Genetic and psychosocial stressors have independent effects on the level of subclinical psychosis: findings from the multinational EU-GEI study

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Abstract

Gene x environment (GxE) interactions have not been reliably established regarding etiology of psychotic disorders, while genes-environment (G-E) associations have been displayed. We studied the role of GxE interaction between psychosocial stressors (childhood trauma, stressful life-events, self-reported discrimination experiences and low social capital) and the polygenic risk scores for schizophrenia (PRS-SZ) on subclinical psychosis in a population-based sample.

Data were drawn from the EU-GEI study, in which subjects without psychotic disorders were included in six countries. The sample was restricted to European descendant subjects (N = 706). Subclinical dimensions of psychosis (positive, negative, and depressive) were measured by the Community Assessment of Psychic Experiences (CAPE) scale. For each dimension, the interactions between genes and environment were assessed comparing explained variances of “Genetic” models (solely fitted with PRS-SZ), “Environmental” models (solely fitted with each environmental stressor), “Independent” models (with PRS-SZ and each environmental factor), and “Interaction” models (with an interaction term between the PRS-SZ and each environmental factor).

There were no direct G-E associations. PRS-SZ was associated with positive dimensions (β = 0.092, R² = 7.50%), and most psychosocial stressors were associated with all three subclinical psychotic dimensions (except for low social capital and positive dimension). Concerning the positive dimension, Independent models fitted better than Environmental and Genetic models. No significant GxE interaction was observed for any dimension.

This study in healthy individuals suggests that i) the etiological continuum hypothesis could concern particularly the positive dimension of subclinical psychosis, ii) genetic and environmental factors have independent effects on the level of this positive dimension, iii) and that interactions between genetic and individual environmental factors could not be identified in this sample.

Introduction

Both environmental and genetic factors are associated with an increased risk of developing psychotic disorders [1]. The relationships between these factors have long been discussed, and the hypothesis of gene x environment (GxE) interactions was suggested several decades ago [2–4]. Such interaction can be defined as a genetic modulation of the sensitivity to environmental factors and/or environmental control of the gene expression [5]. Numerous studies supported this hypothesis [6–8], and particularly one from Caspi et al. [9], in which a significant interaction between cannabis use in adolescence and the genetic variant Val¹⁵⁸Met in the Catechol-O-Methyltransferase (COMT) gene was found. Of note, although discrepant results have been reported in replication studies [10, 11], a meta-analysis showed a small protective effect of the Val/Met heterozygous genotype [12]. Study of GxE interactions is difficult due to the need for large cohorts with well characterized genetic and environmental data.

To deal with these difficulties, the study of subclinical psychosis in the general population is convenient [13, 14], especially in accordance to the etiological psychotic continuum hypothesis. According to this hypothesis, subclinical psychosis have a similar origin/etiology as psychotic disorders [15–18]. Thus, studying genetic or environmental risk factors associated with subclinical psychosis may provide insights into the etiology of psychosis and partly reduce the potential interference of reverse causation, i.e., factors are associated with or caused by the clinical disorders themselves (e.g., hospitalizations, stigma, substance use disorders or social drift after onset [19–21]). Furthermore, in line with the continuum theory, subclinical psychosis can be characterized by continuous variables, improving statistical power, which is a key issue in GxE interaction studies.

Psychotic disorders are characterized by a polygenic architecture, with thousands of common genetic variants with small effect sizes, and a few rare variants with large effect sizes [22]. The genome-wide effects of disease-associated common genetic variants can be summarized in a polygenic risk score (PRS) [23], which offers new opportunities to characterize the complex genetic etiology of psychotic disorders. In subjects included through the EUropean network of national schizophrenia networks studying Gene-Environment Interactions (EU-GEI), the PRS for schizophrenia (PRS-SZ) explained between 7 and 9% of the variance of the case-control status [24, 25], consistent with other studies [26]. Of note, among patients with psychotic disorders, the PRS-SZ is also associated with antipsychotic treatment response, the level of quality of life, or, in the general population, to the intelligence quotient (IQ), and the risk of attention-deficit/hyperactivity disorder (ADHD) [27–30].

Studies of associations between subclinical psychosis and the PRS-SZ have produced contradictory results [27, 28, 31, 32], and further studies are needed. Moreover, to date, four studies have investigated the role of GxE interaction on subclinical psychosis using PRS-SZ. Two studies assessed the interaction between PRS-SZ and childhood trauma, but only one reported a significant interaction [33], whereas the other showed an independent (additive) effects of the PRS-SZ and the trauma without significant interaction [34]. A recent study assessing the associations between momentary stress and subclinical psychotic symptoms showed that higher levels of PRS-SZ was associated with a
higher intensity of symptoms after a momentary stress among controls [35]. In the fourth study, the authors assessed the interaction between PRS-SZ and smoking status, but did not show significant association [36].

In addition to increasing the risk for psychosis by GxE interactions, the PRS-SZ has also been associated with a greater risk of exposure to environmental risk factors for psychosis [37]. For instance, several studies have reported associations between the PRS-SZ and cannabis use [38, 39] or between the PRS-SZ and urbanicity [40–42] or the level of neighborhood deprivation and social fragmentation at birth [43], challenging the traditional gene vs. environment dichotomy. However, these observations could not explain the strength of the associations between cannabis use or urbanicity and the risk of psychotic disorders [44, 45]. To the best of our knowledge, the direct genetic-environment (G-E) associations between PRS-SZ and psychosocial stressors have not been studied to date.

In a former study on population-based controls from the EU-GEI work package 2 (WP2) [46], we showed that psychosocial stressors, i.e., childhood trauma, stressful life-events, self-reported discrimination experiences and low social capital, had independent effects on subclinical psychosis dimensions, without significant environment x environment (ExE) interactions. In the current study, we aimed to study the relationships between these psychosocial stressors, the PRS-SZ, and three dimensions of subclinical psychosis (positive, negative, depressive), looking for GxE interaction. Furthermore, we aimed to study the direct association between psychosocial stressors and the PRS-SZ, looking for G-E associations.

**Methods**

**EU-GEI WP2 study**

Clinical, environmental and genetic data have been collected through the EU-GEI WP2 (named “Functional Enviromics”), a multicentre case-sibling-control study of genetic and environmental determinants of the occurrence and severity of psychotic disorders. Population-based unaffected controls were recruited across 6 countries: Brazil, France, Italy, the Netherlands, Spain, and the United Kingdom. These controls were recruited using a mixture of random and quota sampling to ensure that they were broadly representative of the at-risk populations on predefined variables (age, sex, and migration) [47].

Ethical approval was obtained from local research ethics committees in each country. The EU-GEI Project was funded by the European Community’s Seventh Framework Program under grant agreement no. HEALTH-F2-2010-241909.

**Subclinical psychosis and psychosocial stressors assessment**

The Community Assessment of Psychic Experiences (CAPE) is a 42-item self-report questionnaire that has been developed to assess lifetime subclinical psychotic dimensions in the general population [48]. For each item, 4 answers were possible according to the frequency of their occurrences (from never to nearly always). To construct the dimension scores (positive, negative and depressive [49]), we dichotomized answers of each CAPE item (never vs. sometimes or more) and summed the positive answers. The cross-national invariance of the CAPE score in the EU-GEI WP2 samples was previously demonstrated [50].

Childhood trauma was assessed with a short version of the Childhood Trauma Questionnaire (CTQ), with 25 items assessing five different domains (emotional and physical neglect, emotional, physical and sexual abuse) [51]. Only the total score was used. Lifetime self-reported discrimination experiences were assessed with a modified version of the 12-item Williams’ major experiences of discrimination scale (unfairly fired or not hired because of your ethnicity/sex/weight/etc., unfairly stopped/questioned/physically threatened or abused by the police, etc.) [52, 53]. Perceived social capital in each participant’s immediate neighborhood was assessed using the Social Environment Assessment Tool (SEAT), a 23-item questionnaire, that was designed to capture four dimensions of social capital: civic disorder (CD), impact of civic disorder (ICD), informal social control (ISC), and social cohesion and trust (SCT) [54–57]. Subjects answer according to a five-point Likert-scale (1: unusual, to 5: very common), and a sum of the weighted scores of the 4 subscales were calculated to obtain the total social capital score (SEAT score = zCD + 0.51*zICD + 1.6*zISC + zSCT). Finally, stressful life events were assessed using the List of Threatening Experiences (LTE) which comprises 20 binary items of events usually associated with major stress over the course of the previous 6 months (e.g., serious injury, death of a parent, separation from a partner, financial difficulties) [58, 59].
Calculation of a Polygenic Risk Score for Schizophrenia (PRS-SZ)

Blood samples of the control sample were genotyped by the Medical Research Council Centre for Neuropsychiatric Genetics and Genomics (Cardiff, United-Kingdom) using a custom "Illumina HumanCoreExome-24 BeadChip" genotyping array, covering 570,038 genetic variants. As described elsewhere [24], the PRS-SZ were generated using PRSice from the summary results of the Psychiatric Genomics Consortium (PGC), wave 2 [60]. Clumping was performed to obtain SNPs in approximate linkage disequilibrium with an $r^2 < 0.25$ within a 250kb window. PRS-SZ were calculated, at p-value thresholds of 0.05. The sample was restricted to 706 European descendant unaffected subjects (due to over-representation of European descendant subjects in the PGC2 training sample used to calculate the PRS-SZ).

Statistical analyses

The G-E association has been assessed by Spearman correlation tests between the 4 psychosocial stressors and the PRS-SZ. Then, linear regression models were used to assess the relationships between the CAPE dimensions scores (positive, negative, depressive), environmental and genetic variables, and to look for GxE interactions. Of note, we consider multiplicative interactions [61, 62].

The different models were adjusted for age, sex, and the 10 first principal components (PCs) of the genetic analyses of the ethnic variance. For each CAPE dimension, thirteen models were tested:

- A "Genetic model", with the sole PRS-SZ;
- Four "Environmental models" for each of the 4 psychosocial stressors variables: childhood trauma, stressful life-events, self-reported discrimination experiences and low social capital;
- Four "Independent models": one for each of the 4 psychosocial stressors variables and the PRS-SZ, without interaction term;
- Four "Interaction models": each of the 4 psychosocial stressors variables and the PRS-SZ, with a GxE interaction term.

To compare the fit of the different models (and particularly the Independent and the Interaction models), we compared the explained variances ($R^2$), and use likelihood ration test (LRT) to assess whether the addition of a factor ($E + G$ vs. $G$, $E + G$ vs. 3, $E + G + E*G$ vs. $E + G$) improved the fit of the model.

Psychosocial variables and PRS-SZ were standardized to Z-scores (i.e., to a mean equal to 0, and a standard-deviation equal to 1). The SEAT (social capital) score was inverted, so that higher scores were associated with lower social capital. Missing data of the CAPE (between 3 and 5 % according to the different dimensions) and the psychosocial stressors variables (between 0.5 and 20 %) were imputed with multivariate imputation by chained equations (MICE) in 20 resamples. R software version 3.6.0 was used for the statistical analyses.

Results

Description of the data

The 706 unaffected European individuals included in our study showed a sex-ratio close to 1 (53% women) and a mean age of 38.2 (SD = 13.4). The scores of subclinical psychosis dimensions and psychosocial stressors scales, and the values of PRS-SZ scores are available in the Table 1 (for non-imputed data, see Supplementary Table 1).

Correlation between genetic vulnerability and environment factors
Spearman correlation tests did not suggest any evidence of associations between psychosocial stressors levels and the PRS-SZ (Table 2).

**Influence of genetic vulnerability and environment factors on subclinical psychosis dimensions**

For the three subclinical psychosis dimensions that we studied, we first assessed the variance that might be explained by the PRS-SZ (Genetic models, Figure 1 and Table 3). Only the positive dimension was associated with the PRS-SZ ($\beta = 0.092$, p-value = 0.02, with a $R^2 = 7.50\%$).

We then assessed the variance explained by each of the 4 psychosocial stressors, i.e., discrimination, childhood trauma, stressful events and a low social capital (Environmental models). Each psychosocial stressor was associated with the three subclinical psychosis dimensions, except the low level of social capital which was not associated with the positive dimension (Figure 1 and Table 3). Of note, when associated with subclinical dimensions, the variance explained by Environmental models was always higher than the one explained by Genetic models.

**Combination of genetic and environmental factors**

In the Independent models, the explained variances were better than in the Genetic models, which was confirmed by the LRT, that confirmed that the Independent models fitted better than the Genetic models (p-values < 0.001 for almost all models, Figure 1 and Table 3).

However, concerning the negative and depressive dimensions, in comparison to Environmental models, the Independent models did not fit better, which was confirmed by the LRT. In other words, adding the PRS-SZ to the Environmental factors did not improve the explained variances of these models. Concerning the positive dimension, the Independent models fitted better than both Genetic and Independent models (LRT: p-values between 0.013 and 0.021, Table 3).

In the Interaction models, no significant GxE interaction was observed: adding a GxE interaction term in the Independent models were associated with modest increases of the explained variance (LRT: p-values > 0.05 for all the Interaction models), and no interaction term was significantly associated with one of the 3 subclinical psychosis dimension scores (Table 3).

**Discussion**

In this population-based – without psychotic disorders – transnational study on the relationships between subclinical psychosis and genetic and environmental (psychosocial stressors) risk factors, the PRS-SZ was associated with the positive dimension but not with the negative and the depressive dimensions. By contrast, the psychosocial stressors were positively associated with the 3 dimensions, except for the low level of social capital, which was not associated with positive dimension. Moreover, considering the positive dimension, PRS-SZ and psychosocial stressors were independently associated, without GxE interaction, consistent with independent effects of genetic and environmental risk factors.

**A genetic psychotic continuum?**

The association between the PRS-SZ and the positive dimension is consistent with the hypothesis of an etiological psychotic continuum, with subclinical psychosis and psychotic disorders sharing etiological – genetic and environmental – factors [15]. This hypothesis could not be verified concerning the other dimensions. A precedent EU-GEI study analyzing in controls the relationships between subclinical psychosis and another factor associated with the risk of psychotic disorders, i.e., advanced paternal age, found consistent results: significant association with the positive dimension, but not to negative and depressive dimensions [18]. The etiological psychotic continuum could concern particularly the positive dimension. Indeed, in comparison to the negative and depressive dimensions, the positive symptoms are the most specific of psychotic disorders [63]. Furthermore, in a study analyzing the associations between the PRS-SZ and clinical dimensions among antipsychotic-naïve patients with first episode of psychotic disorders (FEP), Santoro et al. [64] found an association with the positive dimension of the positive and negative syndrome scale (PANSS). Moreover, Markota et al. [65] found higher level PRS-SZ in manic-psychosis
among patient with bipolar disorder. In future studies, it would be interesting to analyze the relationships between the negative and the depressive dimensions with other PRS (e.g., for depression, or bipolar disorder).

Several studies have found association between the PRS-SZ and subclinical psychosis, but not all. Indeed, some of these studies did not find any significant associations [32, 66]. Methodological differences could be involved, including study population (e.g., some of them were conducted in pediatric population [8, 31]), or the tools used to measure subclinical psychosis (e.g., schizotypy scales do not take account of hallucinations [67]). In a recent study from EU-GEI WP6 ("Vulnerability and Severity") sample, van Os et al. [68] did not find any direct associations between PRS-SZ and the 3 dimensions of the CAPE in the healthy controls, although among siblings, a significant association with the negative dimension was found. Among the different studies on association between the PRS-SZ and subclinical psychosis, UK Biobank represents the most closely related to EU-GEI (sample from the general population from United-Kingdom), and two of the three studies conducted in UK Biobank found significant associations [28, 36], contrary to the third, that did not find any significant difference [69].

**Association between environmental and genetic factors**

Several studies found G-E associations. In a transnational study (Australia, Netherlands and United-Kingdom), the PRS-SZ was associated with the population density of the residence [40], i.e., with urbanicity [44]. These findings were replicated recently in the United-Kingdom [41]. Of note, this last study considered also other PRS (for depression, bipolar disorder, etc.) and found analogous results. Other studies found similar associations with the cannabis use [38, 39]. These studies suggest that the association between these environmental factors and the risk of psychotic disorders could partially be explained by the same genetic factors [37]. This hypothesis particularly concerns childhood trauma, that has often been supposed to be associated with vulnerabilities to psychiatric disorders [70–72]. Sharing the same genetic risk factors could explain the association between childhood trauma and psychiatric disorders. However, in our study, we did not find any G-E association neither with childhood trauma nor with the other psychosocial stressors.

**Gene x environment (psychosocial stressors) interactions**

Our study did not show any statistically significant interaction between the psychosocial stressors and the PRS-SZ, but independent effects concerning the positive dimension. Trotta et al. [34] found similar results: the PRS-SZ and childhood trauma history predicted both psychosis status, without interaction between these factors. To our knowledge, two other studies has looked for such interactions, that found a significant GxE interaction between the PRS-SZ and childhood trauma [33, 35]. Another study using the PRS-SZ and conducted in adults looked for interaction with other environmental factor, i.e., smoking status, without finding any GxE interaction [36].

One hypothesis to explain the negative results of this GxE interaction study is that the PRS-SZ is not the appropriate tool for the study of GxE interaction in psychosis [73]. Indeed, this statistical tool summarizes essentially monogenic factors with small effects sizes; GxE interaction could only involve monogenic factors [9, 74, 75]. However, other studies used PRS and found GxE interaction, for instance between childhood trauma and the PRS for depression in the risk of major depressive disorder [76], or between this PRS and stressful life events in the level of depressive symptoms [77], as well as studies on non-psychiatric diseases, as in breast cancer [78, 79]. The problem could concern specifically PRS-SZ, with (i) an insufficient sample of subjects included in the genome-wide association studies (GWAS) used to calculate it, which is a major issue concerning PRSs [80], and (ii) the fact that the PRS-SZ performed better among European descendant (which has prevented the inclusion of subjects from ethnic minorities) [26]. Moreover, the PRS does not take copy number variant (CNVs) or epigenetic factors in account, and they are associated with the risk of schizophrenia (and with childhood trauma concerning epigenetic factors) [81–83]. Furthermore, another hypothesis states that the genes that increase the sensibility to environmental stressors could be different from the genes that increase the risk of schizophrenia (displayed in the GWAS).

**Limitations**

Some limitations should be acknowledged. First, due to the cross-sectional nature of EU-GEI study, the assessment of both subclinical psychosis and psychosocial stressors was retrospective, thus susceptible to be biased (e.g., recall bias) and influenced by clinical variables as depressive or positive symptoms [84]. These potential biases, especially concerning psychosocial stressors assessment (particularly the low level of discrimination experience), have been discussed previously [46]. Moreover, regarding the sample size, that could be considered as insufficient to enhance an GxE interaction, Pries et al. [8] found an interaction between childhood adversity and PRS-SZ concerning subclinical psychosis (with an ecological momentary assessment) with a lower sample (N = 593). The absence of subjects from ethnic minorities, is a major limitation. Indeed, these minorities are exposed to higher levels of psychosocial stress [85]. Moreover, as the sampling was not fully at random, we cannot assume that our sample was representative of the general population.

**Conclusion**
This general population-based study revealed an association between PRS-SZ and the subclinical positive dimension of psychosis, as well as independent effects of the PRS-SZ and of the psychosocial stressors (childhood trauma, stressful life-events, self-reported discrimination experiences) on the positive dimension, contrary to the negative and depressive dimensions. Moreover, concerning the 3 dimensions, this study did not evidence any GxE interaction, nor any G-E association.

Declarations

CONFLICTS OF INTEREST

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Tables
Table 1: Description of the data: socio-demographic, subclinical psychosis, psychosocial stressors and polygenic risk scores variables.

| Variable                                    | Median (IQR), mean (sd) or N (%) | Missing data (%) |
|----------------------------------------------|----------------------------------|------------------|
| Age                                          | 36.00 (22.00), 38.18 (13.35)     | 1 (0.14 %)       |
| Sex                                          |                                  | 0 (0.00 %)       |
| Women                                        | 376 (53.3 %)                     |                  |
| Men                                          | 330 (46.7 %)                     |                  |
| CAPE dimensions scales                       |                                  |                  |
| Positive                                     | 4.00 (4.00), 4.51 (2.81)         | 42 (5.94 %)      |
| Negative                                     | 6.00 (5.00), 6.24 (3.49)         | 34 (4.81 %)      |
| Depressive                                   | 4.00 (3.00), 4.39 (1.82)         | 24 (3.40 %)      |
| Psychosocial stressors measures              |                                  |                  |
| Childhood trauma                             | 31.00 (9.75), 33.34 (9.29)       | 4 (0.57 %)       |
| Self-reported discrimination experiences      | 0.00 (1.00), 0.51 (0.92)         | 24 (3.40 %)      |
| Stressful life events                        | 1.00 (2.00), 1.37 (1.29)         | 146 (20.68 %)    |
| Social capital                               | 0.37 (3.27), 0.37 (2.37)         | 90 (12.75 %)     |
| PRS-SZ                                       | -0.00096 (0.00018), -0.00096 (0.00014) | 0 (0.00 %) |

Abbreviations: CAPE = Community Assessment of Psychic Experiences, IQR = interquartile range, PRS-SZ = polygenic risk score for schizophrenia, sd = standard-deviation.

Table 2: Spearman tests between Z-scores of genetic and environmental factors among subjects with complete data (N = 456)

|                               | Childhood trauma | Self-reported discrimination experiences | Stressful life events | Social capital |
|-------------------------------|------------------|------------------------------------------|-----------------------|---------------|
| Polygenic risk score for schizophrenia | $\rho=0.063$ (p-value=0.18) | $\rho=-0.047$ (p-value=0.32) | $\rho=0.083$ (p-value=0.08) | $\rho=0.032$ (p-value=0.48) |
| Table 3: Model comparison of the explained variances of the subclinical psychosis dimensions |
|-----------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                      | Explaned variance | PRS-SZ | LRT: comparison | Environmental factor | LRT: comparison | Interaction term between the PRS-SZ and the environmental factor | LRT: comparison |
|                                      | by the models   |        | of "G" and "E + G" models | (p-values) | of "E" and "E + G" models | (p-values) | "E + G" and "E + G" models | (p-values) |
|                                      | (R²)            |        | (p-values) | (p-values) | (p-values) | (p-values) | (p-values) | (p-values) |
| Positive dimension                  |                 |        |            |            |            |            |            | |
| G                                     | 7.50 %          | 0.092  | 0.037 | 0.019 | - | - | - | - |
| Self-reported discrimination experiences | 8.21 %          | -    | - | - | - | - | - | - |
| E                                     | 0.090  | 0.037 | 0.020 | 0.006 | 0.123 | 0.037 | 0.001 | 0.015 |
| E + G                                 | -    | - | - | - | - | - | - | - |
| E + G + E*G                           | 0.090  | 0.037 | 0.020 | - | 0.123 | 0.037 | 0.001 | - |
| Childhood trauma                      | 10.55 %         | - | - | - | - | 0.198 | 0.037 | < 0.001 | - |
| E                                     | 0.074  | 0.037 | 0.055 | < 0.001 | 0.191 | 0.037 | < 0.001 | 0.043 |
| E + G                                 | 0.074  | 0.037 | 0.054 | - | 0.188 | 0.038 | < 0.001 | - |
| E + G + E*G                           | -    | - | - | - | - | - | - | - |
| Stressful life events                 | 9.49 %          | - | - | - | - | 0.167 | 0.037 | < 0.001 | - |
| E                                     | 0.082  | 0.037 | 0.035 | < 0.001 | 0.161 | 0.037 | 0.001 | 0.021 |
| E + G                                 | 0.081  | 0.037 | 0.036 | - | 0.162 | 0.037 | 0.001 | - |
| E + G + E*G                           | -    | - | - | - | - | - | - | - |
| Low level of social capital           | 7.10 %          | - | - | - | - | 0.063 | 0.037 | 0.151 | - |
| E                                     | 0.091  | 0.037 | 0.020 | 0.028 | 0.063 | 0.037 | 0.155 | 0.013 |
| E + G                                 | 0.089  | 0.037 | 0.023 | - | 0.060 | 0.037 | 0.174 | - |
| E + G + E*G                           | -    | - | - | - | - | - | - | - |
| Negative dimension                   |                 |        |            |            |            |            |            | |
| G                                     | 4.60 %          | 0.024  | 0.038 | 0.530 | - | - | - | - |
| Self-reported discrimination experiences | 6.26 %          | - | - | - | - | 0.131 | 0.037 | 0.001 | - |
| E                                     | 0.023  | 0.038 | 0.555 | < 0.001 | 0.131 | 0.038 | 0.001 | 0.749 |
| E + G                                 | 0.023  | 0.038 | 0.550 | - | 0.131 | 0.038 | 0.001 | - |
| E + G + E*G                           | -    | - | - | - | - | - | - | - |
| Childhood trauma                      | 8.84 %          | - | - | - | - | 0.207 | 0.037 | < 0.001 | - |
| E                                     | 0.005  | 0.037 | 0.833 | < 0.001 | 0.207 | 0.037 | < 0.001 | 0.920 |
| E + G                                 | 0.002  | 0.037 | 0.861 | - | 0.224 | 0.038 | < 0.001 | - |
| E + G + E*G                           | -    | - | - | - | - | - | - | - |
| Stressful life events                 | 6.11 %          | - | - | - | - | 0.124 | 0.038 | 0.003 | - |
| E                                     | 0.016  | 0.038 | 0.669 | < 0.001 | 0.123 | 0.038 | 0.003 | 0.834 |
| E + G                                 | 0.015  | 0.038 | 0.703 | - | 0.125 | 0.038 | 0.003 | - |
| E + G + E*G                           | -    | - | - | - | - | - | - | - |
| Low level of social capital           | 5.37 %          | - | - | - | - | 0.090 | 0.038 | 0.026 | - |
| E                                     | 0.023  | 0.038 | 0.542 | 0.003 | 0.090 | 0.038 | 0.027 | 0.674 |
| E + G                                 | 0.024  | 0.038 | 0.537 | - | 0.090 | 0.038 | 0.027 | - |
| E + G + E*G                           | -    | - | - | - | - | - | - | - |
| Depressive                            | 6.33 %          | 0.040  | 0.037 | 0.293 | - | - | - | - |
|                          | Self-reported discrimination experiences | Childhood trauma | Stressful life events | Low level of social capital |
|--------------------------|------------------------------------------|------------------|----------------------|-----------------------------|
| **E**                    | 7.78%                                    | -                | -                    | 7.72%                       |
| **E + G**                | 7.93%                                    | 0.038            | 0.037                | 0.308                       |
| **E + G + E*G**          | 7.97%                                    | 0.039            | 0.037                | 0.304                       |
|                          |                                          |                  |                      |                             |
| **E**                    | 9.46%                                    | -                | -                    | 9.46%                       |
| **E + G**                | 9.52%                                    | 0.023            | 0.037                | 0.537                       |
| **E + G + E*G**          | 9.78%                                    | 0.025            | 0.037                | 0.507                       |
|                          |                                          |                  |                      |                             |
| **E**                    | 9.39%                                    | -                | -                    | 7.27%                       |
| **E + G**                | 9.48%                                    | 0.029            | 0.037                | 0.447                       |
| **E + G + E*G**          | 9.76%                                    | 0.026            | 0.037                | 0.483                       |
|                          |                                          |                  |                      |                             |
| **E**                    | 7.43%                                    | -                | -                    | 9.43%                       |
| **E + G**                | 7.60%                                    | 0.039            | 0.037                | 0.303                       |
| **E + G + E*G**          | 7.60%                                    | 0.041            | 0.037                | 0.281                       |

The different models were adjusted on age, sex, and the first ten principal components of the ethnicity-based genetic variance. The significant associations are shown in bold. Abbreviations: E: Environmental model, E + G: Independent model, E + G + E*G: Interaction model, G: Genetic model, LRT: Likelihood ratio test, PRS-SZ: polygenic risk score for schizophrenia.

**Figures**

**Figure 1: Explained variances of the different models**
Figure 1

Explained variances of the different models

Description: bar plot of the explained variances ($R^2$) of the different models

Legends: Abbreviations: PRS-SZ: polygenic risk score for schizophrenia, $R^2$: explained variance

Supplementary Files

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- Supptab1.docx