*Psychological Medicine*

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# Cognitive presentation at psychosis onset through premorbid deterioration and exposure to environmental risk factors

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## Abstract

**Background.** Previous studies identified clusters of first-episode psychosis (FEP) patients based on cognition and premorbid adjustment. This study examined a range of socio-environmental risk factors associated with clusters of FEP, aiming a) to compare clusters of FEP and community controls using the Maudsley Environmental Risk Score for psychosis (ERS), a weighted sum of the following risks: paternal age, childhood adversities, cannabis use, and ethnic minority membership; b) to explore the putative differences in specific environmental risk factors in distinguishing within patient clusters and from controls.

**Methods.** A univariable general linear model (GLS) compared the ERS between 1,263 community controls and clusters derived from 802 FEP patients, namely, low (n = 223) and high-cognitive-functioning (n = 205), intermediate (n = 224) and deteriorating (n = 150), from the EU-GEI study. A multivariable GLS compared clusters and controls by different exposures included in the ERS.

**Results.** The ERS was higher in all clusters compared to controls, mostly in the deteriorating (**β**=2.8, 95% CI 2.3 3.4, $\eta^2$ = 0.049) and the low-cognitive-functioning cluster (**β**=2.4, 95% CI 1.9 2.8, $\eta^2$ = 0.049) and distinguished them from the cluster with high-cognitive-functioning. The deteriorating cluster had higher cannabis exposure ($mean_{difference}$ = 0.48, 95% CI 0.49 0.91) than

## Original Article

**Cite this article:** Ferraro, L., Di Forti, M., La Barbera, D., La Cascia, C., Morgan, C., Tripoli, G., Jongsma, H., Seminerio, F., Sartorio, C., Sideli, L., Tarricone, I., Carloni, A. L., Szoke, A., Pignon, B., Bernardo, M., de Haan, L., Arango, C., Velthorst, E., Gayer-Anderson, C., Kirkbride, J., Rutten, B. P.F., Lasalvia, A., Tosato, S., Del Ben, C. M., Menezes, P. R., Bobes, J., Arrojo, M., Tortelli, A., Jones, P., Selten, J.-P., van Os, J., The WP2 EU-GEI Group, Murray, R., Quattrone, D., & Vassos, E. (2025). Cognitive presentation at psychosis onset through premorbid deterioration and exposure to environmental risk factors. *Psychological Medicine*, **55**, e12, 1–11
https://doi.org/10.1017/S0033291724003507

Received: 01 August 2024
Revised: 27 November 2024
Accepted: 16 December 2024

**Keywords:**
cannabis; childhood abuse; cluster analysis; IQ; risk factors; migration

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the intermediate having identical IQ, and more people from an ethnic minority ($mean_{difference}$ = 0.77, 95% CI 0.24 1.29) compared to the high-cognitive-functioning cluster.
**Conclusions.** High exposure to environmental risk factors might result in cognitive impairment and lower-than-expected functioning in individuals at the onset of psychosis. Some patients' trajectories involved risk factors that could be modified by tailored interventions.

## Introduction

There has been an increased effort to include cognition as a clinically relevant dimension for characterizing premorbid trajectories to psychosis (Lam, Raine, & Lee, 2014; Reichenberg, 2005). A recent approach, cluster analysis, delineated three distinct patterns of cognitive functioning in patients diagnosed with psychosis: high, low, and intermediate (Carter, 2018), with the latter group showing significant internal variations (Carruthers et al., 2019); this statistical approach has enhanced the understanding of premorbid adjustment and cognition trajectories. Indeed, while these variables generally presented a stable course over time (Carruthers et al., 2019), cluster analyses have identified a subgroup of patients at their first episode of psychosis who showed impaired premorbid adjustment and cognitive capacities (Mohn-Haugen et al., 2022), which deteriorated further prior to the onset of psychosis (Green et al., 2020).

Such a premorbid decline might have been associated with exposure to environmental risk factors (Cuesta et al., 2015; Meier et al., 2012; Mollon & Reichenberg, 2018; Velthorst et al., 2021) toward suggested mechanisms affecting brain structure, synaptic function, ion channels, glutamate neurotransmission, and inflammatory and immune processes (Tandon et al., 2024). It has also been suggested that an underlying genetic susceptibility before the onset of psychosis might have contributed to deterioration, at least in some patients (Mollon & Reichenberg, 2018; Ohi et al., 2021; Parellada, Gomez-Vallejo, Burdeus, & Arango, 2017). This latter theory was still reminiscent of Kraepelin's early notion of 'dementia praecox', which was grounded on a negative connotation of schizophrenia and suggested an inevitable disease progression with cognitive decline.

In this regard, in a previous study (Ferraro et al., 2023), we replicated the methodology from Dickinson et al. (2020) by combining empirical stratification of premorbid adjustment measures and current cognitive trajectories to cluster patients with psychosis. These studies tested the association between the resulting clusters and polygenic risk scores. Dickinson et al. (2020) identified a cluster of schizophrenia patients with worsening cognition prior to onset, which showed a higher polygenic risk score for schizophrenia (SCZ_PRS). In contrast, our recent study found a lower SCZ_PRS in a cluster of first-episode psychosis (FEP) patients whose premorbid functioning deteriorated before onset (Ferraro et al., 2023). Notably, FEP research has provided a more accurate assessment of cognitive profiles, potentially less affected by social impairment, symptom duration, and antipsychotic treatment than in long-standing psychosis. Moreover, the cognition measurement in chronic schizophrenia patients might have been skewed toward the most severe cases, the so-called Berkson's fallacy (Maric et al., 2004). This bias could be overcome by using transdiagnostic approaches.

Nonetheless, these factor analyses observed the same phenomenon at different levels, that is, premorbid trajectories and cognition characteristics of patients in their FEP and polygenic profiles. A more comprehensive analysis should also consider additional co-occurring phenomena at the premorbid level, referred to as 'environmental risk factors'. For example, our previous study (Ferraro et al., 2023) reported that, among patients, daily users of high-potency cannabis were more likely to be part of the deteriorating cluster, suggesting that this environmental risk factor often co-occurred with social and cognitive deterioration.

Similar to the polygenic risk scores, Vassos et al. (2020) proposed an approach to measure the cumulative effect of a range of environmental factors, building an Environmental Risk Score for psychosis (ERS). This score aggregated relative risks based on the largest meta-analysis of consistently replicated environmental risk factors for psychosis, such as paternal age, urbanization, obstetric complications, childhood adversities, cannabis use, and ethnic minority membership. The present study hypothesized that specific clusters of FEP could have been differentially exposed to environmental risk factors. We used the ERS to compare derived clusters based on combined environmental exposures. In our previous report, we found that cannabis was more frequently used in the deteriorating cluster. Hence, our study also explored the putative differences in single exposures of the environmental risk factors in distinguishing within patient clusters and from controls.

## Methods

### Participants

FEP patients and population-based controls from the multi-centric EU-GEI study signed an informed consent form after fully explaining the research procedures. The study was carried out in compliance with the Helsinki Declaration and received ethical approval; data were pseudonymized (CORDIS, 2019; EU-GEI, 2009; Gayer-Anderson et al., 2020; Jongsma et al., 2018; Leeson et al., 2011; Roser et al., 2015; Uren et al., 2017) (Supplementary Methods, recruitment).

### The Maudsley environmental risk score

This ERS was a weighted sum of the relevant environmental exposures, using effect sizes extracted from meta-analyses for each risk factor (Vassos et al., 2020), namely, ethnic minority membership, paternal age, cannabis use, childhood adversities, urbanicity, and obstetric complications. Based on our data's availability, we could not include urbanicity because it was measured at a site rather than individual level, and obstetric complications were not collected in our sample. To validate the primary analysis, we used the Exposome (Pries et al., 2019), built by summing log-odds weighted environmental exposures (0–1) on the EUGEI training sample, such as winter birth, hearing impairment, cannabis use, and cumulative exposure to childhood adversities (6/9 points) (Supplementary Methods, The ERS, the Exposome).

### Instruments

The modified version of the Medical Research Council (MRC) socio-demographic scale collected demographic information

https://doi.org/10.1017/S0033291724003507 Published online by Cambridge University Press

(Mallett et al., 2002). Given the multisite design, we could not use the same psychometric test (i.e., a reading test) among countries to assess premorbid IQ. Instead, we used nine scales from the Premorbid Adjustment Scale (PAS) (Brill, Reichenberg, Weiser, & Rabinowitz, 2008; Cannon-Spoor, Potkin, & Wyatt, 1982; Rabinowitz, Levine, Brill, & Bromet, 2007; Shapiro et al., 2009) examining premorbid social (PSF) and academic functioning (PAF), from childhood to age 11 (<12 years) and in early adolescence (12–16 years). The brief version of the Wechsler Adult Intelligence Scale (WAIS), including information, block design, digit symbol, and arithmetic subtests, estimated current IQ in patients and controls according to the imputation standardized strategy in schizophrenic patients (Missar, Gold, & Goldberg, 1994; Velthorst et al., 2013; Wechsler, 1981). The EUGEI modified version of the Cannabis Experience Questionnaire ($CEQ_{Eugei\text{-}mv}$) (Di Forti et al., 2019), including a section from Composite International Diagnostic Interview (CIDI), collected data on cannabis use, other substances of abuse, and tobacco in the last 12 months. We assessed childhood adversities by using two instruments: the Childhood Trauma Questionnaire (CTQ) (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997), a 28-item self-report tool that rates the presence of physical, sexual, and emotional abuse, physical and emotional neglect, and the Childhood Experience of Care and Abuse Questionnaire interview (CECA-Q) (Bifulco, Bernazzani, Moran, & Jacobs, 2005), which additionally included information about loss of parents and bullying before the age of 17, and corroborated CTQ data (Supplementary Methods, instruments). Researchers ensured that patients assessed as soon as they achieved a stable mental state were referred to the pre-onset period. The CEQEugei-mv and PAS interviews were checked by at least one supporting data source (family, clinical notes, and other clinicians).

### Cluster derivation

We clustered 802 FEP patients having complete information on PAS and WAIS from the EU-GEI study, based on assessments of premorbid social (PSF) and academic functioning (PAF) in early childhood (PAS < 12 years) and adolescence (PAS 12–16 years), and IQ at the time of onset (Ferraro et al., 2023). To reduce collinearity between PAS < 12 and PAS 12–16 (r = 0.7 in patients for both scales) and focus on potential deterioration, we used PSF < 12 years, PAF < 12 years and change scores between <12 years and 12–16 years for both social ($PSF_{change}$) and academic domain ($PAF_{change}$), and current IQ as the input variables. Controls were not included and used as a whole reference group. We performed a Two-Step Cluster Analysis procedure in SPSS_version_24. We used the stepwise decrease in log-likelihood as the distance measure for identifying clusters and change in the Bayesian Information Criterion (BIC) to determine the number of clusters to retain (best ratio change of cluster distance at least >1.15) (Liu, Li, Dong, & Wen, 2013). We ran a 50-subject' assignment solution by predetermining the chosen number of clusters with random reordering. Fleiss's kappa index established the extent of agreement in cluster assignment (Fleiss, 1971) between the assignment solutions. To validate clusters, we performed repeated-measures ANOVAs to determine whether there were any statistically significant differences in PSF and PAF changes between childhood and early adolescence within the formed clusters, compared to control changes. Then, we modelled an ANCOVA to compare each cluster to controls for IQ and PAS (Ferraro et al., 2023) (Supplementary Methods, cluster derivation).

### Statistical analyses

Firstly, we used multinomial logistic regression to estimate the odds of belonging to each patient cluster relative to community controls at baseline for exposure to the ERS, including age, sex, and site-level urbanization as covariates. Next, to see the amount of variance explained by the ERS, we estimated the difference between the model's pseudo-R-squares (Nagelkerke $R^2$), including the ERS and covariates only. We then repeated case-only analyses by excluding controls and using the high-cognitive-functioning cluster as the reference category. We also repeated the Nagelkerke $R^2$ estimation for the between-cluster variance explained by the ERS. A univariable general linear model tested the ERS differences by each cluster and controls, adjusting by age, sex, and urbanization, including post hoc multiple comparisons between groups, Bonferroni adjusted. Then, we repeated them in a subsample of matched cases and controls (Supplementary Material, sensitivity analyses). Lastly, we run multivariable general linear models, comparing each cluster with controls by different exposures in the ERS, adjusted by age, sex, and urbanization. We repeated these last multivariable models, taking into account the use of tobacco and other illegal drugs and socioeconomic status (Supplementary Material, sensitivity analyses). Finally, the same analyses tested the Exposome as a cumulative score, and then single exposures were included, adjusted by sex, age, ethnicity, and urbanization. Partial eta squared ($\eta^2$) measured effect sizes.

## Results

### Clusters of patients

The sample included 1,263 population controls and 802 FEP patients with complete data on our variables of interest (EU-GEI, 2009) (Table 1).

We identified four transdiagnostic clusters: high-cognitive-functioning, low-cognitive-functioning, and intermediate and deteriorating functioning (Ferraro et al., 2020). The high-cognitive-functioning cluster (n = 205) displayed high IQ (Mean (M) = 106.1, sd = 14.2), slightly higher than controls' (M = 102.6, sd = 17.6), and highly stable premorbid academic functioning. However, the premorbid sociability was steadily lower than the controls in the two ages. The low-cognitive-functioning cluster (n = 223) displayed low IQ (M = 73.9, sd = 12.7) and poor childhood premorbid academic functioning, increasing in early adolescence, and a close to average and stable premorbid sociability. The intermediate cluster (n = 224) had a middle IQ (M = 80.8, sd = 11.9) compared to the other two clusters and a low premorbid sociability and academic adjustment; both scores slightly improved during early adolescence. Finally, the deteriorating cluster (n = 150) had the same IQ as the intermediate (M = 80.6, sd = 12.9) and a normal premorbid academic and social adjustment in childhood, comparable to controls. Nonetheless, during early adolescence, significantly deviated from normal functioning, both in premorbid sociability and academic functioning (Ferraro et al., 2020) (Supplementary Results, clusters of patients). Clusters differed in some sociodemographic and clinical characteristics (Supplementary Tables 1 and 2, Supplementary Figure 1).

### Clusters and ERS

In comparing the four clusters of patients with controls, the ERS explained 10.8% of extra variance compared to the covariate-only model, including age, sex, and urbanization (Nagelkerke $R^2 = 0.209$

https://doi.org/10.1017/S0033291724003507 Published online by Cambridge University Press

**Table 1.** Sociodemographic and clinical characteristics of the sample by cases and controls

| Variables | Cases | N | Controls | N | test | df | *p-value* |
|---|---|---|---|---|---|---|---|
| Sex, N (%) | | 802 | | 1263 | 34.9 | 1 | $3.39^{-9}$ |
| Male | 491 (61.2) | | 605 (47.9) | | | | |
| Female | 311 (38.8) | | 658 (52.1) | | | | |
| Age, Mean (SD) | 30.5 (10.3) | 802 | 36.1 (13.0) | 1261 | −10.3 | 2061 | $1.48^{-24}$ |
| Self-ascribed ethnicity, N (%) | | 802 | | 1263 | 35.6 | 1 | $2.13^{-9}$ |
| White | 523 (65.2) | | 982 (77.8) | | | | |
| Black | 119 (14.8) | | 109 (8.8) | | | | |
| Other ethnicities | 160 (20) | | 172 (13.6) | | | | |
| Education*, N (%) | | 798 | | 1258 | 191.5 | 1 | $3.58^{-41}$ |
| No qualification | 113 (14.2) | | 46 (3.7) | | | | |
| Compulsory edu. | 207 (25.9) | | 171 (13.6) | | | | |
| 1st level/job related edu. | 345 (43.2) | | 549 (43.6) | | | | |
| University/Post-graduate | 133 (16.7) | | 492 (39.1) | | | | |
| Frequency of cannabis use*, N (%) | | 796 | | 1262 | 138.1 | 1 | $2.15^{-46}$ |
| At least weekly | 328 (40.2) | | 184 (14.6) | | | | |
| Less than weekly | 202 (34.0) | | 430 (25.2) | | | | |
| Never | 272 (33.9) | | 649 (51.4) | | | | |
| Age at first use, (mean, SD) | 16.7 (4.1) | 527 | 17.8 (4.4) | 614 | −4.3 | 1139 | <0.005 |

Legend: SD = standard deviation; df = degree of freedom; edu. = education. * aggregation of categories was made through linear regression.

vs 0.101, respectively) ($\Delta\chi^2$ (4, 16) = 236.5, p = $5.03\times10^{-50}$); it explained 2.2% of the between-cluster variance (Nagelkerke $R^2$ = 0.090 vs 0.068, respectively) ($\Delta\chi^2$ (3, 9) = 17.7, p = 0.0004) in case-only analysis (parameter estimated and odd ratios in Supplementary Tables 3 and 4).

The ERS (Supplementary Table 5) was higher in the high-cognitive-functioning (β=1.4, 95% CI 0.9 1.9, $\eta^2$ = 0.017), the intermediate (β=1.9, 95% CI 1.5 2.4, $\eta^2$ = 0.033), the deteriorating (β=2.8, 95% CI 2.3 3.4, $\eta^2$ = 0.049), and the low-cognitive-functioning group (β=2.4, 95% CI 1.9 2.8, $\eta^2$ = 0.049), compared to controls. Post hoc between-clusters comparison showed that the deteriorating ($mean_{difference}$ = 1.4, 95% CI 0.43 2.38) and the low-cognitive-functioning clusters ($mean_{difference}$ = 0.9, 95% CI 0.09 1.85) had a higher ERS than the high-cognitive-functioning group (Figure 1). These results were confirmed even when limiting comparison only to patients' clusters (Supplementary Table 6). We tested the ERS in a case-control matched sample, by age and gender and the results remained consistent (Supplementary Material, sensitivity analyses).

### *Clusters by single environmental exposures*

When we analyzed each environmental exposure separately, compared to the model with covariates only (Nagelkerke $R^2$ = 0.101), cannabis use explained 5% of the total variance (Nagelkerke $R^2$ = 0.151), childhood adversities the 5.2% (Nagelkerke $R^2$ = 0.153) and ethnic minority status the 3.7% (Nagelkerke $R^2$ = 0.138).

Patients as a whole were more likely to belong to an ethnic minority (F(4, 2058) = 20.5, $\eta^2$ = 0.038) and had higher exposure to cannabis use (F(4, 2058) = 26.4, $\eta^2$ = 0.049) and childhood adversities (F(4, 2058) = 24.5, $\eta^2$ = 0.046) than controls. Paternal age did not differentiate groups (p = 0.619) (Table 2).

Post hoc multiple comparisons showed that the deteriorating cluster had been more exposed to cannabis use than the intermediate cluster ($mean_{difference}$ = 0.48, 95% CI 0.49 0.91).

The high-cognitive-functioning cluster did not show substantial differences with controls in the likelihood of belonging to an ethnic minority ($mean_{difference}$ = -0.24, 95% CI −0.60 0.12). It included fewer people from ethnic minorities than the deteriorating cluster ($mean_{difference}$ = −0.77, 95% CI −1.29–0.24). Finally, there were no appreciable differences between clusters in exposure to childhood adversities (all p > 0.05) (Figure 2, Supplementary Table 7). These results remained consistent in cluster-only comparisons and when considering other drug and tobacco use or socio-economic status (Supplementary Tables 8 and 9 and Supplementary Figure 2).

### *Validation analyses via Exposome*

Measures to calculate Exposome score were available in 1,104 population controls and 641 FEP patients. As compared with the covariates model (Nagelkerke $R^2$ = 0.111), its introduction in the cluster-control analysis explained 9.2% of additional variance (Nagelkerke $R^2$ = 0.203) ($\Delta\chi^2$ (4, 20) = 169.2, p = $1.51\times10^{-35}$), and 2% when tested among patients only (Nagelkerke $R^2$ = 0.069) as compared with the covariate-only model (Nagelkerke $R^2$ = 0.071).

The Exposome yielded identical results to the ERS, with controls having lower scores than all clusters of patients [F(4, 1738) = 40.7, p = $1.217\times10^{-32}$] and the deteriorating group reporting the highest score, significantly higher than the high-cognitive-functioning cluster ($mean_{\_difference}$ = 0.60, 95% CI 0.35 1.17, p = 0.029) (Supplementary Table 5 and Supplementary Figure 3).

Among Exposome risk factors, childhood adversities (F(4, 1738) = 33.4, p = $6.3\times10^{-27}$) and cannabis use (F(4, 1738) = 30.9, p = $5.8\times10^{-25}$) distinguished all patients from controls, the latter

https://doi.org/10.1017/S0033291724003507 Published online by Cambridge University Press

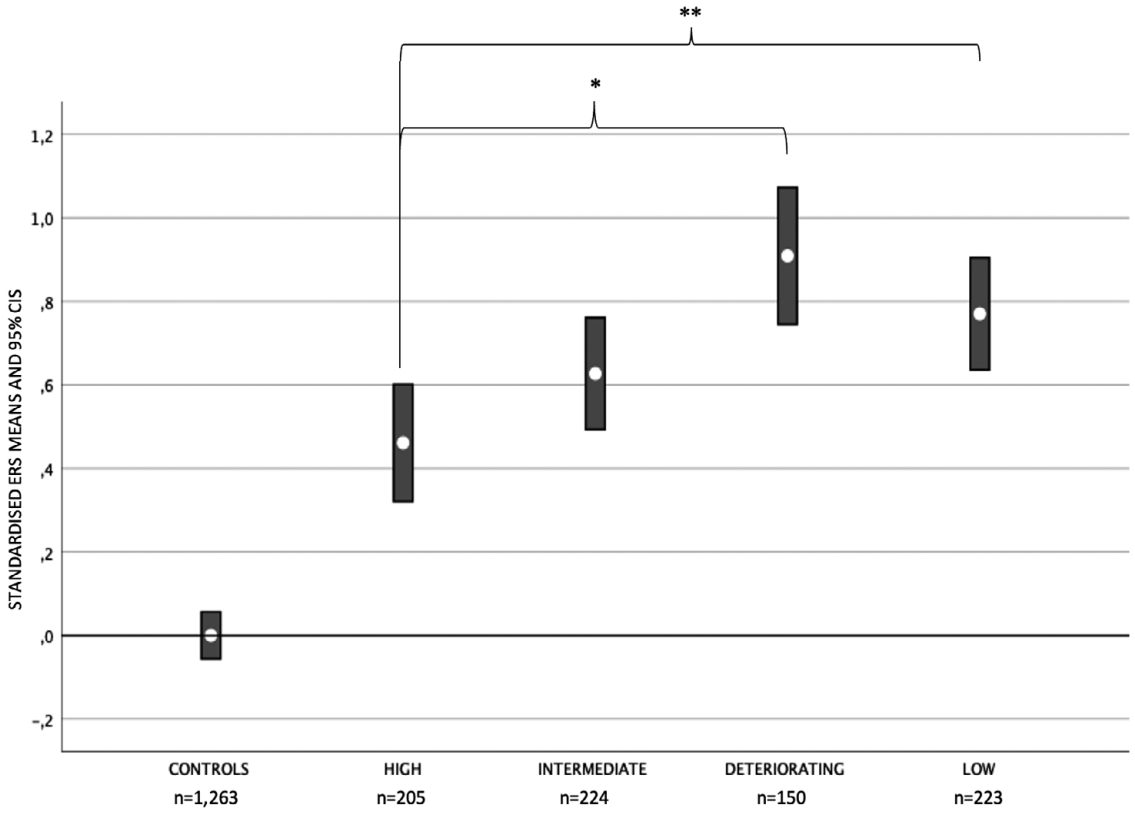


**Figure 1.** ERS by clusters of FEP and controls.
Legend: The Y axis represents ERS means and 95% Cis in each cluster of patients and controls. HIGH = high-cognitive-functioning; LOW = low-cognitive-functioning. The grey braces indicate significant differences between clusters of patients. Braces mark significant differences between patient clusters *($mean_{difference}$ = 0.974, 95% CI 0.09 1.85, p = 0.018); **($mean_{difference}$ = 1.41, 95% CI 0.43 2.38, p = 0.0004).

**Table 2.** Ethnic minority, paternal age, childhood adversities, and cannabis use comparisons between clusters and controls and parameter estimates

| Dependent variable Baseline: controls | Parameter | β | SE | t | 95% CI | | $\eta^2$ |
|---|---|---|---|---|---|---|---|
| Cannabis use | High | .59 | .11 | 5.43 | .38 | .81 | 0.014 |
| | Intermediate | .41 | .10 | 3.92 | .20 | .62 | 0.007 |
| | Deteriorating | .89 | .12 | 7.11 | .65 | 1.14 | 0.024 |
| | Low | .73 | .10 | 6.96 | .53 | .94 | 0.023 |
| Childhood adversities | High | .62 | .14 | 4.23 | .33 | .90 | 0.009 |
| | Intermediate | .88 | .14 | 6.25 | .60 | 1.16 | 0.019 |
| | Deteriorating | .92 | .16 | 5.49 | .59 | 1.25 | 0.014 |
| | Low | .98 | .14 | 6.99 | .71 | 1.26 | 0.023 |
| Paternal age | High | -.01 | .02 | -.41 | -.05 | .03 | 0 |
| | Intermediate | .02 | .02 | 1.11 | -.01 | .06 | 0.001 |
| | Deteriorating | .02 | .02 | 1.09 | -.02 | .07 | 0.001 |
| | Low | .01 | .02 | .27 | -.03 | .04 | 0 |
| Ethnic minority | High | .24 | .13 | 1.86 | -.01 | .49 | 0.002 |
| | Intermediate | .65 | .12 | 5.20 | .40 | .89 | 0.013 |
| | Deteriorating | 1.01 | .14 | 6.78 | .72 | 1.30 | 0.022 |
| | Low | .69 | .12 | 5.51 | .44 | .93 | 0.015 |

Legend: High = high-cognitive-functioning; Low = low-cognitive-functioning.

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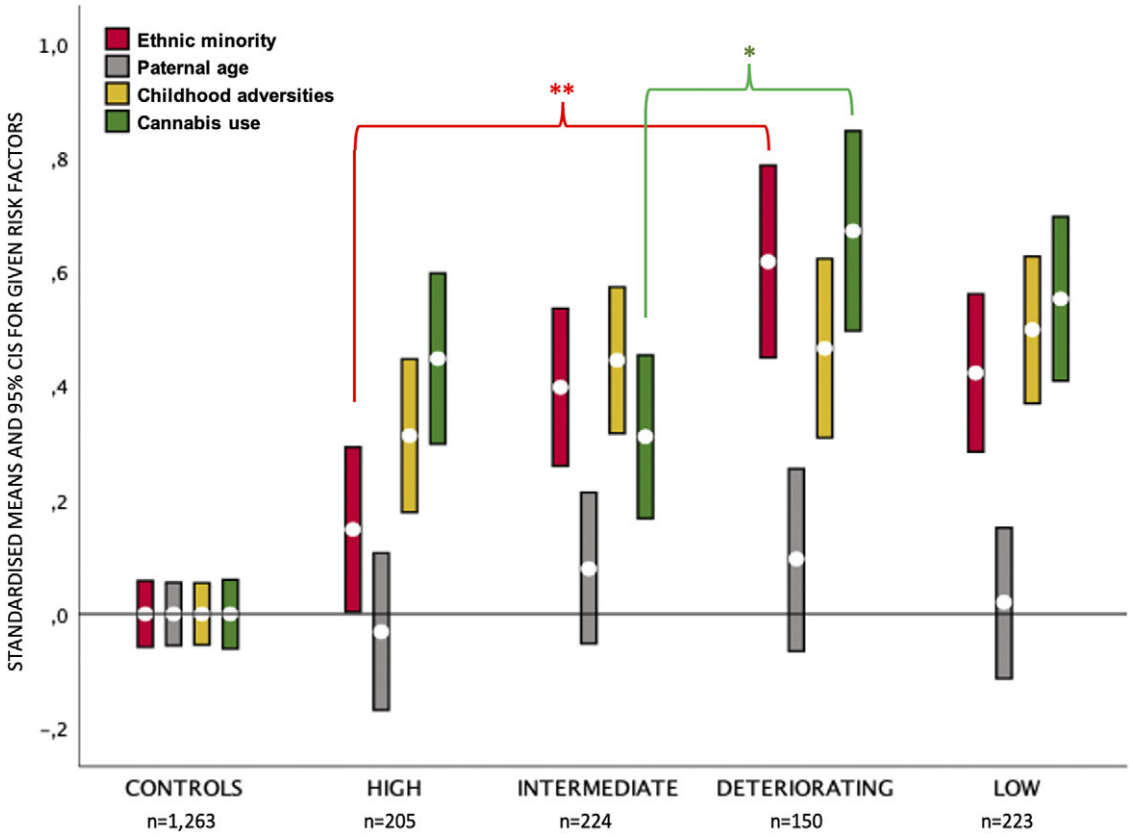


**Figure 2.** Ethnic minority, paternal age, childhood adversities, and cannabis use by clusters of FEP and controls.
Legend: The Y axis represents means, standardized around the controls' mean, and 95% CIs in each cluster of patients and controls. HIGH = high-cognitive-functioning; LOW = low-cognitive-functioning. Braces mark significant differences between the deteriorating and the intermediate (green brace) *($mean_{difference}$ = 0.482, 95% CI 0.49 0.91, p = 0.018) and the high-cognitive-functioning cluster (red brace) **($mean_{difference}$ = 0.771, 95% CI 0.24 1.29, p = 0.0003).

also highlighting between-cluster differences. Winter birth (p = 0.240) and hearing impairment (p = 0.431) were insignificant (Supplementary Table 10).

## Discussion

### *Main findings*

This study showed for the first time that individuals who were highly exposed to environmental risk factors were more likely to have lower cognitive functioning at the onset of psychosis and, more importantly, to present with deteriorating premorbid functioning. This feature distinguished them from those in a cluster with high-cognitive-functioning.

Moreover, the deteriorating cluster had a higher prevalence of ethnic minority membership and cannabis use than the other clusters. This report, coupled with the previous finding of its lower polygenic predisposition to psychosis (Ferraro et al., 2023), could suggest the role of the environment in leading to premorbid social and cognitive deterioration in psychosis.

Lastly, among a range of socio-environmental risk factors, childhood adversities, cannabis use, and ethnic minority membership were the most significant in distinguishing patients from the control group, highlighting their importance when collecting information on environmental risk for psychosis.

### *The role and significance of the ERS*

Our findings showed that the high-cognitive-functioning cluster had the lowest premorbid exposure to environmental risk factors, followed by the intermediate and low-cognitive-functioning clusters with increasingly higher exposure.

Overall, we observed an inverse pattern of environmental versus polygenetic predisposition to psychosis (Ferraro et al., 2023) – when the effect of one increased, the other decreased – more marked in the deteriorating group. This could suggest that lower environmental exposure is required when genetic factors are higher and vice versa in the predisposition to psychosis, in accordance with the liability threshold model (Supplementary Figure 4).

We have already discussed the unique characteristics of patients in the deteriorating cluster, where environmental exposure was the highest. Interestingly, the IQ_PRS (Ferraro et al., 2023) in the deteriorating cluster was slightly higher than that of the intermediate cluster, having identical IQ (Supplementary Figure 4), so their current IQ was presumably lower than expected, also based on their optimal adjustment in childhood and later decline (Stefanatou et al., 2018). These findings suggested the potential role of environmental risk factors in the loss of cognitive and social functioning in the premorbid period.

Although we did not find segregation of any diagnoses into specific clusters, the deteriorating group had the highest depressive and negative symptoms among clusters and more than one AP

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prescription (Supplementary Figure 1 and Supplementary Table 2). While this could have lowered IQ scores at the onset, the relationship between symptomatology and the deterioration of functioning between 12 and 16 years is more likely to be in the opposite direction, losing abilities before symptom presentation (Fusar-Poli et al., 2013). In contrast, the other clusters, particularly the high-cognitive-functioning cluster, presented with more genetically related functioning and a more favourable environmental context in childhood, constituted by higher socio-economic status of parents and higher education as compared with the other clusters (Supplementary Table 1) (see also Ferraro et al., 2023).

The median IQ of patients with low-cognitive-functioning (less than 74) may have included some individuals with neurodevelopmental impairment (Ferraro et al., 2023; Howes & Murray, 2014; Murray, O'Callaghan, Castle, & Lewis, 1992). Additionally, the previous study revealed that the low-cognitive-functioning group was the most disadvantaged in terms of polygenic liability to schizophrenia, bipolar and depressive disorder, and predisposition to lower IQ (Ferraro et al., 2023). Altogether, environmental risk factors could have cumulatively and circularly contributed, with this cognitively disadvantaged profile, to the onset of psychosis (Liu et al., 2021; Sideli et al., 2015).

It could be that individuals with lower cognitive and social functioning or with a genetic predisposition to psychiatric disorders were more likely to encounter environmental risks, like a lower socio-economic status or moving to a more disadvantaged neighbourhood (Lund et al., 2018; Maxwell, Coleman, Breen, & Vassos, 2021). However, previous findings excluded a causal relationship between lower cognitive and social functioning on cannabis use (Ferraro et al., 2013, 2016), childhood adversities (Sideli et al., 2022), and migration (Xu et al., 2018).

Finally, the weighted sum of risk factors could discriminate to some degree between clusters of patients and community controls, explaining 11% of the FEP clusters/control variance, which was satisfactory compared to the 7% estimated in modelling an individual's risk of schizophrenia using the ERS (Gillett, Vassos, & Lewis, 2018). Moreover, it was higher than the 7.9% detected in studies looking at multiple polygenic risk scores and cognitive clusters (Dickinson et al., 2020; Ferraro et al., 2023).

On the other hand, the ERS explained only 2.2% of the between-patients variance, somewhat similar to the 2.7% explained by the PRSs in the cited study (Ferraro et al., 2023). This finding is unsurprising, given that both scores were designed to differentiate between patients diagnosed with psychosis and population controls (Gillett et al., 2018).

### *The putative role of single exposures*

Looking at single exposures, we confirmed the role of childhood adversities (Varese et al., 2012) and cannabis use (Di Forti et al., 2019) in distinguishing all clusters of patients from controls, especially the deteriorating and the low-cognitive-functioning group, both having a good-to-normal premorbid social functioning. This last finding is in line with previous observations suggesting that better premorbid social functioning in patients with a history of cannabis use may have contributed to their likelihood to begin using cannabis (Ferraro et al., 2020).

Ethnic minority membership also distinguished patients (Tarricone et al., 2016) from controls, apart from the high-cognitive-functioning cluster. It is possible that being part of the ethnic majority may be associated with socioeconomic and linguistic benefits in the high-cognitive-functioning cluster, resulting in better IQ. In contrast, minorities and migrants often have shown lower cognitive functioning due to complex mechanisms (Xu et al., 2018). On the other hand, we could not exclude a power limitation in this lack of difference.

Interestingly, patients whose adjustment deteriorated in early adolescence showed higher exposition to cannabis use than the intermediate cluster, and they were also more likely to belong to an ethnic minority, distinguishing this group from the high-cognitive-functioning cluster. One study reported that ethnic minorities are more likely to use cannabis and other drugs (Montgomery, Dixon, & Mantey, 2022). However, we did not find this association in the EUGEI sample (Jongsma et al., 2021). Instead, it has been hypothesized that cannabis could contribute to biases due to abnormal cognitive aberrations in the salience attribution (Wijayendran, O'Neill, & Bhattacharyya, 2018), independent of being part of an ethnic minority (Anglin, Tikhonov, Tayler, & DeVylder, 2021). Indeed, we previously observed a higher probability of belonging to this cluster for patients with a premorbid frequent use of high-potency cannabis (Ferraro et al., 2023). This type of cannabis has a higher addictive, dissociative (Ricci et al., 2021, 2023), psychotic-leading (Di Forti et al., 2019; Quattrone et al., 2020, 2021) and detrimental potential on cognition and premorbid adjustment than low-potency varieties (Meier et al., 2012; Mokrysz et al., 2016). Looking at this finding, we speculated that cannabis use was likely to have played an independent and strategic role in promoting premorbid social and cognitive deterioration and possibly IQ decline in this cluster of patients (Stefanatou et al., 2018).

Finally, paternal age did not distinguish between patients and controls, as observed in the EU-GEI case-control study by Jongsma and colleagues (Jongsma et al., 2021), possibly because of power limitations, as very few subjects had an old father.

The validation analysis via the Exposome was in line with findings obtained with the ERS. Cannabis use and childhood adversities accounted for a high proportion of the 9.2% of the variance explained by this score in our sample, while hearing impairment and winter births gave insignificant results. The role of winter birth has been challenged in previous studies (Demler, 2011; Muntjewerff et al., 2011) and the original construction of the Exposome (Pries et al., 2019). Similarly to paternal age, hearing impairment irrelevance could have suffered from the small number of affected participants and the impossibility of selecting in our sample the severe forms of hearing impairment among those reported, which are more relevant in case/control samples (Shoham et al., 2020).

If we conceptualize environmental risk factors along a temporal line (Howes & Murray, 2014; Lipner et al., 2022; Tandon et al., 2024), hearing impairment, winter birth, and paternal age had an impact very early in life, emerging from an interplay between genetic and perinatal effects, but able to explain a tiny percentage of caseness in psychosis. Thus, detecting their effect would require more extensive meta-analytic studies (Blazer & Tucci, 2019; Coury et al., 2023; Janecka et al., 2017). Childhood adversities, which occurred at a second developmental stage, have been considered more generally predisposing to a vulnerability profile of psychopathology and emotional dysregulation than to cognitive deterioration (Arango et al., 2018; Pries et al., 2020; Sideli et al., 2022; van Os et al., 2017), thus producing an impact on the risk of psychosis but not in differentiating cognitive profiles. This was also true when we looked at the exposome, which considered the cumulative effect of childhood adversities (Pries et al., 2019). At a later stage, we could pose cannabis use, a risk factor specific for psychosis when used in adolescence (Di Forti et al., 2019), as was migration, which had its

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most significant impact as a risk factor for psychosis during adolescence (Andleeb et al., 2024). These risk factors could have favoured psychosis transition also throughout a detrimental effect on subjects' acculturation and social functioning (Andleeb et al., 2024; Castellanos-Ryan et al., 2017).

In summary, among a wide range of risk factors, childhood adversities, ethnic minority status, and cannabis use were the most important predictors and, when used separately, explained more variance (almost 14%) than the model with the risk summed in the ERS (11%), also due to the summative nature of the score (Vassos et al., 2020). This evidence indicated that it may be necessary to collect information on childhood abuse, ethnic minority membership, and cannabis use, at minimum, when no other information is available, to study environmental risk factors in psychosis.

## Limitations

This study used a self-report approach for assessing premorbid characteristics and environmental exposures. Therefore, it was limited by the inability to distinguish between presumed causes and their possible effects. However, we used psychometrically robust measures, completed with input from at least one corroborative source of information, such as family members, clinical notes, and other clinicians (Ferraro et al., 2020), and this should have minimized the recall bias due to the retrospective method. A subsample validation analysis confirmed the reliability of patients' self-reports on cannabis use, and the potency measure was supported by information provided in additional national reports (Di Forti et al., 2019). We did not have data on obstetric complications or urbanicity at an individual level, but only on country of birth, whose non-correspondence with the country of residence matched a migration state (with a prevalence of 22.7% in our sample) (Tarricone et al., 2021). Nonetheless, we adjusted by urbanization at a site level.

Our sample's multicultural characteristics and the unique methodology used by introducing PAS with IQ measures could restrict the replicability of our findings in non-European and more homogeneous samples in which specific characteristics can more robustly emerge. In comparing the ERS and PRS among patients' clusters and controls, the restriction of ancestry to solely white Europeans limited the ability to perform gene-environment interaction analyses. Despite the limited representation of non-European ancestry in the current sample, it is doubtful that this alone could account for the difference in environmental and genetic influences observed in the declining cluster. This is because the ERS was still highest in this group even when considering only subjects with European ancestry (Supplementary Figure 4). We recognize that other models could have been used to compare different class models, such as latent variable mixture modelling (Berlin, Williams, & Parra, 2014). Our study was a follow-up to an original study, this last having replication study characteristics (Dickinson et al., 2020; Ferraro et al., 2023). Thus, we decided to maintain the same methodology to allow comparability.

## Conclusions

The exposure to environmental risk factors partly reflected the cognitive performance at the onset of psychosis in discrete clusters of patients characterized by different patterns of premorbid functioning. It was highest among patients whose social and academic functioning deteriorated from average in the premorbid period. We have previously shown that polygenic predisposition to psychosis is unlikely related to this difference in functioning from childhood to adolescence (Ferraro et al., 2023). Thus, although genetic predisposition to schizophrenia increased the risk in all the clusters, environmental risks, which are potentially modifiable, had a higher effect on the deteriorating group.

If correct, this could have potential clinical relevance because modifying them may have an essential role in the prevention of psychosis or at least in improving the premorbid function. It is known that patients with better premorbid adjustment presented a better prognosis (Amoretti et al., 2022), and discontinuing cannabis use, for example, predicted a better long-term outcome after onset (Schoeler et al., 2016).

Additionally, at the onset of psychosis, patients in the deteriorating cluster had an intermediate IQ, similar to a group with consistently intermediate functioning in the premorbid period. Hence, despite having different premorbid characteristics, they could be mistaken for being part of the most common and undifferentiated intermediate group described in the literature (Green et al., 2020). Therefore, accurately characterizing the trajectory of each patient and identifying associated environmental risk factors may be beneficial in tailoring treatment, psychoeducational, and preventive strategies.

**Supplementary material.** The supplementary material for this article can be found at http://doi.org/10.1017/S0033291724003507.

**Acknowledgments.** Special acknowledgment to all the patients and the EU-GEI team. This study represents independent research part-funded by the NIHR Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. The authors report no financial relationships with commercial interests.

**Author contribution.** Diego Quattrone and Evangelos Vassos have equally contributed to the supervision of the work and share the last authorship.

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