European Neuropsychopharmacology 94 (2025) 4–15

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

Methylation profile scores of environmental exposures and risk of relapse after a first episode of schizophrenia

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https://doi.org/10.1016/j.euroneuro.2025.02.003
Received 25 November 2024; Received in revised form 3 February 2025; Accepted 6 February 2025
Available online 16 February 2025

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ARTICLE INFO

Keywords:
Schizophrenia
Relapse
Epigenetics
Early stressful life events
DNA methylation
Methylation profile scores

ABSTRACT

Both genetic and environmental factors have been found to play a significant role in psychosis relapse, either independently or through their synergistic interaction. Recently, DNA methylation (DNAm) has been proposed through the calculation of methylation profile scores (MPS). The aim of the present study is to evaluate the association of MPS as a surrogate marker of the biological impact of early stressful life events (including stressful intrauterine conditions and obstetric complications, childhood adversity and toxic habits), with the risk of schizophrenia (SCZ) relapse. 91 participants from a cohort of first-episode schizophrenia (FES) patients with less than five years of evolution were classified as non-relapse (patients who had not experienced a relapse after 3 years of enrollment) or relapse (patients who relapsed during the 3-year follow-up). As inclusion criteria, patients fulfilled Andreasen's criteria of symptomatic remission. Genome-wide DNA methylation (DNAm) was profiled and fourteen MPS reflecting environmental exposure were constructed including both early stressful life events (including stressful intrauterine conditions and delivery issues, childhood adversity) and toxic habits. Increased levels of MPS reflecting gestational diabetes ($p = 0.009$), hypertensive disorders during pregnancy ($p = 0.004$), pre-eclampsia ($p = 0.049$), early preterm birth ($p = 0.030$), childhood adversity abuse ($p = 0.021$) and all childhood adversity ($p = 0.030$) were significantly associated with an increased risk of relapse. Our study suggests that changes in specific methylation patterns may represent one of the biological mechanisms linking early stressful life events to an increased risk of relapse.

1. Introduction

The clinical course of schizophrenia (SCZ) is often characterized by recurrent relapses (Emsley et al., 2013). After a first psychosis episode, approximately 30 % of individuals experience a relapse within a year (Brown et al., 2020), and up to 50 % within three years (Bioque et al., 2022). These relapses are associated with worse clinical and psychosocial outcomes (Keepers et al., 2020; Takeuchi et al., 2019), which increase the personal, social and financial burden of the disease (Pennington and McCrone, 2017; Pilon et al., 2021).

Both genetic and environmental factors have been found to play a significant role in psychosis relapse, either independently or through their synergistic interaction (Almuqrin et al., 2023; Mizrahi, 2016). Recent studies have demonstrated that the polygenic basis of neurocognitive function is associated with the risk of relapse following a first episode of schizophrenia (Segura et al., 2023). Environmental factors also play a crucial role, with stressful life events repeatedly linked to an increased risk of relapse (Leff et al., 1983), particularly when they occur after the onset of psychosis (Almuqrin et al., 2023; Bhattacharyya et al., 2023; Colizzi et al., 2023; Martland et al., 2020). Early-life stressful events, such as childhood adversity, have also been related to poorer outcomes (Peralta et al., 2024; Peralta et al., 2022) and are suggested as potential risk factors for relapse (Ottesen et al., 2023). Similarly, obstetric complications, which are widely recognized as risk factors for psychosis, have been linked to more severe psychopathology (Sagué-Vilavella et al., 2022), poor cognitive functions (Amoretti et al., 2022a), brain structural abnormalities (Costas-Carrera et al., 2020) and metabolic abnormalities as epiphenomena (Garcia-Rizo and Bitanihirwe, 2024). However, their effect on the risk of relapse is not fully elucidated (Robinson et al., 1999).

Retrospective assessments of early-life adversities, particularly obstetric complications, present significant methodological challenges. Most patients may be unaware of obstetric complications unless the events were severe, which leads to a potential recall bias (Borrajo et al., 2011). Additionally, reports of childhood adversities are subjective and influenced by the sociocultural background, timing, duration and personal impact of each type of adversity (Maj et al., 2021). While instruments such as the Lewis-Murray checklist for obstetric complications or the Childhood Trauma Questionnaire (CTQ) are reliable tools for retrospectively identifying the presence of these adversities, they do not accurately measure their severity or biological impact.

Recently, DNA methylation (DNAm), the most studied epigenetic mechanism, has been proposed as a surrogate measurement of exposure to environmental factors such as stressful life events (Alameda et al., 2023). DNAm regulates gene expression and, although usually stable and responsible for the lifelong maintenance of cellular identity, it is also a dynamic process that changes with age and is susceptible to environmental inputs (Schrott et al., 2022). Therefore, DNAm has been proposed as a mechanism by which early adversities influence biological processes through the modulation of gene expression, which potentially affects mental health (Alameda et al., 2022; Jaenisch and Bird, 2003). The advancement of array technologies has enabled the proliferation of methylation-wide association studies (MWAS) for numerous environmental exposures and health conditions. Publicly available MWAS data can be used as a discovery sample to calculate methylation profile scores (MPS) using similar approaches to those used for the construction of polygenic risk scores (PRS) (Nabais et al., 2023). These MPS can be tested in independent datasets to examine their relationship with a wide range of measured variables. The first generation of methylation scores were trained on methylation sites associated with chronological age, known as "epigenetic clocks". A second generation of these scores characterized methylation profiles associated with aging-related phenotypes, including physiological functioning, health, mortality and telomere length (Raffington, 2024). Recent studies have utilized MWAS data to estimate MPS for a wide range of traits, including smoking, inflammatory protein levels, body mass index, cognition, and pathologies such as schizophrenia, major depressive disorder, Parkinson's disease and amyotrophic lateral sclerosis (Nabais et al., 2023).

The aim of the present study is to evaluate the association of MPS as a surrogate marker of the biological impact of environmental exposures including both early stressful life events (including stressful intrauterine conditions and delivery issues, childhood adversity) and toxic habits, with the risk of schizophrenia (SCZ) relapse over a three-year follow-up period in a cohort of first-episode schizophrenia (FES) patients with less than five years of evolution. We hypothesize that relapse will be associated with higher exposure to stressful life events in the intrauterine environment, during early life stages and induced by drug use.

[#] Both authors contributed equally to this work.

2. Experimental procedures

2.1. Study design

This study is part of the project "Clinical and neurobiological determinants of second episodes of schizophrenia. Longitudinal study of first episode of psychosis" (PI11/00325) (2EPs project) (Bernardo et al., 2021). The 2EPs project is a naturalistic, multicenter, coordinated, multimodal study of patients with a FES of <5 years of evolution. The aim of the biological module is to identify biomarkers that are potentially involved in second episodes (Gassó et al., 2021; Martínez-Pinteño et al., 2022; Rodríguez et al., 2022; Segura et al., 2023; Segura et al., 2022). The 2EPs project rationale and study design can be found elsewhere.

2.2. Subjects

The inclusion criteria for the 2EPs project were a) age between 16 and 40 years at the time of first assessment (baseline visit), b) meeting diagnostic criteria according to DSM-IV-TR for schizophrenia or schizophreniform disorder (American Psychiatric Association, 1994), c) being in remission from the first psychotic episode (which should have occurred within the last 5 years), according to Andreasen's criteria (Andreasen et al., 2005), d) not having relapsed after the first psychotic episode, e) speaking Spanish fluently and f) signing the informed consent form. The exclusion criteria were a) having experienced a traumatic brain injury with loss of consciousness, b) presenting intellectual disability, with an intelligence quotient (IQ) <70 and presenting malfunctioning and problems with adaptive processes, and/or c) presenting somatic pathology with mental repercussion.

Ninety-one patients completed the study and participated in the biological module providing a biological sample for DNA methylation analysis at baseline.

Informed consent was obtained from all participants. For children under the age of 18 years old, parents or legal guardians provided written informed consent before the study started, and patients agreed to participate. When requested, participants in the study were given a report on their test results. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human subjects/patients were approved by the Hospital clinical research ethic committee (HCB 2008/4232).

2.3. Clinical assessment

At baseline, demographic data, toxic habits and the complete personal and family history were collected in a systematic, self-devised interview. Diagnoses were determined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria (American Psychiatric Association, 1994), using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (Williams et al., 1992) or the Kiddie-Schedule for Affective Disorders & Schizophrenia (SADS) (Kaufman et al., 1997), depending on age.

Clinical symptomatology was assessed using the Spanish validated version of the Positive and Negative Syndrome Scale (PANSS) (Peralta and Cuesta, 1994) and the Marder PANSS Factor Scores (Marder et al., 1997) were constructed.

Pharmacological treatment was recorded during all visits. The prescribed daily doses of antipsychotics were converted to chlorpromazine equivalent daily dose (CEED) (Leucht et al., 2016).

2.4. Cognitive assessment

The neuropsychological battery, assessed at baseline, included: the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997); the California Verbal Learning Test (CVLT) (Delis et al., 1987); the Continuous Performance Test–II (CPT-II) (Conners et al., 2003), version 5, corrected by age and educational level; the Trail Making Test (Form A) (TMT-A) (Reitan and Wolfson, 1995); the Tower of London (TOL) (Shallice, 1982); the Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict and Groninger, 1995); and semantic (animal naming) (Peña-Casanova, 1991) and phonemic (F-A-S) fluency tests (Loonstra et al., 2001). A principal component analysis (PCA) was performed between neuropsychological battery tests to identify the seven cognitive domains: verbal memory, visual memory, executive function, sustained attention, working memory, verbal fluency and processing speed (see Supplementary Table S1). Higher scores corresponded to better performance in all cognitive domains except for sustained attention.

To assess cognitive reserve (CR), the three most commonly proposed proxy indicators of CR were used (Amoretti et al., 2022b; Amoretti et al., 2016; González-Ortega et al., 2020): (1) the estimated premorbid IQ was calculated using the vocabulary subtest of WAIS-III (Wechsler, 1997) (Wechsler, 1997); (2) education was assessed considering the degree of schooling attained and passed by subject; and (3) lifetime participation in leisure, social and physical activities was assessed using the Premorbid Adjustment Scale (PAS) (scholastic performance) (Cannon-Spoor et al., 1982) and the Functioning Assessment Short Test (FAST) scale (Rosa et al., 2007), which allowed us to assess specific life-domains such as interpersonal relationships and leisure time.

2.5. Relapse definition

The main outcome variables were relapse rates. Accordingly, the participants in the study were classified as non-relapse (patients who had not experienced a relapse after 3 years of enrollment) or relapse (patients who relapsed during the 3-year follow-up). As inclusion criteria, patients fulfilled Andreasen's criteria of symptomatic remission to enter the study, as they were considered at risk of relapse over the 3-year period (Andreasen et al., 2005).

Relapse was defined as a failure to meet remission criteria for at least one week of the follow-up, scoring 4 or more on any of the 8 items of the PANSS used to define these criteria: delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect, social withdrawal and lack of spontaneity. Hospitalization was also reported in every follow-up visit and considered a relapse only if related to SCZ symptoms (and not to other causes). Follow-up visits to detect relapses were scheduled every 3 months. Information from the entire period between visits was collected, and the patients, family members or caregivers, and clinical teams in charge of the clinical follow-up could notify the research team of the possible relapse of a participant.

2.6. Biological samples

Blood samples were collected in EDTA tubes (K2EDTA BD Vacutainer EDTA tubes; Becton Dickinson, Franklin Lakes, New Jersey, USA), and genomic DNA was extracted with the MagNA Pure LC DNA Isolation Kit III and a MagNA Pure LC system (Roche Diagnostics GmbH, Mannheim, Germany). DNA concentration and quality were measured spectrophotometrically using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Epsom, Surrey, UK).

2.7. Methylation data collection

DNA methylation β-values were obtained at the Centro Nacional de Genotipado (CEGEN-PRB3-ISCIII) using the Illumina Infinium MethylationEPIC v1 BeadChip Kit. Raw intensity data (.IDAT) files were generated and parallel bioinformatics analyses were conducted in-house using the Chip Analysis Methylation Pipeline (ChAMP) Bioconductor package (Tian et al., 2017). The raw .IDAT files were used to load the data into the R environment (R Core Team, 2023) with the champ.

import function, which also enabled the undertaking of probe QC and removal steps. Probes with weak signals ($p < 0.010$), cross-reactive probes, non-CpG probes, probes with <3 beads in at least 5 % of the samples per probe, probes that bind to SNP sites and sex chromosomes were considered problematic for the accurate detection of downstream methylation and were therefore removed with the champ.filter function. After removing them, 735,248 probes remained for downstream analysis. β-values were normalized using the champ.norm function, specifically with the beta-mixture quantile method (BMIQ function). Next, the singular value decomposition (SVD) method was performed with champ.SVD to assess the amount and significance of the technical batch components in our dataset. Using the champ.runCombat function, ComBat algorithms were applied to correct for slides and arrays (significant components detected by the SVD method).

2.8. Methylation profile score calculation

MWAS were selected for the construction of fourteen MPS reflecting environmental exposure: stressful intrauterine conditions and obstetric complications (maternal age at conception, pre-pregnancy overweight/obesity, maternal smoking during pregnancy, gestational diabetes, hypertensive disorders of pregnancy, pre-eclampsia, birthweight, early preterm birth), childhood adversity (abuse, neglect, all) and toxic habits (current tobacco smoking, lifetime tobacco smoking, lifetime cannabis use) (Alameda et al., 2023; Antoun et al., 2020; Fang et al., 2024; Joehanes et al., 2016; Joubert et al., 2016; Kazmi et al., 2019; Knijnenburg et al., 2019; Küpers et al., 2019; Markunas et al., 2016; Sharp et al., 2017). For their construction, methylation sites that reported $p \leq 0.050$ in the MWAS summary statistics and passed the quality control after quantification were used. The individual MPS were calculated as the sum of all methylation site values, each weighted by the estimated effect associated with environmental exposure:

$$MPS_i = \sum_j^{m_{MPS}} \widehat{b_j} \cdot C_p G_{ij}$$

where

- i represents the subject,
- j represents the methylation probe,
- m_{MPS} represents the total number of probes for the MPS,
- $\widehat{b_j}$ represents the estimated effect size for probe *j*,
- CpG_{ij} represents the methylation value of the probe *j* in the individual *i*.

The code for computing MPS using the described method was developed in our research group and is accessible via the following public repository on GitHub: https://github.com/agonse/methylscore. MPS were standardized by subtracting the mean and dividing by the standard deviation (SD) (Table 1 provides further details on MPS).

2.9. Statistical analysis

Means and standard deviations were computed for continuous variables. The normality of these variables was tested using the Kolmogorov–Smirnov and Shapiro–Wilk tests, and the equality of the variance between groups (relapse vs. non-relapse) was assessed using Levene's test. Between-group differences in continuous variables were analyzed using either Student's *t*-test or Mann–Whitney U-test, as appropriate. Spearman's rank correlation coefficients and their significance were computed to assess the monotonic relationship between MPS and between MPS and clinical and cognitive variables.

Multivariate logistic regression models were fitted to estimate the association between relapse status and each MPS. Odds ratios (ORs) were adjusted for putative confounders (age, sex, tobacco consumption at baseline and the PRS for educational attainment), with 95 % confidence intervals reported. Model assessment and comparison were conducted using the Akaike information criterion (AIC) and deviances were reported. Age, sex and tobacco consumption were selected as covariates in the models due to its potential impact on methylation profiles and computed MPS. The PRS of educational attainment was included in the model as it was significantly associated with the risk of relapse in our previous study (Segura et al., 2023).

Time-to-event analyses were performed to assess the time until the endpoint among MPS groups. The endpoint considered was relapse incidence (RI), defined as the time from the date of patient inclusion in the study to the occurrence of relapse. MPS groups were defined with the cut-off point that maximized the statistic of the Log-rank test and dichotomized into high and low exposure groups. Cumulative probabilities of RI were estimated by the Kaplan–Meier method and groups were compared with the Log-rank test. The Cox proportional-hazards model was used to estimate the hazard ratio (HR) and its 95 % CI. The multivariable Cox model was used to adjust for putative confounders (age, sex, tobacco consumption at baseline and the PRS for educational attainment). The proportional hazards assumption was analyzed through the Schoenfeld test and Schoenfeld residuals plots. The median cumulative incidence, defined as the time at which the probability of relapse reaches 0.5, was assessed for each group.

All the analyses were performed in statistical software R (R version 4.3.2) (R Core Team, 2023).

Table 1
Detailed information of the selected MWAS used to construct the MPS.

Type	Phenotype	Sample Size[1]	CpG[2]	Reference
Stressful intrauterine conditions and obstetric complications	Maternal age at conception	890	9	Markunas et al., 2016
	Pre-pregnancy overweight/obesity	2855/7666	4037	Sharp et al., 2017
	Maternal smoking pregnancy	1646/6685	845	Joubert et al., 2016
	Gestational diabetes, maternal BMI-adjusted (yes/no)	159/557	277	Antoun et al., 2020
	Hypertensive disorders of pregnancy (yes/no)	476/5242	1075	Kazmi et al., 2019
	Pre-eclamplsia (yes/no)	135/2219	542	Kazmi et al., 2019
	Birthweight	8825	50,879	Küpers et al., 2019
	Early preterm birth (yes/no)	117/791	273	Knijnenburg et al., 2019
Childhood adversity	Abuse	883	36	Alameda et al., 2023
	Neglect	883	21	Alameda et al., 2023
	All	883	36	Alameda et al., 2023
Toxic habits	Current tobacco smoking (yes/no)	6518/6956	16,015	Joehanes et al., 2016
	Lifetime tobacco smoking (yes/no)	2433/6956	2203	Joehanes et al., 2016
	Lifetime cannabis use (tobacco adjusted) (yes/no)	4152/5284	659	Fang et al., 2024

[1] Sample size of the MWAS used as discovery sample.
[2] CpGs significantly associated ($p < 0,05$) with the phenotype in the discovery sample and used to create the MPS.

3. Results

Table 2 shows the sociodemographic features, substance use and

Table 2
Demographic, substance use and clinical data at baseline of the 91 participants in the study. Group differences between relapse and non-relapse groups were assessed.

	Non-relapse	Relapse	Statistics
N	49	42	
Age (years), mean±SD	26.6 ± 5.8	25.9 ± 5.9	$t_{89} = 0.60$ $p = 0.545$
Age at first diagnosis (years), mean±SD	24.9 ± 5.6	24.7 ± 5.8	$t_{88} = 0.19$ $p = 0.851$
Gender, male, N (%)	38 (77.6)	27 (64.3)	$X_1^2 = 1.95$ $p = 0.163$
Ethnicity, Caucasian, N (%)	44 (89.8)	36 (85.7)	$X_1^2 = 1.81$ $p = 0.771$
Cannabis use, N (%)	5 (10.4)	8 (19.0)	$X_1^2 = 1.35$ $p = 0.245$
Tobacco use, N (%)	24 (49.0)	24 (57.1)	$X_1^2 = 0.60$ $p = 0.437$
Alcohol use, N (%)	18 (36.7)	21 (50.0)	$X_1^2 = 1.65$ $p = 0.202$
Antipsychotic CEDD, mean±SD	254.8 ± 228.9	302.2 ± 305.8	$t_{89} = -0.84$ $p = 0.401$
Antipsychotic			$X_7^2 = 1.95$ $p = 0.165$
Amusulpride, N (%)	0 (0)	2 (4.9)	
Aripiprazole, N (%)	14 (28.6)	12 (29.3)	
Clozapine, N (%)	6 (12.2)	2 (4.9)	
Olanzapine, N (%)	5 (10.2)	8 (19.5)	
Paliperidone, N (%)	9 (18.4)	5 (12.2)	
Risperidone, N (%)	4 (8.2)	7 (17.1)	
Zipsasidone, N (%)	0 (0)	1 (2.4)	
No Antipsychotic, N (%)	11 (22.4)	4 (9.8)	
Symptomatology			
PANSS Positive, mean±SD	9.3 ± 2.8	9.3 ± 3.0	$t_{89} = -0.11$ $p = 0.991$
PANSS Negative, mean±SD	14.0 ± 5.0	12.9 ± 5.4	$t_{89} = 0.99$ $p = 0.323$
PANSS General, mean±SD	24.4 ± 6.9	23.5 ± 6.7	$t_{89} = 0.64$ $p = 0.521$
PANSS Total, mean±SD	47,8 ± 13.3	45.8 ± 12.9	$t_{89} = -0.73$ $p = 0.469$
Marder Positive symptoms, mean±SD	11.6 ± 3.5	11.5 ± 3.9	$t_{89} = 0.15$ $p = 0.882$
Marder Negative symptoms, mean±SD	14.2 ± 5.1	13.1 ± 5.6	$t_{89} = 0.97$ $p = 0.333$
Cognitive domains[1]			
Working memory, mean±SD	77.8 ± 15.1	73.9 ± 14.2	$t_{88} = 1.24$ $p = 0.216$
Verbal memory, mean±SD	237.7 ± 68.9	221.4 ± 69.9	$t_{86} = 1.07$ $p = 0.286$
Executive function, mean±SD	224.2 ± 34.5	228.5 ± 33.4	$t_{75} = -0.47$ $p = 0.640$
Visual memory, mean±SD	88.4 ± 27.3	82.5 ± 23.7	$t_{87} = 1.06$ $p = 0.289$
Verbal fluency, mean±SD	65.3 ± 15.2	62.0 ± 9.9	$t_{87} = 1.18$ $p = 0.238$
Sustained attention, mean±SD	125.2 ± 22.6	135.3 ± 32.6	$t_{83} = -1.67$ $p = 0.090$
Processing speed, mean±SD	68.1 ± 19.2	62.3 ± 17.8	$t_{88} = 1.48$ $p = 0.142$
Cognitive reserve, mean±SD	61.4 ± 9.2	60.0 ± 7.6	$t_{83} = 0.79$ $p = 0.430$

CEDD, chlorpromazine equivalent daily dose.
[1] Identified through principal components analysis.

clinical characteristics of the 91 participants at study entry, classified as non-relapse (53.8 %) and relapse (46.2 %). No significant differences in baseline variables were observed between two groups.

In our cohort, MPS exhibited high correlations among themselves (Fig. 1). As expected, MPS reflecting environmental exposure during pregnancy and pregnancy complications were positively correlated with each other and with MPS for early preterm birth, and negatively correlated with MPS for birth weight (except pre-pregnancy overweight). Positive correlations were also observed between MPS measuring pre- and perinatal events and childhood adversity scores. Surprisingly, MPS reflecting lifetime cannabis use showed negative correlations with almost all other MPS.

Increased levels of MPS reflecting gestational diabetes ($\beta = 0.65 \pm 0.25$, OR = 1.97, 95 % CI [1.21–3.41], $p = 0.009$), hypertensive disorders during pregnancy ($\beta = 0.77 \pm 0.27$, OR = 2.22, 95 % CI [1.32–4.04], $p = 0.005$), pre-eclampsia ($\beta = 0.46 \pm 0.24$, OR = 1.67, 95 % CI [1.04–2.81], $p = 0.041$), early preterm birth ($\beta = 0.53 \pm 0.24$, OR = 1.80, 95 % CI [1.12–3.04], $p = 0.020$), childhood adversity abuse ($\beta = 0.60 \pm 0.26$, OR = 1.82, 95 % CI [1.12–3.12], $p = 0.021$) and all childhood adversity ($\beta = 0.51 \pm 0.23$, OR = 1.74, 95 % CI [1.07–2.96], $p = 0.031$) were significantly associated with an increased risk of relapse (Fig. 2).

We performed a survival analysis using the MPS significantly associated with relapse (Fig. 3). For all six MPS, the HR of relapse increased with higher scores and was statistically significant for the high compared to the low groups. Similarly, the Kaplan–Meier cumulative probabilities of RI showed significant differences between the high and low groups for the six MPS according to the Log-rank test (Fig. 3).

As a secondary analysis, we examined the correlation between the significant MPS and symptom severity according to the standard Marder PANSS factors, the seven cognitive domains identified in the PCA analysis and the cognitive reserve. Only the total childhood adversity MPS showed significant correlations with verbal fluency ($r = -0.22$ $p = 0.037$), processing speed ($r = -0.30$ $p = 0.004$) and cognitive reserve ($r = -0.28$ $p = 0.010$) (Supplementary Table 3).

4. Discussion

Our results provide evidence of the involvement of specific epigenetic profiles associated with exposure to environmental exposures in the risk of relapse in a cohort of first-episode schizophrenia patients in remission and with <5 years of evolution, evaluated over a 3-year follow-up period. Patients who relapsed during the follow-up showed higher epigenetic loads from exposure to stressful intrauterine conditions and obstetric complications, and higher scores for childhood adversities, especially those related to abuse. Our study also demonstrates the utility of methylation profile scores (MPS) in studying environmental exposure, reflecting the dose-response relationship between environmental exposure and psychopathological outcomes, with an increasing biological impact of exposure being associated with increasingly poor outcomes (Pries et al., 2022).

In our study, we computed several MPS as surrogate markers of the biological impact of environmental exposures, including: stressful intrauterine conditions and delivery issues, childhood adversity and toxic habits. The computed MPS showed high correlations among themselves, which support the strong interconnection between some of these stressful events. For example, environmental exposures during pregnancy (such as smoking during pregnancy) could lead to pregnancy complications (like gestational diabetes) and birth complications (such as low birthweight or early preterm birth). Similarly, exposure during pregnancy (e.g., maternal smoking) or pregnancy complications (e.g., gestational diabetes) could indicate poor childcare in the future (Davies et al., 2024; Sandsæter et al., 2023).

These correlations could also indicate common biological mechanisms underlying types of early stressful life events. Childhood adversities and intrauterine conditions or delivery issues may have profound and lasting effects on brain development and behavior through several biological mechanisms. These mechanisms involve a complex interplay between genetic, epigenetic, neuroendocrine, immune and neural processes, including hypothalamic-pituitary-adrenal (HPA) axis dysregulation, immune system activation and alterations in various neurotransmitter systems (monoaminergic, GABA and glutamate systems) (Andersen, 2022; Chiang et al., 2024; Lippard and Nemeroff, 2023; Maayan and Maayan, 2024; Simon and Admon, 2023; Volqvartz et al., 2023). These alterations could lead to structural brain changes and

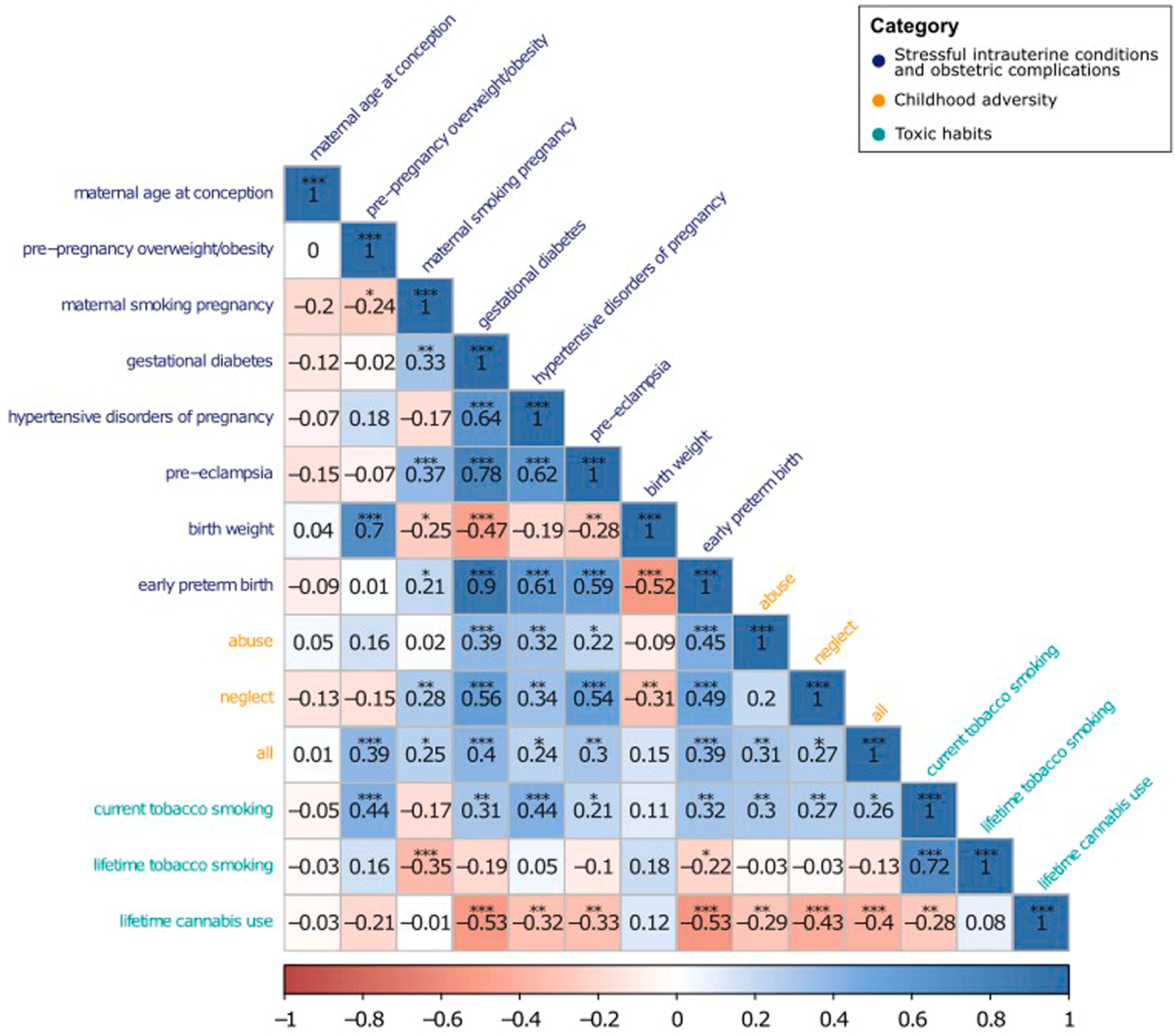

Fig. 1. Relationship between MPS, displayed in a correlation matrix plot together with the significance of the correlation test (significance codes: 0.001 ***, 0.01**, 0.05 *).

contribute to common psychopathological and behavioral issues manifesting later in life. The psychopathological changes may underlie our findings and demonstrate that the biological impact of early-life stressful events, as reflected in DNA methylation, increases the risk of relapse in patients experiencing first-episode psychosis.

Among the common psychopathological effects of early life stressors, cognitive impairment is among the first symptoms to emerge (Amoretti et al., 2022a; Lipner et al., 2023). Multiple cognitive functions at early stages of the disease have been identified as predictive of relapse in psychosis in both short-term and long-term follow-ups (Chen et al., 2005; Hui et al., 2019; Hui et al., 2016; Rund et al., 2016; Verdoux et al., 2000; Wölwer et al., 2008). In our 2EPS cohort, relapse was significantly associated with poor performance in working memory, social cognition and global cognitive score at follow-up (Cuesta et al., 2022). Patients who relapsed and had higher cognitive reserve showed less deterioration in attention, while those with higher cognitive reserve who did not relapse showed better performance in processing speed and visual memory (Sánchez-Torres et al., 2023). Additionally, in the same cohort, we demonstrated that patients with higher PRS for educational attainment showed both a lower risk and a later onset of relapse (Segura et al., 2023). In the present study, MPS reflecting childhood adversity have been negatively correlated with cognitive functions. Therefore, we hypothesize that the higher risk of relapse observed in patients showing epigenetic marks of higher exposure to early life stressful events could be mediated by the impact of these events on cognition. We recently demonstrated in a cohort of first-episode psychosis patients that the cognitive reserve moderated the association between childhood maltreatment and cognition and functioning (Fares-Otero et al., 2024) . Therefore, early interventions focused on improve cognitive reserve in individuals exposed to childhood adversity would be beneficial to improve cognitive and psychosocial outcomes and to prevent relapse. However, considering the exploratory nature of our study and our limited sample size, we cannot rule out that early life stressors could impact in several and independent mechanism beyond cognition and relapse. Further studies using larger cohorts will be needed to elucidate and explore such associations, to establish the hypothetical mediating role of cognition in the association between MPS and the risk of relapse.

Previous findings in the 2EPS cohort indicated that patients who

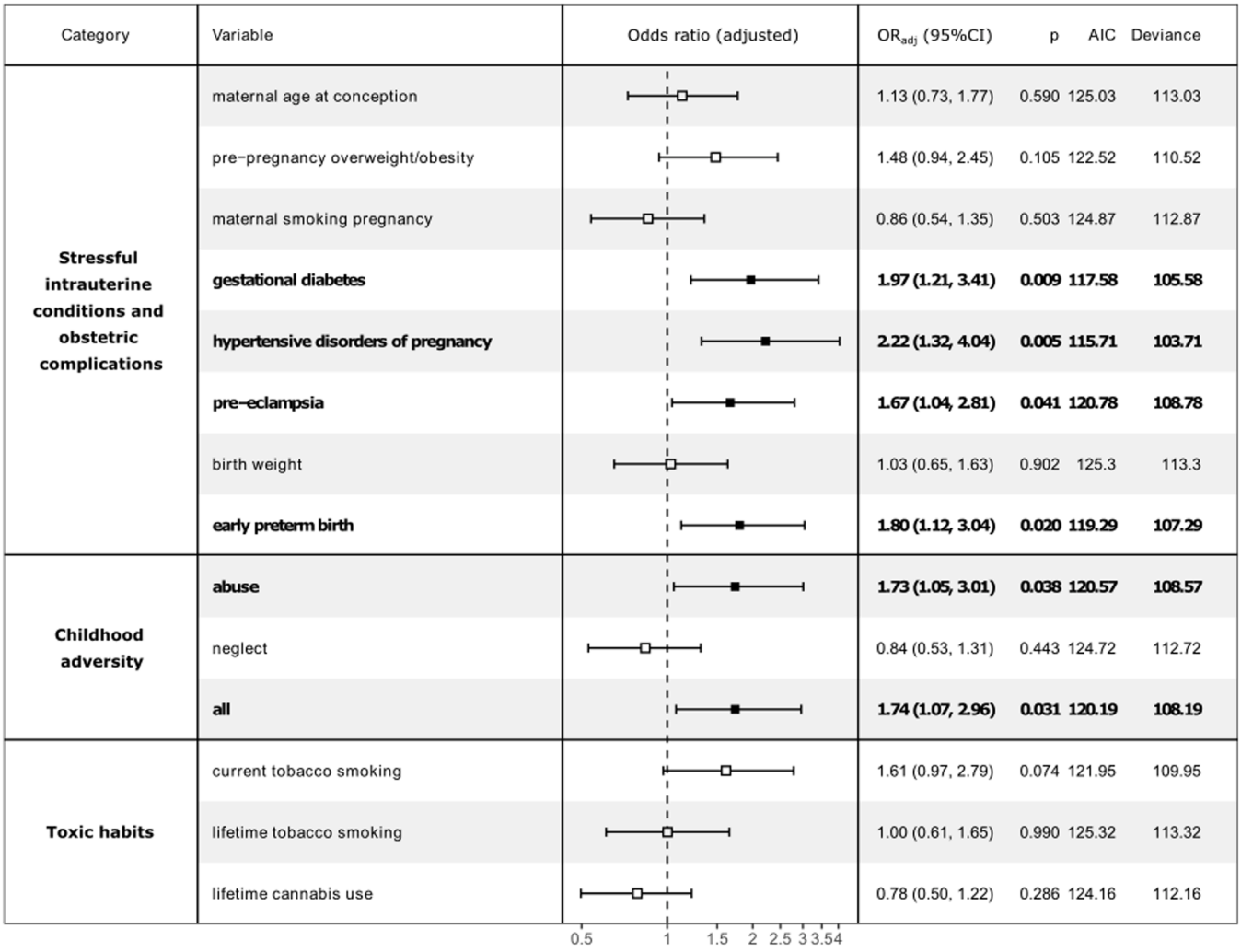

Fig. 2. Multivariate logistic regression models to estimate the association between relapse status and each MPS. Odds ratios (ORs) adjusted by sex, age, tobacco consumption and PRS-EA at baseline with 95 % confidence intervals (CI) were reported in a forest plot. AIC: Akaike information criterion.

relapsed during the follow-up period exhibited accelerated telomere shortening, as measured by methylation data (Segura et al., 2022). Similar to the MPS for childhood adversity, accelerated telomere shortening was associated with poorer cognitive performance and lower cognitive reserve, while telomere length was also linked to more severe negative symptoms. These results suggest that relapse in schizophrenia may be influenced by epigenetic alterations caused by early life stress, potentially leading to biological effects such as premature cellular senescence.

One of the most replicated risk factors for relapse has been cannabis consumption (González-Ortega et al., 2015; González-Pinto et al., 2011). In our study, the MPS measuring lifetime cannabis consumption did not show any association with the risk of relapse. A previous study with our cohort demonstrated that cannabis consumption during follow-up increased the risk of relapse, but not a previous history of cannabis use (Bioque et al., 2022). Since MPS were measured with the sample collected at study entry, the effect of cannabis use during follow-up is not captured by the computed MPS.

These results should be interpreted in light of some limitations. Firstly, the sample size might limit the statistical power to detect a difference between groups. Secondly, we were unable to separately analyze secondary relapse, which is commonly associated with non-adherence, and natural or primary relapse, which represents relapse in the absence of this influencer. Thirdly, due to the naturalistic design, drug treatment was not controlled, and the study participants maintained their usual treatment. Finally, the reference data used for constructing MPS were sourced from publicly available EWAS datasets, which, although unlikely to perfectly match the methylation array, tissue, age, and ethnicity of the study sample, encompass greater sample sizes. Genome-wide epigenetic constructs, particularly MPS, currently lack standardized methods and complementary procedures to optimize the technique, such as the imputation of CpG methylation sites. In this study, we implemented a thresholding method for CpG selection, building upon previous studies (Kiltschewskij et al., 2024; Nabais et al., 2023) and publicly shared the code for replication and refinement (Segura, 2025). Besides these limitations, the strength of this study lies in the inclusion of a consistent well-characterized first-episode schizophrenia patient sample in remission due to its naturalistic and longitudinal design.

In conclusion, our study suggests that changes in specific methylation patterns may represent one of the biological mechanisms linking early stressful life events to an increased risk of relapse. MPS offer a promising solution to overcome certain limitations of retrospective assessments by allowing the quantification of the long-lasting biological repercussions of environmental inputs in peripheral tissues. The future integration of epigenetic data into prediction models (Yousefi et al., 2022) in personalized psychiatry could enhance the detection of individuals at high risk of relapse.

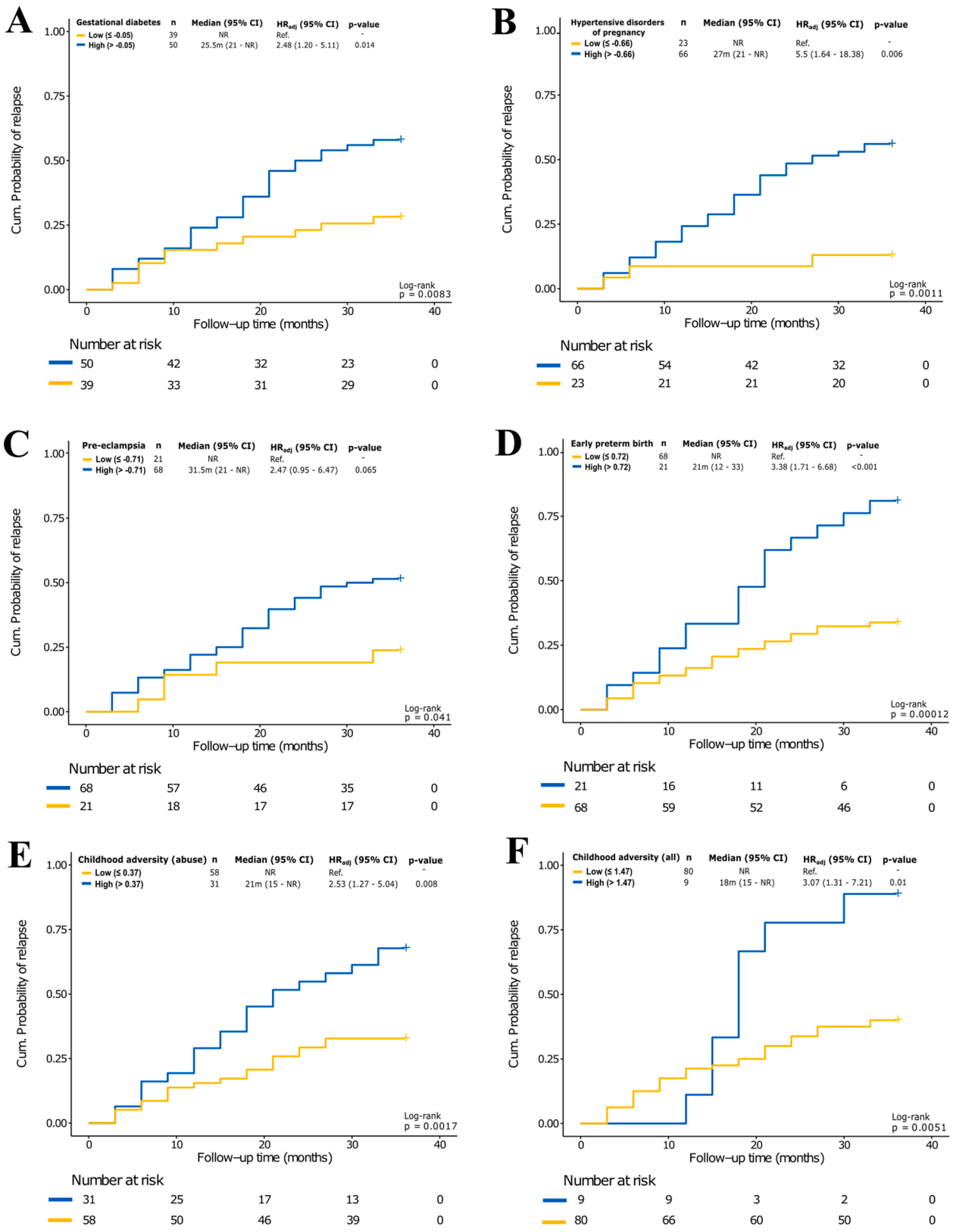

Fig. 3. Cumulative incidence of relapse for high and low MPS reflecting gestational diabetes (A) hypertensive disorders during pregnancy (B), pre-eclampsia (C), early preterm birth (D), childhood adversity abuse (E) and childhood adversity all types (F). Cumulative probabilities of relapse incidence were estimated by the Kaplan-Meier method and groups were compared with the Log-rank test. The legend includes the optimal cut-off determined by the method that maximizes the log-rank statistic, the number of individuals in each group (n), the median cumulative incidence, the hazard ratio (HR) adjusted for sex, age, tobacco consumption and PRS-EA, and its p-value. Abbreviations: CI: confidence interval; NR: not reached.

Author disclosure

Role of funding source

This study was supported by the Carlos III Healthcare Institute, the Spanish Ministry of Science, Innovation and Universities, the European Regional Development Fund (ERDF/FEDER) (PI08/0208, PI11/00325, PI14/00612, PI20/00574); Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM); CERCA Program; Catalan Government, the Secretariat of Universities and Research of the Department of Enterprise and Knowledge (2021 SGR 00672) and Institut de Neurociències, Universitat de Barcelona. Founders had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Author contributions

The results presented here are part of a broader project, the 2EPS study. MBe is the coordinator of the 2EPS study. AGS and LlP performed the statistical analysis and wrote the first draft of the manuscript, and both authors contributed equally to this work. LJ participated in the statistical analysis. NF performed the sample isolation and preparation and participated in the statistical analysis. CGR participated in the coordination of the sample shipment, the maintenance of the 2EPS database and in the recruitment and assessment of the sample. EB is the coordinator of the Biological module of the 2EPS study. SA, MR, LPC, GCE, AM, RRJ, AR, SS, AI, JU, AL, MJC, MP and AGP participated in the recruitment and assessment of the sample. SM designed, supervised and performed the statistical analysis, performed the interpretation of the results and wrote the first draft of the manuscript. All the authors, including the 2EPSs group authors listed in the acronym, contributed to the final draft of the manuscript.

Declaration of competing interest

Dr. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen–Cilag, Menarini, Rovi and Takeda

Dr. González–Blanco has received CME-related honoraria unrelated to the present work from Angelini, Janssen–Cilag, Casen Recordati, Lundbeck, Otsuka and Pfizer.

Dr. Gonzalez–Pinto has received grants and served as consultant, advisor or CME speaker for the following entities: Janssen–Cilag, Lundbeck, Otsuka, Pfizer, Sanofi–Aventis, Exeltis.

Dr. Ibañez has received research support from or served as speaker or advisor for Janssen–Cilag, Lundbeck, Otsuka Pharmaceutical SA, Alter and Rovi, with no financial or other relationship relevant to the subject of this article.

Dr. Mané has received financial support to attend meetings, travel support, or served as speaker for Otsuka, Angelini, Rovi, Neuraxpharm and Janssen Cilag

Dr. Rodriguez–Jimenez has been a consultant for, spoken in activities of, or received grants from JanssenCilag, Lundbeck, Otsuka, Pfizer, Ferrer, Juste, Takeda, Exeltis, Casen–Recordati, Angelini, Rovi

Dr. Roldán has served as advisor or speaker for the companies Otsuka, Rovi, Angelini and Casen Recordati

The rest of the authors reported no biomedical financial interests or potential conflicts of interest.

Acknowledgements

The authors thank the Language Advisory Service at the University of Barcelona for manuscript revision. The authors also thank all subjects and their families for the time and effort spent on this study as well as Ana Meseguer for sample collection assistance.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2025.02.003.

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