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# **Cognitive presentation at psychosis onset through premorbid deterioration and exposure to environmental risk factors - Supplementary Material**

## Supplementary methods

## Recruitment.

Centrally trained researchers screened all potential FEP patients, aged 18-64 years between 2010 and 2015, presenting to mental health services with a clinical diagnosis for an untreated non-affective or affective FEP, based on ICD-10 (ICD-10 F20-33). Patients excluded were previously treated for psychosis or met criteria for organic psychosis (ICD-10: F06) or transient psychotic symptoms resulting from acute intoxication (ICD-10: F1X.5). The 17 catchment areas were distributed across six countries: United Kingdom, Italy, Spain, Holland, France, and Brazil (CORDIS, 2019; EU-GEI, 2009; Gayer-Anderson et al., 2020; Jongsma et al., 2018).

Population controls were aged 18-64 years and residents in the same catchment areas as the patients and recruited using a combination of random and quota sampling to ensure representativeness of each local population in terms of age, sex, and self-ascribed ethnicity. They did not report any lifetime treatment for psychosis. We included 802 of the 1130 consented and assessed patients and 1263 of 1497 consented and assessed controls. 134 subjects (5.1% of the original sample) were excluded for having incomplete data on one of the measures of interest. Maison-Blanche (France) (N=36 subjects) was not included in the case/control analysis because it did not recruit controls. Finally, due to a deviation from the protocol in Veneto (Italy), there were no available data on the WAIS and PAS instruments (n=174 subjects) because patients were collected as part of an earlier study [the Psychosis Incident Cohort Outcome Study (PICOS); 2005–2007](Gayer-Anderson et al., 2020). Similarly, Part of the subjects recruited in London (N=108) and Palermo (N=30) were derived from a previous study, the GAP (Genetic and psychosis) study (Ferraro et al., 2019)and 80 subjects from Brazil were included from the Schizophrenia and Other Psychosis Translational Research: Environment and Molecular Biology (STREAM) study, with sufficiently similar methods to be pooled with that collected for this study (Del-Ben et al., 2019), but without any data on PAS or WAIS.

## The Maudsley Environmental Risk Score (ERS).

The ERS comprises the following risk factors: 1) Ethnic minority membership, scored -0.5 if non-migrant majority ethnic group; when migrant, minority ethnic group or both conditions, ethnicity was scored 5.5 if black ethnic group, 2 if white ethnic group, and 2.5 if other ethnic group. 2) Paternal age, scored as 0 if less than 40, 0.5 between 40 and 50, and 2 if more than 50. 3) Any lifetime cannabis use scored as -1 when no exposure occurred, 0 for little/moderate exposure, and 3 for at least weekly cannabis use (Di Forti et al., 2019). 4) Childhood adversities scored -1.5 for no exposure and 2.5 for any exposure. 5) Urbanicity scored -1.5 if low, 0 if medium, and 1 if high. 6) Obstetric complications, scored as 2 if birth weight is less than 2.5 kg and as 0 if more. The ERS ranges from -4.5 (lowest risk) to 16 (maximum risk). Without information on some risk factors, they are scored as “zero” (Vassos et al., 2020). Ethnic minority status was derived from a combination of self-referred ethnicity and status of first or second-generation migrant. We were also able to include paternal age at birth. We considered high life-time exposure to cannabis, at least weekly cannabis use, and little exposure, ranging from less than weekly to use at least once (Di Forti et al., 2019). Childhood adversities included parental separation, neglect, physical, psychological and sexual abuse, and bullying before 17 years (Trotta et al., 2013). We calculated urbanicity by deriving population density, estimated from national statistics institutions (number of inhabitants per square Kilometers). Then, we split the population densities of the 17 cities where subjects were steady residents for at least six months and at the time of the FEP diagnosis into three tertiles (Vassos et al., 2020). As this variable was measured at a site-level (depending on the recruitment site) compared with other risk factors, which were measured at an individual-level, we did not include the urbanicity in our modified ERS. Instead, we used it as a site-level urbanisation covariate in all analyses to adjust the potential differential effect of urbanicity between recruitment sites. Lastly, we could not include obstetric complicationsin our calculation because this information was not collected.

## The Exposome Score for Schizophrenia

The Exposome Score for Schizophrenia (Exposome), which was constructed on the WP6 EUGEI study (recruiting chronic patients) and a replication sample. (Pries et al., 2019) Is constituted by summing log-odds weighted environmental exposures.

It includes cannabis use, hearing impairment, winter-spring birth, and childhood adversity domains, including physical, emotional and sexual abuse and physical and emotional neglect and bullying. Cannabis use and childhood adversities were calculated consistently with the Environmental score but scored as absent = 0 or present = 1 for cannabis use and as absent = 0 or present = 1 for each exposure to childhood adversities (bullying, neglect, physical abuse, sexual abuse, psychological abuse); hearing impairment was self-reported and scored as absent = 0 or present =1. Winter birth was calculated between the 21 of December and the 20 of March for the European countries and between the 21 of June and the 22 of September in Brazil and scored as absent = 0 or present = 1. The final score was between 0 (lowest risk) and 9 (maximum risk). Cases presenting missing values were excluded listwise.

## Instruments.

The modified version of the Medical Research Council (MRC) socio-demographic scale collected demographic information, such as date of birth, age, self-ascribed gender (referred to as sex in the manuscript), ethnicity, paternal age, and self-referred hearing impairment (Mallett et al., 2002).

Sex and race in the EUGEI sample were ascertained genetically for studies including the polygenic risk scores, and 12 participants were excluded for sex/gender incompatibility in these analyses. Each subject received a research-based diagnosis based on the OPCRIT algorithm5. The Cannabis Experience Questionnaire modified version (CEQEugei-mv) collected cannabis and other substance use information (Di Forti et al., 2019) categorized as “no use,” “occasional,” and “daily” use. Based on available information on potency of cannabis used, a category included “no use,” “daily use of high potency cannabis” [tetrahydrocannabinol (THC) 10%], and “any other pattern of use”.

Clusters derivation.

In SPSS, version 24, we conducted a two-step cluster analysis. To determine the number of clusters to retain, we used the stepwise decrease in log-likelihood as the distance measure for identifying clusters, assuming that the variables included are independent and normally distributed. The first step constructed a Cluster Features (CF) Tree containing a summary of the data file. The second step uses an agglomerative clustering algorithm with es a range of solutions compared using Schwarz’s Bayesian Criterion (BIC) (best ratio change of cluster distance at least > 1.15) (Liu et al., 2013). Unsupervised clustering was run 1000 times by changing the random order of the subjects to determine the optimal number of clusters (maximum solution expected=6). Secondly, we ran a 50 subjects’ assignment solution by pre-determining the chosen number of clusters with random reordering. Then, subjects were allocated to the category they were assigned most of the time and Fleiss' kappa index determined the degree of agreement in the assignment of a subject to a cluster among the fifty repetitions. To measure the descriptive significance of the variable "self-ascribed ethnicity" (white/black/other) when comparing clusters, we added it to the "evaluation" field of the two-step cluster analysis. However, this variable resulted in a negligible descriptive power (predictor importance=0.04). Finally, we performed repeated-measures ANOVAs to determine whether there were any statistically significant differences in PSF and PAF changes between the two age ranges within the formed clusters and controls. Controls were used as an unique group. Clusters of patients and the control group served as the between-group factor, and it was adjusted for age, country, and self-ascribed sex and ethnicity. This analysis allowed an internal validation of clusters’ differences, meaning, and profile. Based on the demographic data of each site, a weighted score was generated to reduce the probability for biased estimation of the prevalence of exposures among controls. This score was used in each case/control analysis.

## Sensitivity analyses.

##### *Case-control matching*

We performed a case-control matching among patients with complete measures on ERS and SCZ\_PRS based on gender and age, resulting in 467 controls and 467 patients (133 high-cognitive-functioning, 137 intermediate, 75 deteriorating and 122 low-cognitive-functioning). Consistently, the deteriorating cluster showed higher exposure to ERS than controls (mean\_difference=3.5, 95% CI 2.57 4.53), high-cognitive-functioning cluster (mean\_difference=1.4, 95% CI 0.36 2.59) and intermediate cluster (mean\_difference=1.5, 95% CI 0.45 2.66).

##### *Other drugs*

The dysregulation of dopamine in the brain caused by cannabis (Murray et al., 2017) is similar to the effects of other substances like stimulants (Boileau et al., 2007) and tobacco (Leroy et al., 2012). This model took into account the use of tobacco in the past 12 months (i.e., whether the participants were current tobacco users or not) and any history of using at least one illegal drug other than cannabis (i.e., whether the participants had a history of using other illegal drugs or not) as predictive factors to ensure the accuracy of the overall results in comparisons between clusters and controls in exposure to cannabis use. Consistently, the low-cognitive-functioning cluster had higher exposure to cannabis than controls (mean\_difference=.34, 95% CI .06 .62), and the deteriorating had higher exposure than both controls (mean\_difference=.53, 95% CI .21 .86) and intermediate cluster (mean\_difference=.47, 95% CI .09 .85) (Supplementary-Table 8).

*Socio-economic status (SES)*

One study reported that individuals with low income were more likely to engage in higher frequency cannabis use (Jeffers et al., 2021). Thus, we run the model comparing clusters and controls in different exposures to cannabis use, firstly adjusted for main parents’ SES and, secondly, by main patients’ SES. The deteriorating group was still more exposed to cannabis than the intermediate cluster in both analyses (Supplementary-Table 9).

## Supplementary Results

## Clusters of patients.

Agreement in the assignment of subjects to the clusters was good in the deteriorating cluster (Fleiss’ kappa=0.608, 95% CI 0.606, 0.610), moderate in the high- (Fleiss’ kappa=0.563, 95% CI 0.561, 0.565) and mild in the low-cognitive-functioning cluster (Fleiss’ kappa=0.40, 95% CI 0.39, 0.402), and poor in the intermediate cluster (Fleiss’ kappa=0.156, 95% CI 0.154, 0.158). The clusters showed significantly different IQ from each-other, i.e. the low-cognitive-functioning cluster had significantly lower IQ (mean=73.9, 95% CI 72.2 75.7) as compared with the deteriorating (mean=80.6, 95% CI 78.5 82.7), intermediate (mean=80.8, 95% CI 79.1 82.5) and high-cognitive-functioning cluster (mean=106.1 95% CI 104.3 107.9). The intermediate cluster, having identical IQ as the deteriorating cluster, showed an improvement in academic (PAFchange Mean difference=0.130, 95% CI 0.039 0.222) and social adjustment (PSFchange Mean difference=0.244, 95% CI 0.152 0.336) between the two ages, as opposite to the deteriorating cluster, whose both scores were decreasing (PAFchange Mean difference=-0.968, 95% CI -1.081 -0.854; PSFchange Mean difference=-0.741, 95% CI -0.854 -0.627). We considered this information of clinical relevance.

Research findings show distinct cognitive profiles in nonaffective psychosis, with studies identifying clusters of high, intermediate, and low-cognition, and others suggesting four clusters when including affective psychoses (Green et al., 2020). These cognitive clusters are associated with different symptoms and functional outcomes, making them important for prognosis and treatment (Reser et al., 2015; Tan et al., 2022).

Cluster analysis also revealed three developmental trajectories of IQ: (a) stable impairment, (b) normal premorbid function with a high-current IQ, and (c) a decline from average premorbid levels (Dickinson et al., 2019). Additionally, using the Premorbid Adjustment Scale (PAS), six clusters of social and academic adjustments have been identified, highlighting different developmental trajectories from childhood to adolescence (Allen et al., 2005). Consistently with the poor agreement in assignment to the intermediate cluster, we could expect intermediate phenotypes in clinical practice with stable premorbid adjustment and intermediate IQ and therefore not classifiable as either high or low group in terms of IQ, nor in the deteriorating cluster. In line with this finding, symptoms profile of this intermediate cluster (Supplementary-figure 1) appeared balanced among the five dimensions, like describing a “prototypical patient”. Thus, we decided to retain this cluster as in previous works (Dickinson et al., 2019; Green et al., 2020).

## Preliminary correlations between ERS ad the measures of interest in cluster solution.

While in controls ERS score was inversely related with IQ (r=-.22, p<0.001), PAF (r=-.16, p<0.001), and PSF (r=-.09, p=0.001), in cases it was only related to IQ (r=-.08, p=0.013) and PAF (r=-.15, p<0.001), but not PSF (r=.04, p=0.172).

## Supplementary-Table 1. Sociodemographic and Clinical Characteristics by Patients’ Clusters

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **HIGH** | **INTERMEDIATE** | **DETERIORATING** | **LOW** | **F or**  **χ2 (df)** | **p** |
| **Sex**, N (%) |  |  |  |  | 6.6 (3) | 0.084 |
| Male | 119 (58) | 129 (57.6) | 91 (60.7) | 152 (68.2) |  |  |
| Female | 86 (42) | 95 (42.4) | 59 (39.3) | 71 (3.8) |  |  |
| **Age**, mean (sd) | 31.3 (9.8) | 32.4 (10.5) | 28.2 (9.6) | 29.3 (10.5) | 6.5 (3) | **<0.001** |
| **Education**, N (%) |  |  |  |  | 109.7 (9) | **<0.001** |
| No qualification | 8 (3.9) | 32 (14.4) | 24 (16) | 49 (22) |  |  |
| Compulsory edu. | 31 (15.3) | 62 (27.9) | 44 (29.3) | 70 (31.4) |  |  |
| 1st level/job related edu. | 90 (44.3) | 93 (41.9) | 70 (46.7) | 92 (41.3) |  |  |
| University/Post-graduate | 74 (36.5) | 35 (15.8) | 12 (8) | 12 (5.4) |  |  |
| **Occupation**, N (%) |  |  |  |  | 18.9 (3) | **<0.001** |
| Unemployed | 92 (45.8) | 122 (55.5) | 95 (64.2) | 141 (64.7) |  |  |
| Student/Employed | 109 (54.2) | 98 (45.5) | 53 (35.8) | 77 (35.3) |  |  |
| **Parents’ main social class** |  |  |  |  | 57.7 (9) | **<0.001** |
| Salaried | 86 (44.8) | 43 (21.6) | 35 (25.9) | 34 (17.3) |  |  |
| Intermediate | 50 (26) | 56 (28.1) | 43 (31.9) | 47 (23.9) |  |  |
| Working-class | 53 (27.6) | 95 (29.9) | 55 (40.7) | 115 (58.4) |  |  |
| Long-term unemployed | 3 (1.6) | 5 (2.5) | 2 (1.5) | 1 (0.5) |  |  |
| **Patients’ main social class** |  |  |  |  | 73.6 (9) | **<0.001** |
| Salaried | 45 (29.2) | 20 (10.3) | 12 (10.7) | 4 (2.1) |  |  |
| Intermediate | 39 (25.3) | 37 (19) | 21 (18.8) | 36 (18.8) |  |  |
| Working-class | 65 (42.2) | 134 (68.7) | 74 (66.1) | 141 (73.4) |  |  |
| Long-term unemployed | 5 (3.2) | 4 (2.1) | 5 (4.5) | 11 (5.7) |  |  |
| **Relationship**, N (%) |  |  |  |  | 7.2 (6) | 0.302 |
| Married/Steady rel. | 67 (32.8) | 67 (29.9) | 42 (28) | 57 (25.8) |  |  |
| Separated/widowed | 13 (6.4) | 17 (7.6) | 4 (2.7) | 15 (6.8) |  |  |
| Single | 124 (60.8) | 140 (62.5) | 104 (69.3) | 149 (67.4) |  |  |
| **Living Status**, N (%) |  |  |  |  | 9.4 (6) | 0.147 |
| Partner/Friend/Child | 64 (31.4) | 67 (30.2) | 33 (22.1) | 54 (24.7) |  |  |
| Alone | 34 (16.7) | 32 (14.4) | 22 (14.8) | 25 (11.4) |  |  |
| Parents/Other | 106 (52) | 123 (55.4) | 94 (63.1) | 140 (63.9) |  |  |
| **Family history of psychosis** | 21 (10.7) | 34 (16.6) | 23 (16.8) | 29 (13.9) | 3.7 (3) | 0.294 |
| **DUP in weeks** | 52.9 (142.2) | 52.7 (115.9) | 78.5 (262.4) | 65.9 (188.4) | 0.76 (3) | 0.516 |
| **AP treatment** |  |  |  |  |  |  |
| AP free | 119 (59.2) | 149 (68.7) | 78 (52.7) | 139 (63.5) | 13.1 (6) | **0.041** |
| 1 AP | 53 (26.4) | 37 (17.1) | 37 (25) | 46 (21) |  |  |
| more than 1 AP | 29 (14.4) | 31 (14.3) | 33 (22.3) | 34 (14.5) |  |  |
| **ICD-10 Diagnoses** |  |  |  |  | 38 (39) | 0.515 |
| Bipolar Affective disorder | 6 (3) | 3 (1.4) | 5 (3.4) | 4 (1.8) |  |  |
| Delusional disorder | 9 (4.5) | 7 (3.2) | 7 (4.7) | 10 (4.6) |  |  |
| Hypomanic disorder | 4 (2) | 2 (0.9) | 3 (2) | 3 (1.4) |  |  |
| Mania with psychosis | 23 (11.4) | 11 (5.1) | 10 (6.8) | 16 (7.3) |  |  |
| Manic disorder | 6 (3) | 4 (1.8) | 0 (0) | 4 (1.8) |  |  |
| Mild depression disorder | 7 (3.5) | 6 (2.8) | 3 (2) | 7 (3.2) |  |  |
| Moderate depression | 4 (2) | 6 (2.8) | 2 (1.4) | 3 (1.4) |  |  |
| Moderate depression with somatic syndrome | 4 (2) | 8 (3.7) | 4 (2.7) | 9 (4.1) |  |  |
| Other non-organic psychotic syndrome | 64 (31.8) | 93 (42.9) | 55 (37.2) | 71 (32.4) |  |  |
| Schizoaffective disorder, bipolar type | 2 (1) | 0 (0) | 0 (0) | 0 (0) |  |  |
| Schizoaffective disorder, depressed type | 3 (1.5) | 3 (1.4) | 4 (2.7) | 2 (0.9) |  |  |
| Schizoaffective disorder, manic type | 3 (1.5) | 1 (0.5) | 3 (2) | 3 (1.4) |  |  |
| Schizophrenia | 62 (30.8) | 64 (29.5) | 45 (30.4) | 82 (37.4) |  |  |
| Severe depression with psychotic symptoms | 4 (2) | 9 (4.1) | 7 (4.7) | 5 (2.3) |  |  |
| **ICD-10 Categories** |  |  |  |  |  |  |
| Non-affective | 143 (71.1) | 168 (77.4) | 114 (77) | 168 (76.7) | 2.8 (3) | 0.414 |
| Affective | 58 (28.9) | 49 (22.6) | 34 (23) | 51 (23.3) |  |  |

**Legend:** HIGH=*high-cognitive-functioning*; LOW=*low-cognitive-functioning.*

There were some differences within clusters in terms of socio-demographic characteristics, with the high-cognitive-functioning cluster presenting patients more educated (χ2(9)=109.7, p<0.001) and more likely to be employed or student (χ2 (3)=18.9, p<0.001) and patients in the deteriorating younger than those in the intermediate cluster (F2 (3)=6.5, p<0.001). Patients in the low-cognitive-functioning cluster were the less likely to have parents with a salaried work, the highest socio-economic status (SES), as compared with the other three clusters (χ2 (9)= 57.7, p<0.001). Main SES in the adult life was instead very similar between clusters, a part from the higher probability for the low-cognitive-functioning cluster to not have a salaried employment compared to those in the high-cognitive-cluster (χ2 (9)= 73.6, p<0.001) (Supplementary Table 1).

In terms of clinical characteristics, the deteriorating cluster presented lower manic symptoms (Mdiff=-0.28, 95% CI -0.49, -0.06, p=0.010) and higher negative symptoms (Mdiff=0.36, 95% CI 0.15, 0.57, p=0.001) than the high functioning cluster; it also presented higher depressive symptoms than the high- (Mdiff=0.32, 95% CI 0.12, 0.52, p=0.002) and the low-cognitive-functioning cluster (Mdiff=0.40, 95% CI 0.20, 0.60, p>0.001). Similarly, the intermediate cluster presented lower manic symptoms (Mdiff=-0.19, 95% CI -0.38, -0.004, p=0.046) and higher negative symptoms (Mdiff=0.23, 95% CI 0.04, 0.42, p=0.016) than the high functioning cluster. The high functioning cluster was more likely to did not have any antipsychotic prescription at the onset as compared to the other clusters (χ2 (6)=13.1, p=0.041) (Supplementary Table 2, supplementary Figure 1).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***High*** | ***Intermediate*** | ***Deteriorating*** | ***Low*** | **F (3,778)** | ***p*** | **Comparisons** |
| **General** | 0.358 (0.06) | 0.3 (0.06) | 0.157 (0.07) | 0.323 (0.05) | 1.875 | 0.132 | H>D\* |
| **Positive** | -0.006 (0.08) | 0.206 (0.07) | 0.084 (0.09) | 0.237 (0.07) | 2.163 | 0.091 | L=I>H\* |
| **Negative** | -0.087 (0.08) | 0.147 (0.07) | 0.277 (0.08) | 0.105 (0.07) | 4.128 | **0.006** | **L=I=D>H#** |
| **Disorganization** | -0.111 (0.07) | 0.063 (0.07) | -0.051 (0.08) | -0.009 (0.06) | 1.199 | 0.309 | I=H=D=L |
| **Mania** | 0.323 (0.08) | 0.128 (0.07) | 0.043 (0.08) | 0.251 (0.07) | 2.848 | **0.037** | **H=L>D=I##** |
| **Depressive** | 0.109 (0.07) | 0.259 (0.06) | 0.431 (0.08) | 0.027 (0.06) | 6.186 | **0.0003** | **D=I>L=H###** |

## Supplementary-Table 2. Comparisons by Standardized Symptom Dimensions

**Legend: estimated marginal means and standard errors from Multivariate GLM by clusters are provided for Z-Scores of symptom dimensions. Adjusted by age, sex, country, and self-ascribed** **ethnicity. Bonferroni corrected.** \*differences between these groups are significant. Nonetheless, they cannot be considered because the general F-test for that dimension is not significant. **#** L>H (p=0.053) **##**. L>D (p=0.052). ##**#**I=H (p=0.195). HIGH=*high-cognitive-functioning*; LOW=*low-cognitive-functioning.*

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## Supplementary-Figure 1. Symptom dimensions in clusters. the diagram shows symptom dimensions presentation at the onset of psychosis in the four clusters. The asterisks and dashed lines mark significant differences between clusters (as described in the Supplementary Table 1).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Supplementary-Table 3. Parameter Estimates from the multinomial regression on clusters and controls comparisons and likelihood ratio test | | | | | | | | | |
| CLUSTERSa | | B | Std. Error | Wald | df | Sig. | Exp(B) | 95% Confidence Interval for Exp(B) | |
| Lower Bound | Upper Bound |
| HIGH-cognitive-funcTIONING | Intercept | -1.605 | .296 | 29.379 | 1 | <.001 |  |  |  |
| Age | -.027 | .007 | 15.238 | 1 | <.001 | .974 | .961 | .987 |
| Male sex | .284 | .156 | 3.307 | 1 | .069 | 1.329 | .978 | 1.805 |
| High urbanisation | .084 | .197 | .181 | 1 | .671 | 1.087 | .739 | 1.599 |
| **Environmental Score** | **.156** | **.023** | **44.935** | **1** | **<.001** | **1.169** | **1.117** | **1.224** |
| INTERMEDIATE | Intercept | -1.903 | .287 | 43.818 | 1 | <.001 |  |  |  |
| Age | -.016 | .006 | 6.475 | 1 | .011 | .984 | .972 | .996 |
| Male sex | .257 | .151 | 2.893 | 1 | .089 | 1.293 | .962 | 1.737 |
| High urbanisation | .137 | .184 | .558 | 1 | .455 | 1.147 | .800 | 1.644 |
| **Environmental Score** | **.198** | **.022** | **77.531** | **1** | **<.001** | **1.219** | **1.166** | **1.274** |
| DETERIORATING | Intercept | -1.711 | .375 | 20.800 | 1 | <.001 |  |  |  |
| Age | -.050 | .009 | 27.927 | 1 | <.001 | .951 | .934 | .969 |
| Male sex | .253 | .187 | 1.830 | 1 | .176 | 1.288 | .893 | 1.858 |
| High urbanisation | -.136 | .245 | .307 | 1 | .580 | .873 | .541 | 1.410 |
| **Environmental Score** | **.285** | **.028** | **107.717** | **1** | **<.001** | **1.330** | **1.261** | **1.404** |
| LOW-cognitive-funcTIONING | Intercept | -1.380 | .307 | 20.189 | 1 | <.001 |  |  |  |
| Age | -.041 | .008 | 29.677 | 1 | <.001 | .960 | .946 | .974 |
| Male sex | .658 | .162 | 16.592 | 1 | <.001 | 1.931 | 1.407 | 2.650 |
| High urbanisation | .086 | .179 | .228 | 1 | .633 | 1.089 | .767 | 1.547 |
| **Environmental Score** | **.238** | **.023** | **108.395** | **1** | **<.001** | **1.269** | **1.213** | **1.327** |
| a. The reference category is: CONTROLS. | | | | | | | | | |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Likelihood Ratio Tests** | | | | |
| Effect | Model Fitting Criteria | Likelihood Ratio Tests | | |
| -2 Log Likelihood of Reduced Model | Chi-Square | df | Sig. |
| Sex | 3968.468 | 19,115 | 4 | <.001 |
| Urbanisation | 3985.498 | 36,145 | 8 | <.001 |
| Age | 4014.565 | 65,212 | 4 | <.001 |
| **Environmental Score** | 4185.943 | 236,590 | 4 | <.001 |

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| Supplementary-Table 4. Parameter Estimates from the multinomial regression on clusters’ comparisons and likelihood ratio test | | | | | | | | | |
| CLUSTERSa | | B | Std. Error | Wald | df | Sig. | Exp(B) | 95% Confidence Interval for Exp(B) | |
| Lower Bound | Upper Bound |
| INTERMEDIATE | Intercept | -.402 | .419 | .920 | 1 | .338 |  |  |  |
| Age | .013 | .009 | 1.842 | 1 | .175 | 1.013 | .994 | 1.032 |
| Male sex | .007 | .202 | .001 | 1 | .974 | 1.007 | .677 | 1.496 |
| High urbanisation | .031 | .244 | .017 | 1 | .897 | 1.032 | .640 | 1.664 |
| **Environmental Score** | **.047** | **.030** | **2.510** | **1** | **.113** | **1.048** | **.989** | **1.111** |
| DETERIORATING | Intercept | -.062 | .489 | .016 | 1 | .899 |  |  |  |
| Age | -.022 | .012 | 3.386 | 1 | .066 | .978 | .956 | 1.001 |
| Male sex | -.122 | .229 | .285 | 1 | .593 | .885 | .565 | 1.386 |
| High urbanisation | -.286 | .290 | .975 | 1 | .323 | .751 | .425 | 1.326 |
| **Environmental Score** | **.131** | **.033** | **15.537** | **1** | **<.001** | **1.139** | **1.068** | **1.216** |
| LOW-cognitive-funcTIONING | Intercept | .173 | .431 | .160 | 1 | .689 |  |  |  |
| Age | -.012 | .010 | 1.295 | 1 | .255 | .989 | .969 | 1.008 |
| Male sex | .341 | .210 | 2.638 | 1 | .104 | 1.407 | .932 | 2.123 |
| High urbanisation | -.025 | .238 | .011 | 1 | .917 | .975 | .611 | 1.556 |
| **Environmental Score** | **.084** | **.030** | **7.921** | **1** | **.005** | **1.087** | **1.026** | **1.153** |
| a. The reference category is: HIGH-cognitive-funcTIONING | | | | | | | | | |
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| **Likelihood Ratio Tests** | | | | |
| Effect | Model Fitting Criteria | Likelihood Ratio Tests | | |
| -2 Log Likelihood of Reduced Model | Chi-Square | df | Sig. |
| Sex | 1966.721 | 5.047 | 3 | .168 |
| Urbanisation | 1988.532 | 26.858 | 6 | <.001 |
| Age | 1973.143 | 11.468 | 3 | .009 |
| **Environmental Score** | **1979.444** | **17.769** | **3** | **<.001** |

**Supplementary-Table 5. ERS score and single exposures mean scores in controls and clusters of patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **CLUSTERS** | | **Mean (SD)** |  | **N (%)** |
| **CONTROLS** | Cannabis Use | -.07 (1.3) | Cannabis Use (yes) | 184 (14.6) |
| Childhood Adversities | -.10 (1.9) | Childhood Adversities (>=1) | 753 (61.1); median=1 |
| Paternal Age | .08 (.26) | Hearing impairment (yes) | 100 (8.8) |
| Ethnic Minority | .81 (1.6) | Winter birth (yes) | 333 (26.4) |
| **ERS** | **1.1** (**3.1**) | **EXPOSOME (mean, sd)** | **1.7 (1.5)** |
| **HIGH** | Cannabis Use | .79 (1.7) | Cannabis Use (yes) | 75 (36.6) |
| Childhood Adversities | .43 (2.0) | Childhood Adversities (>=1) | 158 (80.6); median=2 |
| Paternal Age | .07 (.24) | Hearing impairment (yes) | 18 (8.8) |
| Ethnic Minority | 1.1 (1.5) | Winter birth (yes) | 53 (25.9) |
| **ERS** | **2.9** (**3.2**) | **EXPOSOME (mean, sd)** | **2.6 (1.7)** |
| **INTERMEDIATE** | Cannabis Use | .55 (1.7) | Cannabis Use (yes) | 72 (32.1) |
| Childhood Adversities | .56 (1.9) | Childhood Adversities (>=1) | 174 (82.9); median=2 |
| Paternal Age | .10 (.34) | Hearing impairment (yes) | 14 (6.3) |
| Ethnic Minority | 1.5 (1.9) | Winter birth (yes) | 54 (24.1) |
| **ERS** | **3.4** (**3.5**) | **EXPOSOME (mean, sd)** | **2.8 (1.8)** |
| **DETERIORATING** | Cannabis Use | 1.2 (1.8) | Cannabis Use (yes) | 76 (50.7) |
| Childhood Adversities | .76 (1.9) | Childhood Adversities (>=1) | 121 (84.6); median=2 |
| Paternal Age | .10 (.28) | Hearing impairment (yes) | 14 (9.3) |
| Ethnic Minority | 1.9 (2.0) | Winter birth (yes) | 47 (31.3) |
| **ERS** | **4.6** (**3.6**) | **EXPOSOME (mean, sd)** | **3.4 (2.1)** |
| **LOW** | Cannabis Use | 1.05 (1.8) | Cannabis Use (yes) | 105 (47.1) |
| Childhood Adversities | .44 (1.9) | Childhood Adversities (>=1) | 167 (83.9); median=2 |
| Paternal Age | .08 (.27) | Hearing impairment (yes) | 13 (5.8) |
| Ethnic Minority | 1.7 (2.1) | Winter birth (yes) | 45 (20.2) |
| **ERS** | **4.1** (**3.4**) | **EXPOSOME (mean, sd)** | **3 (1.9)** |

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| Supplementary-Table 6. ERS differences between clusters of patients using the high-cognitive-functioning cluster as the baseline. | | | | | | | | | | | | | | |
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| **(I)** | | **(J)** | | **Meandifference (I-J)** | | **SE** | | **p-value** | | **95% CI for meandifferenceb** | | | | |
| **High** | | **Intermediate** | | -.52 | | .32 | | .639 | | -1.37 | | | .33 | |
| **Deteriorating** | | -1.41 | | .35 | | **<.001** | | -2.36 | | | -.46 | |
| **Low** | | -.97 | | .32 | | **.016** | | -1.82 | | | -.11 | |
| **Intermediate** | | **Deteriorating** | | -.88 | | .35 | | .072 | | -1.82 | | | .04 | |
| **Low** | | -.45 | | .31 | | .922 | | -1.28 | | | .38 | |
| **Deteriorating** | | **Low** | | .43 | | .35 | | 1.000 | | -.49 | | | 1.37 | |
| Based on estimated marginal means. In bold significant differences.  b. Adjustment for multiple comparisons: Bonferroni. | | | | | | | | | | | | | | |
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| **Supplementary-Table 7. Pairwise Comparisons between clusters in different exposures included in the ERS.** | | | | | | | | | | | | | | |
|  | **(I) Clusters** | | **(J) Clusters** | | **Mdiff (I-J)** | | **SE** | | **p-valueB** | |  | | |
| **95% CI for Mdiffb** | | |
| **Cannabis use** | **High** | | **Intermediate** | | .183 | | .141 | | 1.000 | | -.214 | .579 | |
| **Deteriorating** | | -.299 | | .157 | | .569 | | -.740 | .142 | |
| **Low** | | -.140 | | .141 | | 1.000 | | -.537 | .257 | |
| **Intermediate** | | **Deteriorating** | | -.482\* | | .154 | | **.018** | | -.915 | -.049 | |
| **Low** | | -.323 | | .138 | | .195 | | -.711 | .065 | |
| **Childhood adversities** | **Deteriorating** | | **Low** | | .159 | | .154 | | 1.000 | | -.275 | .592 | |
| **High** | | **Intermediate** | | -.263 | | .188 | | 1.000 | | -.792 | .265 | |
| **Deteriorating** | | -.304 | | .209 | | 1.000 | | -.892 | .283 | |
| **Low** | | -.368 | | .188 | | .505 | | -.897 | .161 | |
| **Intermediate** | | **Deteriorating** | | -.041 | | .205 | | 1.000 | | -.618 | .536 | |
| **Low** | | -.105 | | .184 | | 1.000 | | -.623 | .412 | |
| **Deteriorating** | | **Low** | | -.064 | | .205 | | 1.000 | | -.642 | .513 | |
| **Paternal age** | **High** | | **Intermediate** | | -.033 | | .028 | | 1.000 | | -.112 | .047 | |
| **Deteriorating** | | -.037 | | .031 | | 1.000 | | -.125 | .051 | |
| **Low** | | -.015 | | .028 | | 1.000 | | -.094 | .065 | |
| **Intermediate** | | **Deteriorating** | | -.004 | | .031 | | 1.000 | | -.091 | .082 | |
| **Low** | | .018 | | .028 | | 1.000 | | -.060 | .095 | |
| **Deteriorating** | | **Low** | | .022 | | .031 | | 1.000 | | -.065 | .109 | |
| **Ethnicity** | **High** | | **Intermediate** | | -.409 | | .167 | | .144 | | -.879 | .060 | |
| **Deteriorating** | | -.771\* | | .186 | | **<.001** | | -1.293 | -.249 | |
| **Low** | | -.450 | | .167 | | .072 | | -.920 | .020 | |
| **Intermediate** | | **Deteriorating** | | -.362 | | .182 | | .476 | | -.874 | .151 | |
| **Low** | | -.041 | | .164 | | 1.000 | | -.500 | .419 | |
| **Deteriorating** | | **Low** | | .321 | | .183 | | .790 | | -.192 | .834 | |
| Based On Estimated Marginal Means. Corrected by age, sex, and urbanization. | | | | | | | | | | | | | |
| \*. The Mean Difference Is Significant At The .05 Level. | | | | | | | | | | | | | |
| B. Adjustment For Multiple Comparisons: Bonferroni. | | | | | | | | | | | | | |

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| |  | | --- | | Supplementary-Table 8. Pairwise Comparisons between clusters and controls in different exposure to cannabis use, taking into account other drug abuse in the lifetime (controls=150; FEP=179) and tobacco use in the last 12 months (controls=297; FEP=430). | | | | | | | | |
| **Dependent Variable** | **(I) Clusters** | **(J) Clusters** | **Mdiff (I-J)** | **SE** | **p-valueB** |  | |
| **95% CI for Mdiffb** | |
| **Cannabis use** | **Controls** | **High** | -.225 | .099 | .240 | -.504 | .055 |
| **Intermediate** | -.063 | .096 | 1.000 | -.332 | .205 |
| **Deteriorating** | -.538 | .115 | **<.001** | -.861 | -.215 |
| **Low** | -.345 | .098 | **.005** | -.621 | -.069 |
| **High** | **Intermediate** | .161 | .123 | 1.000 | -.185 | .508 |
| **Deteriorating** | -.313 | .137 | .226 | -.698 | .072 |
| **Low** | -.120 | .124 | 1.000 | -.468 | .228 |
| **Intermediate** | **Deteriorating** | -.474 | .135 | **.004** | -.853 | -.096 |
| **Low** | -.281 | .121 | .198 | -.620 | .058 |
| **Deteriorating** | **Low** | .193 | .134 | 1.000 | -.184 | .570 |
| Based on Estimated Marginal Means. Corrected for sex, age, urbanization. | | | | | | | |
| \*. The Mean Difference Is Significant At the .05 Level. | | | | | | | |
| B. Adjustment For Multiple Comparisons: Bonferroni. | | | | | | | |

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| |  | | --- | | Supplementary-Table 9. Pairwise Comparisons between clusters and controls in different exposures to cannabis use taking into account main parents’ socio-economic status (SES) and main patients’ SES. | | | | | | | | |
| **Dependent Variable** | **(I) Clusters** | **(J) Clusters** | **Mdiff (I-J)** | **SE** | **p-valueB** |  | |
| **95% CI for Mdiffb** | |
| **Cannabis use**  **Adjusted by main parents’ SES** | **Controls** | **High** | -.603 | .114 | **<.001** | -.923 | -.283 |
| **Intermediate** | -.382 | .112 | **.007** | -.697 | -.066 |
| **Deteriorating** | -.906 | .133 | **<.001** | -1.278 | -.534 |
| **Low** | -.743 | .113 | **<.001** | -1.061 | -.426 |
| **High** | **Intermediate** | .222 | .149 | 1.000 | -.196 | .639 |
| **Deteriorating** | -.303 | .164 | .655 | -.764 | .159 |
| **Low** | -.140 | .150 | 1.000 | -.561 | .281 |
| **Intermediate** | **Deteriorating** | -.524 | .163 | **.013** | -.981 | -.067 |
| **Low** | -.362 | .147 | .138 | -.774 | .051 |
| **Deteriorating** | **Low** | .163 | .163 | 1.000 | -.296 | .621 |
| **Cannabis use**  **Adjusted by main patients’ SES** | **Controls** | **High** | -.488 | .125 | **<.001** | -.839 | -.137 |
| **Intermediate** | -.356 | .115 | **.021** | -.680 | -.031 |
| **Deteriorating** | -.891 | .146 | **<.001** | -1.301 | -.481 |
| **Low** | -.654 | .118 | **<.001** | -.986 | -.321 |
| **High** | **Intermediate** | .132 | .157 | 1.000 | -.309 | .573 |
| **Deteriorating** | -.403 | .180 | .256 | -.910 | .104 |
| **Low** | -.166 | .159 | 1.000 | -.612 | .280 |
| **Intermediate** | **Deteriorating** | -.535 | .171 | **.018** | -1.017 | -.054 |
| **Low** | -.298 | .147 | .431 | -.712 | .116 |
| **Deteriorating** | **Low** | .237 | .172 | 1.000 | -.246 | .720 |
| Based on Estimated Marginal Means. Corrected for sex. age. urbanization. | | | | | | | |
| \*. The Mean Difference Is Significant At the .05 Level. | | | | | | | |
| B. Adjustment For Multiple Comparisons: Bonferroni. | | | | | | | |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| Supplementary-Table 10. Pairwise Comparisons between clusters and controls in different exposures included in the Exposome. | | | | | | | |
| **Dependent Variable** | **(I) Clusters** | **(J) Clusters** | **Mdiff (I-J)** | **SE** | **p-valueB** |  | |
| **95% CI for Mdiffb** | |
| **Cannabis use** | **Controls** | **High** | -.156 | .032 | **<.001** | -.245 | -.068 |
| **Intermediate** | -.118 | .031 | **.002** | -.207 | -.030 |
| **Deteriorating** | -.289 | .038 | **<.001** | -.395 | -.182 |
| **Low** | -.254 | .031 | **<.001** | -.342 | -.166 |
| **High** | **Intermediate** | .038 | .041 | 1.000 | -.078 | .155 |
| **Deteriorating** | -.133 | .047 | .**044** | -.263 | -.002 |
| **Low** | -.097 | .041 | .186 | -.214 | .019 |
| **Intermediate** | **Deteriorating** | -.171 | .046 | **.002** | -.301 | -.040 |
| **Low** | -.136 | .041 | **.010** | -.251 | -.020 |
| **Deteriorating** | **Low** | .035 | .046 | 1.000 | -.095 | .165 |
| **Childhood adversities** | **Controls** | **High** | -.621 | .120 | **<.001** | -.957 | -.285 |
| **Intermediate** | -.853 | .119 | **<.001** | -1.188 | -.518 |
| **Deteriorating** | -.988 | .144 | **<.001** | -1.392 | -.584 |
| **Low** | -.894 | .119 | **<.001** | -1.228 | -.561 |
| **High** | **Intermediate** | -.232 | .157 | 1.000 | -.673 | .209 |
| **Deteriorating** | -.367 | .176 | .375 | -.862 | .128 |
| **Low** | -.273 | .156 | .812 | -.713 | .167 |
| **Intermediate** | **Deteriorating** | -.135 | .176 | 1.000 | -.629 | .360 |
| **Low** | -.041 | .156 | 1.000 | -.480 | .398 |
| **Deteriorating** | **Low** | .094 | .176 | 1.000 | -.400 | .587 |
| **Winter birth** | **Controls** | **High** | .004 | .036 | 1.000 | -.097 | .105 |
| **Intermediate** | .008 | .036 | 1.000 | -.093 | .108 |
| **Deteriorating** | -.078 | .043 | .695 | -.199 | .043 |
| **Low** | .044 | .036 | 1.000 | -.056 | .144 |
| **High** | **Intermediate** | .004 | .047 | 1.000 | -.128 | .136 |
| **Deteriorating** | -.082 | .053 | 1.000 | -.231 | .066 |
| **Low** | .040 | .047 | 1.000 | -.092 | .172 |
| **Intermediate** | **Deteriorating** | -.086 | .053 | 1.000 | -.234 | .062 |
| **Low** | .036 | .047 | 1.000 | -.095 | .168 |
| **Deteriorating** | **Low** | .122 | .053 | .201 | -.025 | .270 |
| **Hearing impairment** | **Controls** | **High** | -.007 | .023 | 1.000 | -.071 | .058 |
| **Intermediate** | .008 | .023 | 1.000 | -.057 | .073 |
| **Deteriorating** | -.031 | .028 | 1.000 | -.109 | .047 |
| **Low** | .006 | .023 | 1.000 | -.058 | .071 |
| **High** | **Intermediate** | .015 | .030 | 1.000 | -.071 | .100 |
| **Deteriorating** | -.024 | .034 | 1.000 | -.120 | .071 |
| **Low** | .013 | .030 | 1.000 | -.072 | .098 |
| **Intermediate** | **Deteriorating** | -.039 | .034 | 1.000 | -.134 | .057 |
| **Low** | -.002 | .030 | 1.000 | -.086 | .083 |
| **Deteriorating** | **Low** | .037 | .034 | 1.000 | -.058 | .132 |
| Based on Estimated Marginal Means. Corrected for sex, age, ethnicity, and urbanization. | | | | | | | |
| \*. The Mean Difference Is Significant At The .05 Level. | | | | | | | |
| B. Adjustment For Multiple Comparisons: Bonferroni. | | | | | | | |

Immagine che contiene testo, diagramma, linea, Parallelo

Descrizione generata automaticamente

Supplementary-Figure 2. Cannabis exposure mean scores by clusters and controls. Legend: Y axis represents and 95% Cis in each cluster of patients with FEP and controls. HIGH = high-cognitive-functioning; LOW = low-cognitive-functioning. The blue braces indicate a significant difference between specific clusters and controls and the red brace indicates significant differences between cluster of patients.

Supplementary-Figure 3. Exposome mean scores by clusters and controls. Legend: Y axis represents and 95% Cis in each cluster of patients with FEP and controls. HIGH = high-cognitive-functioning; LOW = low-cognitive-functioning. The grey brace indicates a significant difference between deteriorating and high-cognitive-functioning cluster.

Exposome mean scores

## Supplementary-Figure 4

## Graphical comparisons of the level of ERS and schizophrenia polygenic risk scores (SCZ\_PRS)

In order to assess differential genetic and environmental predisposition to the four patients’ clusters, we compared ERS and SCZ\_PRS results based on our previous study, which described the genotyping and polygenic risk score (PRS) calculation in detail (Ferraro et al., 2023). As previously reported, in the deteriorating group SCZ\_PRS was the lowest and the ERS the highest among the patient clusters. Notably, the ERS measured in the whole sample was similar to that measured in the subsample of people with European ancestry.



**IQ PRS**

**SCH PRS**

**Environmental score, EU ancestry**

Standardized mean scores for IQ PRS, SCH PRS and ERS

Supplementary-Figure 4. Mean scores by clusters and controls for IQ\_PRS, SCZ\_PRS (Ferraro et al., 2023), and Environmental score in people having European ancestry. Legend: The Y axis represents means and 95% Cis in each cluster of patients with patients and controls on IQ\_PRS (green bars) SCH\_PRS (red bars) (Ferraro et al., 2023) and Environmental score, measured in the subjects with European ancestry (yellow bars), respectively. HIGH = high-cognitive-functioning; LOW = low-cognitive-functioning. The lines draw the trend of the measurements of genetic aspects (IQ\_PRS and SCH\_PRS) and Environmental score for schizophrenia in the different clusters of patients.

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