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Polygenic and Polyenvironment Interplay in Schizophrenia-Spectrum Disorder and Affective Psychosis; the EUGEI First Episode Study

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***Background*: Multiple genetic and environmental risk factors play a role in the development of both schizophrenia-spectrum disorders and affective psychoses. How they act in combination is yet to be clarified.**

***Methods*: We analyzed 573 first episode psychosis cases and 1005 controls, of European ancestry. Firstly, we tested whether the association of polygenic risk scores for schizophrenia, bipolar disorder, and depression (PRS-SZ, PRS-BD, and PRS-D) with schizophrenia-spectrum disorder and affective psychosis differed when participants were stratified by exposure to specific environmental factors. Secondly, regression models including each PRS and polyenvironmental measures, including migration, paternal age, childhood adversity and frequent cannabis use, were run to test potential polygenic by polyenvironment interactions.**

***Results*: In schizophrenia-spectrum disorder vs controls comparison, PRS-SZ was the strongest genetic predictor, having a nominally larger effect in nonexposed to strong environmental factors such as frequent cannabis use (unexposed vs exposed OR 2.43 and 1.35, respectively) and childhood adversity (3.04 vs 1.74). In affective psychosis vs controls, the relative contribution of PRS-D appeared to be stronger in those exposed to environmental risk. No evidence of interaction was found between any PRS with polyenvironmental score.**

***Conclusions*: Our study supports an independent role of genetic liability and polyenvironmental risk for psychosis, consistent with the liability threshold model. Whereas schizophrenia-spectrum disorders seem to be mostly associated with polygenic risk for schizophrenia, having an additive effect with well-replicated environmental factors, affective psychosis seems to be a product of cumulative environmental insults alongside a higher genetic liability for affective disorders.**

Key words: psychosis; affective psychosis; schizophrenia-spectrum disorder; environmental risk factor; polygenic risk score; GxE interaction; cannabis; childhood adversity.

Introduction

Psychotic disorders have been classically divided into schizophrenia-spectrum disorders and affective psychoses, the latter including bipolar disorder (BD) and psychotic depression.[1] These disorders carry a detrimental societal and economical cost,[2–4] with considerable individual impact on reducing quality of life[5,6] and life expectancy,[7,8] particularly death by suicide.[9–11] However, their pathogenesis remains unclear to date, partly due to limited knowledge on how the putative causative factors interrelate. Exploring the relationship between well-established risk factors for psychosis could shed light on their role in predisposing to specific psychotic disorders.

The genetic components of schizophrenia (SZ), BD, and major depressive disorder (MDD) are well-established,[12,13] with an estimated heritability of 64%-80%,[14,15] 60%-80%,[16] and 37%[13] respectively. This heritability is partially carried by the combined effect of many single nucleotide polymorphisms (SNPs) detected in genome-wide association studies (GWAS)[17,18] that account for up to 24%, 20%, and 9% of genetic variance, respectively.[19–21] Despite the notable "heritability gap," polygenic risk scores (PRS) have proved effective estimates of these combined genetic effects with significant predictive ability of disease status.[22,23]

On the other hand, multiple so-called "environmental risk factors" (ERF) play an important role in both schizophrenia-spectrum disorder and affective psychosis, although one must note the difficulty in excluding potential genetic contributions to those exposures.[24] In our recent meta-analysis on ERF for affective psychoses (psychotic depression and BD), we found suggestive evidence of an increased risk for advanced paternal age, early or late gestational age, cannabis use, parental death or separation during childhood, and ethnic minority status,[25] whose association with schizophrenia-spectrum disorder has been more solidly established.[26] Some factors, such as ethnic minority or childhood adversity, appear to have a transdiagnostic effect on risk for psychosis, while studies have shown tentative evidence of specificity to schizophrenia-spectrum disorder for other factors such as living in urban areas, childhood social withdrawal, and possibly childhood exposure to Toxoplasma gondii.[27] Regarding risk factors for depression, strong evidence supports the role of childhood trauma[28] and stressful life events.[29]

The fact that not all individuals exposed to these environmental insults develop a disorder, and considering the unknown neurobiological mechanisms underlying these effects, raises the possibility that these exposures act in combination with a preexisting vulnerability, more so given the known genetic contribution to these disorders. In this respect, studies of gene-environment interactions (GxE) have gained much more attention in the last decade, but replication of results has been limited.[30] GxE studies using candidate genes have not been generally replicated,[31] and GxE studies using PRS have just started to be published.[32–34]

There is evidence that it is not only the type, but also the extent of environmental exposure that can influence the risk of psychosis, as demonstrated with an increase in risk according to the severity of exposures to childhood adversity[35,36] or cannabis use.[37] Besides, risk factors often co-occur and interplay, eg, trauma and cannabis use,[38,39] so studying them in isolation is not always representative of real life. Several methods have been proposed to compile the load of environmental exposure into quantitative scores, including the "psychosis polyrisk score" as a prediction tool for transition to psychosis in high risk individuals,[40] the "exposome score for schizophrenia,"[41] and the Maudsley environmental

risk score (MERS),[42] a simple to calculate, aggregate measure of environmental liability to disease. MERS combines the most robust published evidence of association of six environmental exposures (ethnic minority status, urbanicity at birth, high paternal age, obstetric complications, cannabis use, and childhood adversity), which makes it particularly interesting to use in models exploring interplay with genetics.

Given the above, the current work aims to: (1) explore if exposure to specific ERF (migration, cannabis, stressful life events, and childhood adversity) moderates the association of polygenic vulnerability to different psychiatric disorders (SZ, BD, depression) and (2) test for interaction between cumulative polygenic and polyenvironmental exposures (PRSxMERS) in schizophrenia-spectrum disorder and affective psychosis.[43]

Methods

Sample

The present study is based on the case-control sample from the EU-GEI study (European Network of national schizophrenia networks studying Gene-Environment Interactions), a multisite incidence and case-control study of genetic and environmental determinants involved in the development of psychotic disorders.[44]

The baseline sample comprises a total of 2627 participants, including 1130 patients aged 18-64 years who were resident within the study areas and presented with first episode psychosis (FEP) to the adult psychiatric services between May 1, 2010 and April 1, 2015 in 17 sites across 6 countries: England, the Netherlands, Italy, France, Spain and Brazil). All participants provided informed, written consent. Ethical approval was provided by relevant research ethics committees in each of the study sites. All data was stored anonymously. In addition, 1497 unaffected screened controls with no lifetime psychotic disorder were also recruited in the areas served by the services with a quota sampling approach, a nonprobability sampling method in which a specific subgroup is chosen in order to represent the local population. Further information about the methodology of the study is available in previous publications.[44–48]

Given the fact that the majority of the EUGEI participants were of European ancestry and the limited predictive power of current PRS in multi-ethnic samples,[49–51] for the scope of the present study we constrained the sample to those categorized as of European ancestry based on principal component analyses (PCA) (details provided in Supplementary Material).

Measures

Diagnoses. DSM-IV diagnoses[52] from interviews and mental health records utilizing the Operational Criteria Checklist (OPCRIT) at baseline[53] were produced by centrally trained investigators, whose reliability was assessed throughout the study ($\kappa = 0.7$). These diagnoses were grouped into schizophrenia-spectrum disorder (DSM-IV codes 295.1-295.9 and 297.1-298.9) or affective psychosis (psychotic subtypes within DSM-IV codes 296-296.9). For those subjects with missing information for DSM-IV output from OPCRIT, we reconverted ICD-10 diagnoses ($n = 5$) into DSM-IV codes, leaving eventually diagnostic data for 12 cases missing. Those who did not have enough data for a diagnosis ($n = 12$) or did not meet criteria from OPCRIT (ie, undefined diagnosis; $n = 52$) were not grouped into either of the groups and were excluded from further analyses.

Environmental Risk Factor Measures. Information on cannabis use was collected at baseline with the Cannabis Experience Questionnaire (CEQ) modified version,[54] where subjects were dichotomized based on frequency into those who reported never or occasional use (up to few times per month) and those with frequent cannabis use (at least weekly or daily bases). In order to define advanced paternal age, we established a cutoff at 45 year of age based on previous evidence for schizophrenia[55] and BD with psychotic symptoms.[56] From the information on place of birth and age of migration collected as part of the MRC Socio-demographic Schedule modified version,[57] we created a binary variable indicating whether a participant had a migration history or not; only first generation migrants were considered, as information on parental migration was not available. Given the exclusion on non-European ancestry from genetic analyses, this was mostly migration within Europe and North Africa and we used the corresponding weighting in MERS (presented below). A combined binary variable indicating the presence of any childhood trauma was created based on the presence of at least one of the five trauma types ranked as "severe" from the Childhood Experience of Care and Abuse Questionnaire (CECA.Q).[58] Lastly, a modified version of the List of Threatening Experiences[59] was used to categorize individuals in "none or less than three events" and "at least three events" in order to capture those with high exposure to threatening life events in the year prior to the onset of symptoms (details provided in Supplementary Material).

In order to estimate the cumulative environmental exposure, we adapted the MERS,[42] by removing obstetric complications and urbanicity at birth, which was not available in our sample. Definitions and values attributed per risk factors are provided in Supplementary material Table S1.

Genotyping and PRS Building. DNA from blood or saliva were obtained at baseline from the majority of participants (573 -73.6%- of cases and 1005 -78.5%- of controls of European ancestry) (Supplementary section1.1 and Table S2). The DNA collected was genotyped at the

Cardiff University Institute of Psychological Medicine and Clinical Neurology, with quality control performed locally (details provided in Supplementary material). A principal component analysis generating 10 principal components (PC) was run on pruned variants to control for population stratification.

Following the procedures reported previously,[48] PRS for SZ, BD, and depression (PRS-SZ, PRS-BD, and PRS-D) were built on PRSice2,[60] using summary statistics from the largest GWAS available,[61–63] excluding overlapping individuals with the current sample and also excluding the major histocompatibility complex (MHC) region. For our analyses, we used PRS at the *P*-value threshold of 0.05 that better predicted most phenotypes in the original GWAS publications. Each PRS was standardized to a mean of zero and standard deviation of one.

Statistics

Descriptive Statistics. We described sodiodemographics using frequencies, percentages, mean, and standard deviations (SD) alongside case-control group comparisons (schizophrenia-spectrum disorder and affective psychosis vs controls) using Chi-square and Student t-test as appropriate. Correlations between polygenic and environmental predictors were tested, followed by tests for associations between recruiting sites with PRSs and environmental measures.

Association Analyses. Multinomial univariable and multivariable logistic regressions were run for individual environmental risks factors (advanced paternal age, migration, frequent cannabis use, stressful life events, and childhood adversity) to explore their independent associations with each clinical group (schizophrenia-spectrum disorder and affective psychosis) when compared with controls; and simple logistic regression for case-only comparisons (schizophrenia-spectrum disorder vs affective psychosis). All analyses were controlled for sex and site. Only subjects with full data were included in the analyses and we did not impute missing data due to the low percentage of missingness (Supplementary material Table S5).

Secondly, separate multiple logistic regression models adjusted for sex, site, and 10PCs were used to explore case-control associations of the three polygenic risk scores (PRS-SZ, PRS-BD, and PRS-D) with schizophrenia-spectrum disorder and affective psychosis when stratifying the analyses by exposure to those ERF that were significantly associated with any of the diagnostic groups in the previous analyses. To test for differences between the associations of the two case groups (schizophrenia-spectrum disorder and affective psychosis) versus controls in unexposed vs exposed, we estimated z scores by dividing the difference of regression coefficients $d = \log(OR_1) - \log(OR_2)$ by the combined standard error $SE(d) = \sqrt{(SE[OR_1]^2 + SE[OR_2]^2)}$.[64,65] Additionally, gene and environment interactions between individual ERF with the PRSs were tested though independent logistic regression models including the three PRSs, the individual ERF, and its product with each PRS to test departure from a multiplicative effect.[66] Analyses were adjusted for sex, site, 10PCs, and their interaction with PRS and ERF.[67,68] The false discovery rate (FDR) method using the Benjamini-Hochberg procedure was employed for multitesting correction for the above association analyses to preserve statistical power due to using correlated variables.

Third, potential polygenic by polyenvironment interaction as deviation from a multiplicative effect of PRS and MERS was tested by independent logistic regression models including the three PRSs, the aggregated measure of environmental exposure MERS, and its product with each PRS; adjusted for same sex, site, 10PCs, and their interaction with PRS and MERS. To compare simple with progressively more complex logistic regression models, we tested the goodness of fit of data of the joint use of PRSs and MERS alongside their interaction terms through likelihood-ratio test (see Supplementary material for more details).

Given previous evidence of interaction measured as deviation from an additive combination of risk factors and using a similar approach,[33] we performed a secondary analysis dichotomizing PRS and MERS using the 75% cutoff point in the control distribution and examining the relative excess risk due to interaction (RERI).[69]

Power Calculation. We performed post-hoc power calculation for the PRS by MERS interaction using a simulation method in R (version 4.2.1) using the standardised coefficients for PRS-SZ, MERS, and PRS-SZxMERS, from the comparison of SSD vs controls. These parameters were selected as the PRS-SZxMERS interaction had the larger effect size and the lowest *P*-value, which suggests that the power for interaction with PRS-BD or PRS-D or in affective psychosis would be lower and the minimum sample size larger.

Results

Description of the Sample

The total sample, following quality control of the genetic data and exclusion of individuals of non-European ancestry, comprised 573 cases with genotyping and defined psychotic disorder (composed of 409 schizophrenia-spectrum disorder and 164 affective psychosis) and 1005 controls. Description of the sociodemographics and distribution of ERF on schizophrenia-spectrum disorder, affective psychosis, and controls is shown in **Table 1**.

The main sociodemographic differences were a lower proportion of women in the schizophrenia-spectrum disorder group (32% vs 53% in controls), higher

Table 1. Sociodemographic and Environmental Risk Factors Distribution Across Clinical Groups of European Ancestry

	Control	Schizoprenia-spectrum			Affective psychosis		
	Mean (SD)/*N* (%)[a]	Mean (SD)/*N* (%)[a]	Statistics[b]	*P*-value	Mean (SD)/*N* (%)[a]	Statistics [b]	*P*-value
Age	36.9 (13.02)	31.63 (10.92)	*t* 7.21	*P* < .001	32.84 (11.56)	*t* 3.76	*P* < .001
Gender (% female)	531 (52.84)	131 (32.03)	X^2 50.54	*P* < .001	81 (49.39)	X^2 0.67	*P* = .413
Years of education	14.68 (4.19)	12.94 (4.12)	*t* 7.07	*P* < .001	12.58 (3.84)	*t* 5.96	*P* < .001
Living independently (% no)	314 (31.49)	198 (62.46)	X^2 96.97	*P* < .001	63 (46.32)	X^2 11.85	*P* = .001
Marital status (% single)	378 (37.65)	266 (71.70)	X^2 126.13	*P* < .001	80 (51.95)	X^2 11.42	*P* = .001
Unemployment (% yes)	383 (38.38)	169 (54.52)	X^2 25.26	*P* < .001	56 (41.48)	X^2 0.48	*P* = .487
Urbanicity *N* (%)			X^2 19.9	*P* < .001		X^2 0.4655	*P* = .792
Low (< 1000/km2)	445 (44.28)	129 (31.54)			68 (41.46)		
Medium (1000-5000/km2)	359 (35.72)	185 (45.23)			61 (37.2)		
High (>5000/km2)	201 (20)	95 (23.23)			35 (21.34)		
Lifetime cannabis (% yes)	469 (47.04)	262 (65.83)	X^2 40.26	*P* < .001	103 (63.98)	X^2 15.9	*P* < .001
Frequent cannabis (% yes)	122 (12.24)	173 (44.02)	X^2 170.05	*P* < .001	51 (32.08)	X^2 42.32	*P* < .001
Parental age >45y (%yes)	31.62 (6.67)	32.01 (7.34)	*t* −0.94	*P* = .347	31.8 (6.97)	*t* −0.31	*P* = .621
Migration (% yes)	88 (8.76)	57 (14.39)	X^2 9.73	*P* = .002	17 (10.37)	X^2 0.45	*P* = .504
Age migration	18.49 (12.51)	14.85 (10.68)	*t* 1.84	*P* = .067	15.79 (9.73)	*t* 0.98	*P* = .332
Stressful life events (% >3)	168 (16.72)	92 (22.49)	X^2 6.4	*P* = .011	57 (34.76)	X^2 29.52	*P* < .001
Childhood trauma (% yes)							
Physical abuse	61 (6.12)	59 (15.53)	X^2 30.61	*P* < .001	21 (12.98)	X^2 9.76	*P* = .002
Psychological abuse	64 (6.42)	40 (10.55)	X^2 6.72	*P* = .010	25 (15.43)	X^2 15.97	*P* < .001
Sexual abuse	27 (2.71)	16 (4.23)	X^2 2.08	*P* = .149	9 (5.59)	X^2 3.8	*P* = .051
House discord	277 (28.27)	154 (40.53)	X^2 19.02	*P* < .001	69 (42.07)	X^2 12.7	*P* < .001
Bullying	142 (14.56)	114 (30.4)	X^2 44.2	*P* < .001	52 (33.55)	X^2 33.89	*P* < .001
Total childhood trauma	413 (42.98)	225 (60.65)	X^2 33.49	*P* < .001	107 (67.72)	X^2 33.4	*P* < .001

Abbreviation: SD, standard deviation.
P-values correspond to difference from controls.
[a]Continuous variables are recorded as mean (SD); categorical variables as *N* (%).
[b]Statistics include "*t*" for *t*-test for continuous variables or "X^2" for Chi-square for categorical variables.

unemployment in schizophrenia-spectrum disorder (54% vs 38% in controls), and a higher proportion of both clinical groups of being single and not living independently (63% in schizophrenia-spectrum and 42% in affective psychosis vs 31% in controls).

Several significant correlations arose from the exploratory variate correlation analyses (Supplementary Table S3). All three PRSs were correlated among themselves (large between PRS-SZ and PRS-BD, $r = 0.53$; moderate between PRS-SZ and PRS-D, $r = 0.30$ and PRS-BD and PRS-D, $r = 0.28$). Childhood adversity showed a small correlation with PRS-D ($r = 0.11$), frequent cannabis use ($r = 0.20$) and stressful life events ($r = 0.14$), with a further small correlation between frequent cannabis and stressful life events ($r = 0.14$). MERS score was significantly correlated with all three standardised residuals of PRS after adjusting for 10PCs and site; and the five individual ERFs. Anova's and Chi²'s tests showed that ERF but not PRS differed between sites (Supplementary material Table S4 and S5).

ERF Association with Clinical Groups

Univariable regression analyses showed that frequent cannabis use was associated with both schizophrenia-spectrum disorder (OR 4.95, 95% CI, 3.69-6.66) and affective psychosis (OR 3.41, 95% CI, 2.28-5.10), when compared with controls. Being a migrant was significantly associated with schizophrenia-spectrum disorder (OR 1.77, 95% CI, 1.19-2.63) but not with affective psychosis (OR 1.27, 95% CI, .71-2.28). Both forms of social adversity were associated with both clinical groups: stressful life events (schizophrenia-spectrum disorder OR 1.50, 95% CI, 1.12-2.08; affective psychosis OR 2.54, 95% CI, 1.74-3.72) and childhood adversity (schizophrenia-spectrum disorder OR 2.39, 95% CI, 1.83-3.13; affective psychosis OR 2.87, 95% CI, 1.97-4.17). Similarly, the combined measure of MERS was higher in both schizophrenia-spectrum disorder (OR 1.28, 95% CI, 1.22-1.35) and affective psychosis (OR 1.25, 95% CI, 1.17-1.33) than in controls. In case-only comparisons, only stressful life events had a nominally significant association with affective psychosis, which does not survive multiple testing correction (detailed results are provided in **Table 2**).

In the multivariable analyses, where the effect of each risk factor was adjusted for the others, frequent cannabis use (schizophrenia-spectrum OR 3.79, 95% CI, 2.76-5.21; affective psychosis OR 2.61, 95% CI, 1.69-4.01) and childhood adversity (schizophrenia-spectrum OR 1.87, 95% CI, 1.40-2.51; affective psychosis OR 2.44, 95% CI, 1.63-3.66) were associated with both clinical groups, with stressful

Table 2. ERF Associations in Univariable and Multivariable Model with Affective Psychosis and Schizophrenia-Spectrum Disorder Versus Controls; and for Affective Psychosis vs Schizophrenia-Spectrum Disorder

	SSD vs control			AP vs control			AP vs SSD		
	OR	*P*-value	95% CI	OR	*P*-value	95% CI	OR	*P*-value	95% CI
Univariable									
Paternal age >45y	1.51	.157	0.85-2.65	1.64	.186	0.79-3.41	0.99	0.986	0.44-2.25
Migration	**1.75**	**.005**	**1.19-2.59**	1.27	.417	0.71-2.27	0.71	0.283	0.38-1.33
Frequent cannabis	**4.95**	**<.001**	**3.69-6.66**	**3.41**	**<.001**	**2.28-5.1**	0.67	0.071	0.44-1.03
SLE	**1.53**	**.007**	**1.12-2.08**	**2.54**	**<.001**	**1.74-3.72**	1.63	0.029	1.05-2.53
Childhood adversity	**2.39**	**<.001**	**1.83-3.13**	**2.87**	**<.001**	**1.97-4.17**	1.14	0.549	0.74-1.75
MERS	**1.28**	**<.001**	**1.22-1.35**	**1.25**	**<.001**	**1.17-1.33**	0.97	0.435	0.91-1.04
Multivariable									
Paternal age >45	1.38	.322	0.73-2.61	1.46	.354	0.66-3.26	1.05	0.916	0.43-2.57
Migration	1.51	.077	0.96-2.39	1.26	.481	0.66-2.38	0.83	0.601	0.41-1.67
Frequent cannabis	**3.79**	**<.001**	**2.76-5.21**	**2.61**	**<.001**	**1.69-4.01**	0.68	0.098	0.42-1.07
SLE	1.26	.186	0.89-1.79	**2.13**	**<.001**	**1.42-3.20**	1.62	0.045	1.01-2.60
Childhood adversity	**1.87**	**<.001**	**1.40-2.51**	**2.44**	**<.001**	**1.63-3.66**	1.26	0.325	0.79-2.00

Abbreviations: AP, affective psychosis; CI, confident interval; OR, odds-ratio; SLE, stressful life events; SSD, schizophrenia-spectrum disorder.
In bold statistically significant after controlling for the False Discovery Rate multitesting method by Benjamin-Hochberg. The top section of the table presents univariable analyses (each predictor associated with the outcome in separate regression models). The bottom section of the table presents the results of a multivariable model, where each predictor is adjusted for the others.

life events being more associated with affective psychosis (OR 2.13, 95% CI, 1.42-3.20) than with schizophrenia-spectrum disorder (OR1.26, 95% CI, .89-1.79) when compared with controls. No significant associations were observed in the case-only multivariable comparisons.

Differences Between Polygenic Prediction in Individuals Stratified by Exposure to ERF

Schizophrenia-Spectrum Disorder vs Control. PRS-SZ was significantly associated with schizophrenia-spectrum disorder in those unexposed to any type of ERF and those exposed to social adversity (stressful life events and childhood adversity). We observed larger effects of PRS-SZ for those unexposed to frequent cannabis use (unexposed OR 2.43, 95% CI, 1.87-3.16; vs exposed OR 1.35, 95% CI, .88-2.06) and childhood adversity (unexposed OR 3.04, 95% CI, 2.11-4.38; vs exposed OR 1.74, 95% CI, 1.32-2.3) compared to those exposed to these two ERF. The effect of PRS-BD on schizophrenia-spectrum disorder was lower than the effect of PRS-SZ and PRS-D was not associated with schizophrenia-spectrum disorder in any of the stratified by exposure analyses (**Figure 1**; Supplementary Table S6).

Affective Psychosis vs Control. Associations with PRS-SZ and PRS-BD, were mostly significant among those unexposed to ERF although the effect sizes were similar in exposed individuals, but their numbers were smaller with wider confidence intervals. On the contrary, the observed associations with PRS-D were generally larger in affective psychosis cases exposed to environmental factors. None of the comparisons of PRS effects between individuals exposed and unexposed to environmental risk were statistically significant.

Polygenic and Environmental Interaction

In the combined model including polygenic and polyenvironmental measures and their interaction, schizophrenia-spectrum disorder was positively associated with PRS-SZ (OR 1.90, 95% CI, 1.23-2.95), PRS-BD (OR 1.78, 95% CI, 1.14-2.78) and with MERS (OR 1.32, 95% CI, 1.20-1.45). Affective psychosis was associated with PRS-BD (OR 1.99, 95% CI, 1.18-3.36) and with MERS (OR 1.37, 95% CI, 1.19-1.57). No evidence of interaction as departure from the multiplicative model was found between any of the PRS with MERS (**Table 3**). Simulation using the standardised regression coefficients of the PRS-SZ by MERS interaction yielded a power estimation of 52%. With the same parameters, we estimated that the minimum sample size to reach a power of 80% would be 2600 individuals.

Similarly, none of the interactions terms in combined models including the three PRS, each individual ERF and their interaction in schizophrenia-spectrum disorders and affective psychosis were significant (Supplementary Table S7). In the model comparison with likelihood-ratio test, adding MERS to the model with PRSs increased the variance explained for both schizophrenia-spectrum disorder vs control (R^2 = 0.32 vs 0.25; $\Delta\chi^2(1)$ = 78.06, P < .001) and affective psychosis vs control (R^2 = 0.22 vs 0.16; $\Delta\chi^2(1)$ = 40.93, P < .001); while adding the interaction terms made no difference (Supplementary Table S8).

Analyses for polygenic scores by polyenironmental exposure interactions in all psychosis cases vs control and

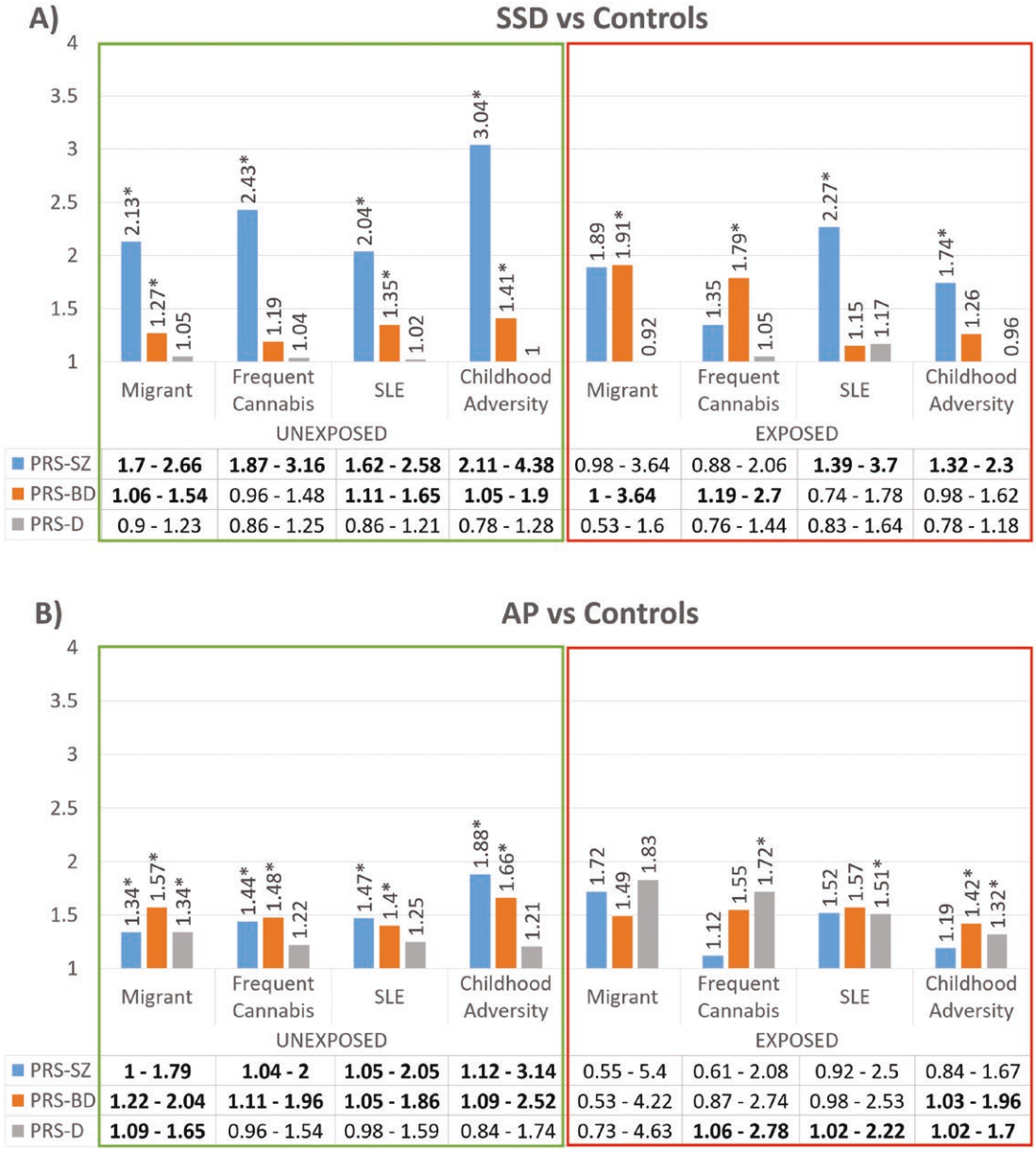

Figure 1. Stratified Polygenic Associations of Schizophrenia-Spectrum Disorder vs Controls and Affective Psychosis vs Controls Based on Exposure to Relevant ERF. Results of OR on Top of Bars and Corresponding 95% CIs in the Bottom Table Based on Individual Simple Logistic Regressions in Subgroups Based on Exposure to the Different ERF; Adjusted by Sex, 10PCs and Site. Figure Shows by * and Bold CIs the Significant Results at $P < .05$. SSD, Schizophrenia-Spectrum Disorder; AP, Affective Psychosis; SLE, Stressful Life Event; PRS, Polygenic Risk Score; BD, Bipolar Disorder; SZ, Schizophrenia; D, Depression

in case-only comparisons between affective psychosis and schizophrenia-spectrum disorder groups were also negative (Supplementary Table S9). Secondary analyses testing interaction under an additive model did not produce any significant results for schizophrenia-spectrum disorder. However, the combined effect of polyenvironmental exposure and PRS-SZ (RERI 4.98, 95% CI, 0.11-9.85) as well as PRS-BD (RERI 3.97, 95% CI, 0.05-7.89) was greater than the sum of each alone in affective psychosis at a nominal level of significance (Supplementary material, section 2.7 and Figures S11–S16).

Discussion

To the best of our knowledge, this is the largest study to examine jointly the effect of polygenic and selected environmental exposures on specific diagnostic categories (schizophrenia-spectrum disorders and affective psychosis) in FEP patients of European ancestry. The key finding from the results was the lack of evidence of multiplicative interaction between polygenic and polyenvironmental exposure or individual risks factors in schizophrenia-spectrum disorder and affective psychosis. Our study supports an additive combination

Table 3. Association of Aggregated Environmental Exposure Independently (Top Section) and in Interaction (Bottom Section) with Different PRSs (SZ, BD, and MDD) Across Diagnostic Categories

	SSD vs control PRSs (n = 1271)				AP vs control PRSs (n = 1078)			
	OR	Z	*P*-value	95% CI	OR	Z	*P*-value	95% CI
PRS-SZ	**2.08**	**7.04**	**<.001**	**1.7-2.56**	**1.46**	**2.3**	**.006**	**1.11-1.91**
PRS-BD	**1.30**	**2.94**	**.003**	**1.09-1.55**	**1.50**	**3.34**	**.001**	**1.18-1.91**
PRS-D	1.05	0.62	.533	0.91-1.21	**1.34**	**2.92**	**.004**	**1.1-1.63**
MERS	**1.27**	**8.71**	**<.001**	**1.2-1.34**	**1.28**	**6.85**	**<.001**	**1.19-1.37**
PRS-SZ	**1.90**	**2.88**	**.004**	**1.23-2.95**	1.10	0.33	.740	0.63-1.93
PRS-BD	**1.78**	**2.54**	**.011**	**1.14-2.78**	**1.99**	**2.56**	**.010**	**1.18-3.36**
PRS-D	1.14	0.74	.458	0.80-1.63	1.33	1.24	.216	0.85-2.09
MERS	**1.32**	**5.61**	**<.001**	**1.2-1.45**	**1.37**	**4.52**	**<.001**	**1.19-1.57**
MERS × PRS-SZ	0.95	-0.98	.329	0.87-1.05	1.00	0.06	.955	0.89-1.13
MERS × PRS-BD	0.98	-0.45	.654	0.91-1.06	0.96	-0.75	.456	0.87-1.07
MERS × PRS-D	1.01	0.15	.882	0.94-1.07	1.03	0.75	.452	0.95-1.12

Abbreviations: AP, affective psychosis; CI, confident interval; MERS, maudsley environmental risk score; OR, odds-ratio; SSD, schizophrenia-spectrum disorder.
In bold statistically significant after controlling for the False Discovery Rate multitesting method by Benjamin-Hochberg.
Top section: Four logistic regressions for main efects of PRS-SZ, PRS-BD, PRS-D and MERS; adjusted for sex, 10PCs and site.
Bottom section: Logistic regression for main effects and interaction between each PRS with MERS; adjusted for sex, 10PCs and site and their interactions.

of genetic and ERF in the development of psychotic disorders.

We observed that among the polygenic scores we used, in the schizophrenia-spectrum disorder vs control comparisons, PRS-SZ was the strongest predictor, with a higher effect in those unexposed to frequent cannabis use and childhood adversity, the most significant ERF for schizophrenia-spectrum disorder.[26,42,70] This is consistent with the liability threshold model, under which a disease occurs when the combined liability from all the risk factors exceeds a threshold. In this context, in cases with high genetic risk, one might expect less environmental exposure, because their genetic risk alone brings them near the threshold for developing the disease and vice versa. Similarly, a previous study examining the contribution of PRS in copy number variants (CNV) carriers found that schizophrenia cases with a high OR CNV had a lower PRS for schizophrenia.[71] This adheres to an additive model, where the overall liability for disease is the sum of the contributions from different factors, without one modifying the effect of the other.

When we compared affective psychosis vs controls, our findings point towards an overall stronger effect of PRS-BD and PRS-D compared to PRS-SZ, as we have previously reported.[48] Indeed, affective psychosis was significantly associated with PRS-D among those exposed to frequent cannabis, stressful life events, and childhood adversity. Similarly, a previous study reported that childhood adversity, cannabis use, and to a lesser extent urbanicity, displayed departure from additivity in those with family history for depression.[72] Our findings and those from Radhakrishnan et al. suggest that social adversity may trigger psychosis in those with higher genetic vulnerability for mood disorders and support the hypothesis of an "affective pathway to psychosis," which postulates that low mood and anxiety as well as emotional dysregulation may precede the onset of psychosis in those exposed to social adversity.[73–75]

In the combined models, including polygenic and polyenvironment exposure alongside their interaction terms, we observed that our data fitted better a multiplicative model of combining genes and ERF. All the regression coefficients of the product of each PRS with MERS were close to 1, and the addition of interaction terms did not improve the goodness of fit of the model. On the contrary, our secondary analyses exploring departure from additivity showed that the combined effect of polyenvironmental exposure and polygenic risk for schizophrenia and BD was greater than the sum of each alone in affective psychosis, with nominal significance. The two methods cannot be directly compared in this study, as the multiplicative model uses continuous measures of PRS and MERS, while in the additive the two predictors were dichotomized with an arbitrary cutoff. Further studies in much larger samples are necessary to explore whether differential modes of combining genetic with environmental risk between schizophrenia and affective psychosis exist.

Our results replicate a consistent observation in psychosis,[26,76] showing that having frequently used cannabis, being a migrant, and having been exposed to either childhood or recent adversity were more prevalent in cases with either schizophrenia-spectrum disorder or affective psychosis than controls. Similarly, the polyenvironmental score appears strongly associated with both clinical groups compared to controls. Moreover, we also showed that adding MERS increases the predictive ability of PRS in both schizophrenia-spectrum disorder and affective

psychosis, which supports its use in future prediction models.

These results should be interpreted in the context of various strengths and limitations. We examined a well-characterized sample of FEP from a multisite study designed with the purpose of exploring both genetic and environmental aspects of psychosis. Moreover, rather than limiting investigation to one environmental risk factor, this study shows individual but also combined associations of up to five different ERF consistently associated with psychosis. Lastly, combining polygenic scores of three major psychiatric disorders with polyenvironmental exposures can provide a more holistic picture of how the cumulative exposure to risk factors can add to the genetic vulnerability.

However, a number of limitations should be acknowledged: First, this is a cross sectional study, which prevents any causal interpretation of the role of environmental exposures. Second, these were all reported retrospectively, which increase the risk of recal bias.[77] Third, only selected individual-level environmental exposures were included, not accounting for other individual- or neighbor-level ERF. Fourth, sample size is small for the higher requirements of GxE interaction in case-control studies[78,79]; according to our power analysis, we would need approximately twice as big sample size to reach 80% power. Fifth, we have based the clinical groups on the dichotomy of affective and schizophrenia-spectrum disorder, which sometime is an arbitrary distinction. As diagnosis was determined during the first episode, another consideration is the diagnostic instability over time.[80,81] Sixth, limiting our analyses to those of European ancestry underestimates the effect of some environmental factors as migration; while limiting generalisability to the wider population. Seventh, this study is cross sectional and lacks prognostic prediction; it is paramount to replicate our findings in samples with a prospective design, combining traditional analysis with machine learning tools. Last, further limitations pertaining to the use of PRSs should be noted. When polygenic scores are employed for diagnostic associations, one needs to bear in mind the high heterogeneity of training GWAS samples with varied psychopathology.[82] Furthermore, there is some evidence that current GWAS may be enriched for chronic or more severe patients, leading to a lower liability explained by PRS in incident samples, as noted previously.[83] Additionally, in relation to the PRS performance in GxE studies, current SNPs derived from case-control GWAS may imply that part of the signals is also reflecting exposures to environment, which may alter potential interaction of environmental risk with PRS.[24,84] This could possibly explain the significant correlation of PRS-SZ with frequent cannabis use and of PRS-D with childhood adversity in our sample.

To conclude, our study supports that patients with schizophrenia-spectrum disorder and low load of environmental exposure tend to have higher polygenic score for schizophrenia, consistent with the liability threshold model; that the genetic load for depression is more important in affective psychoses, specifically in those with a high environmental load, which supports the idea of an affective pathway to psychosis; and lastly, our study was unable to detect any significant GxE interactions and supports the independent role of genetic and environmental exposures in the development of psychotic disorders.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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