
	> Sz_{75}	1.89 [0.91;3.91]	0.088	0.053	1.71	1.96 [0.93;4.15]	0.078	0.081	1.76

[Ω] Adjusted for gender and age, and if PRS was included, adjusted additionally for two PCs

Sz: Schizophrenia. Nagel: Nagelkerke

Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351

Supplementary Table 2: Polygenic risk score, exposome risk score and family load score of schizophrenia interactions on poor long-term outcome based on logistic regression models without adjustment for age, gender and PC

	Interaction PRS and ERS		Interaction FLS and ERS	
	PRS ≤ Sz_{75}	**PRS>Sz_{75}**	**FLS≤ Sz_{75}**	**FLS> Sz_{75}**
	OR (95%CI)	**OR(95%CI)**	**OR (95%CI)**	**OR(95%CI)**
ERS ≤ Sz_{75}	1	1.05 [0.47;2.36]	1	2.60 [1.27; 5.33]
ERS > Sz_{75}	1.91 [0.82;4.45]	2.70 [0.64;11.45]	1.94 [0.95; 3.99]	3.33 [1.26; 8.81]
RERI	0.74 [-3.33; 4.81]		-0.21 [-3.89, 3.46]	
R^2 Nagelkerke	0.031		0.067	
Variable Importance				
ERS	1.50		1.81	
PRS or FLS	PRS: 0.12		FLS: 2.62	
Interaction	PRS*ERS: 0.34		FLS*ERS: 0.62	

CI: Confidence interval; ERS: Exposome risk score; PRS: polygenic risk score; FLS family load score; RERI: Relative excess risk due to interaction. Unadjusted

Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351

Supplementary Table 3: Polygenic risk score, exposome risk score and family load score of schizophrenia interactions on poor long-term outcome based on logistic regression models using continuous variables

	OR(95%CI)	Variable importance	Adjusted OR$^{\Omega}$	Variable importance
PRS & ERS				
Additive model				
PRS-Sz	1.22 [0.89,1.67]	1.22	1.29 [0.93,1.79]	1.53
ERS-Sz	1.29 [0.94,1.77]	1.60	1.38 [0.99,.93]	1.88
R^2 Nagelkerke	0.032		0.068	
With interaction				
PRS-Sz	1.25 (0.91,1.75)	1.36	1.34 (0.96,1.90)	1.68
ERS-Sz	1.29 (0.94,1.78)	1.58	1.37 (0.98,1.95)	1.82
PRS-Sz *ERS-Sz	1.31(0.92,1.92)	1.44	1.38 (0.95,2.07)	1.65
RERI (95%CI BCa)	0.57 (-0.17, 2.93)		0.83 (-0.14,3.83)	
R^2 Nagelkerke	0.049		0.090	
FLS & ERS				
Additive model				
FLS-Sz	1.21 [0.83,1.77]	0.99	1.21 [0.83,1.77]	0.99
ERS-Sz	1.25 [0.97,1.62]	1.73	1.30 [1.00,1.70]	1.96
R^2 Nagelkerke	0.025		0.033	
With interaction				
FLS-Sz	1.31 (0.83,3.24)	0.82	1.30 (0.82,3.18)	0.81
ERS-Sz	1.35 (1.01,1.96)	1.87	1.41 (1.05,2.06)	2.08
FLS-Sz*ERS-Sz	2.44 (0.90,26.83)	1.05	2.55 (0.93,27.28)	1.09
RERI (95%CI BCa)	2.66 (-7834.6, 5608.6)		2.97 (-11260.6,3786.0)	
R^2 Nagelkerke	0.040		0.050	

CI: Confidence interval; ERS: Exposome risk score; PRS: polygenic risk score; FLS family load score; RERI: Relative excess risk due to interaction

Ω Adjusted for gender and age, and if PRS was included, adjusted additionally for two PCs

Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351

Supplementary Table 4: Polygenic risk score, exposome risk score and family load score of schizophrenia interactions using each of the ERS dimensions on poor long-term outcome based on logistic regression models

	Interaction PRS & ERS dimension		Interaction FLS & ERS dimension	
	PRS ≤ Sz_{75} OR (95%CI)	PRS>Sz_{75} OR(95%CI)	FLS≤ Sz_{75} OR (95%CI)	FLS> Sz_{75} OR(95%CI)
Urbanicity				
Rural	1	0.52 [0.16;1.71]	1	2.39 [0.93;6.18]
Urban/semi	0.62 [0.29; 1.32]	1.19 [0.43;3.29]	0.86 [0.45;1.65]	2.15 [0.89;5.20]
RERI*		NC$^{\Omega}$		NC$^{\Omega}$
R^2 Nagelkerke		0.051		0.058
Variable Importance				
Urbanicity		1.24		0.45
PRS or FLS	PRS:	1.07	FLS:	1.80
Interaction	Urbanicity*PRS:	1.70	Urbanicity*FLS:	0.07
Cannabis use				
No	1	1.21 [0.51;2.86]	1	3.73 [1.69;8.22]
Yes	0.86 [0.38;1.98]	0.81 [0.20;3.24]	0.82 [0.41;1.63]	1.06 [0.41;2.74]
RERI*		NC$^{\Omega}$		NC$^{\Omega}$
R^2 Nagelkerke		0.030		0.086
Variable Importance				
Cannabis		0.34		0.57
PRS or FLS	PRS:	0.44	FLS:	3.26
Interaction	Cannabis*PRS:	0.30	Cannabis*FLS:	1.60
Obstetric complications				
No	1	1.08 [0.50;2.35]	1	2.51 [1.27;4.96]
Yes	2.04 [0.72;5.80]	6.22 [0.66;58.80]	3.63 [1.44;9.11]	5.49[1.66;18.09]
RERI	4.10 [-9.86; 18.05]		0.35 [-6.78; 7.48]	
R^2 Nagelkerke		0.063		0.108
Variable Importance				
Obstetric complications		1.34		2.74
PRS or FLS	PRS:	0.19	FLS:	2.64
Interaction	Obstetric*PRS:	0.80	Obstetric*FLS:	0.63
Childhood adversity				
No	1	1.42 [0.61;3.32]	1	2.30 [1.06;5.00]
Yes	3.55 [1.55; 8.14]	3.23 [0.81;12.79]	3.07 [1.49;6.31]	5.33[2.15;13.20]
RERI	-0.75 [-5.75; 4.26]		0.94 [-4.09; 6.02]	
R^2 Nagelkerke		0.109		0.121
Variable Importance				
Childhood adversity		3.00		3.04
PRS or FLS	PRS:	0.81	FLS:	2.10
Interaction	Childhood *PRS:	0.52	Childhood*FLS:	0.42

* RERI could not be calculated as at least one of the odds ratios was below 1.

CI: Confidence interval; ERS: Exposome risk score; PRS: polygenic risk score; FLS family load score; RERI: Relative excess risk due to interaction. Adjusted for gender and age, and if PRS was included, adjusted additionally for two PCs

$^{\Omega}$ NC: RERI Not Calculable, as at least one of the OR <1

Cuesta, M. J., Papiol, S., Ibañez, B., García de Jalón, E., Sánchez-Torres, A. M., Gil-Berrozpe, G. J., … SEGPEPs Group. (2023, March 6). Effect of polygenic risk score, family load of schizophrenia and exposome risk score, and their interactions, on the long-term outcome of first-episode psychosis. Psychological Medicine. Cambridge University Press (CUP). http://doi.org/10.1017/s0033291723000351