UNIVERSITAT DE BARCELONA

Genetic and Epigenetic Contributions to Psychotic Disorders: From Early Vulnerability to Clinical Onset in Precision Psychiatry

Àlex Gonzalez Segura

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Doctoral thesis dissertation presented by

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to apply for the degree of doctor at the University of Barcelona

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Una vegà eren dos:

el amo i el gos

que primer va nàxer el fill que el pare

se carregaen los bous a pasturar

corrien, corrien

i no se podien alcançar

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Table of Contents

List of Tables and Figures

Abbreviations and acronyms

ChAMP: Chip Analysis Methylation Pipeline

CNV: Copy Number Variant

CoMeBack: Co-Methylation with Genomic CpG Background

DSM: Diagnostic and Statistical Manual of Mental Disorders

eQTL: Expression Quantitative Trait Loci

EWAS: Epigenome-Wide Association Study

FAST: Functioning Assessment Short Test

FEP: First Episode of Psychosis

FHR: Familial High Risk

GxE: Gene-Environment Interaction

GWAS: Genome-Wide Association Study

HRC: Haplotype Reference Consortium

ICD: International Classification of Diseases

LD: Linkage Desequilibrium

MPS: Methylation Profile Score

p+T: p-value clumping and thresholding

PGx: Pharmacogenomics

PRS: Polygenic Risk Score

QC: Quality Control

RCV: Rare Coding Variants

SNP: Single Nucleotide Polymorphism

List of Articles

Thesis in compendium of publications format. The thesis consists of two main objectives, four sub-objectives and six articles articles

Article 1

Segura AG*, Mezquida G*, Martínez-Pinteño A, Gassó P, Rodriguez N, Moreno-Izco L, Amoretti S, Bioque M, Lobo A, González-Pinto A, García-Alcon A, Roldán-Bejarano A, Vieta E, de la Serna E, Toll A, Cuesta MJ, Mas S, Bernardo M; PEPs Group.

*both authors contributed equally

Link between cognitive polygenic risk scores and clinical progression after a first-psychotic episode.

Psychol Med. 2023 Jul;53(10):4634-4647

Impact factor: 6.9; Quartile: 1

Article 2

Clougher D*, **Segura AG***, Forte MF, Mezquida G, J Cuesta M, Vieta E, Amoretti S, Lobo A, González-Pinto A, M Díaz-Caneja C, Roldán A, Fico G, de la Serna E, Bergé D, Gassó P, Rodriguez N, Verdolini N, Tortorella A, Menculini G, Ribasés M, Bernardo M, Mas S; PEPs Group.

*both authors contributed equally

The role of cognitive reserve and clinical symptoms in the association between ge-

netic liability for educational attainment and functioning in first-episode psychosis: a mediation analysis.

Eur Psychiatry. 2024 Jan 5:1-31.

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Article 3

Segura AG*, Mané A*, Prohens L, Rodriguez N, Mezquida G, Cuesta MJ, Vieta E, Amoretti S, Lobo A, González-Pinto A, Diaz-Caneja CM, Bejarano AR, Jimenez E, Baeza I, Legido T, Saiz-Ruiz J, Bernardo M, Mas S; PEPs Group.

*both authors contributed equally

Exploration of cannabis use and polygenic risk scores on the psychotic symptom progression of a FEP cohort.

Psychiatry Res. 2023 Jul;325:115249.

Impact factor: 4.2; Quartile: 1

Article 4

Segura AG, de la Serna E, Sugranyes G, Baeza I, Valli I, Martínez-Serrano I, Díaz-Caneja CM, Andreu-Bernabeu Á, Moreno DM, Gassó P, Rodríguez N, Martínez-Pinteño A, Prohens L, Torrent C, García-Rizo C, Mas S, Castro-Fornieles J.

Polygenic risk scores mediating functioning outcomes through cognitive and clinical features in youth at family risk and controls.

Eur Neuropsychopharmacol. 2024 Apr;81:28-37.

Impact factor: 6.1; Quartile: 1

Article 5

Segura AG, de la Serna E, Sugranyes G, Baeza I, Valli I, Díaz-Caneja C, Martín N, Moreno DM, Gassó P, Rodriguez N, Mas S, Castro-Fornieles J.

Epigenetic age deacceleration in youth at familial risk for schizophrenia and bipolar

disorder.

Transl Psychiatry. 2023 May 8;13(1):155.

Impact factor: 5.8; Quartile: 1

Article 6

Segura AG*, Martinez-Serrano I*, de la Serna E, Sugranyes G, Baeza I, Picouto MD, Parrilla S, Moreno DM, Gasso P, Rodriguez N, Martinez-Pinteño A, Julia L, Torrent C, Garcia-Rizo C, Mas S, Castro-Fornieles J.

*both authors contributed equally

Epigenetic signatures in children and adolescents at familial high risk: linking early-life environmental exposures to psychopathology

Under review at Clinical Epigenetics.

Thesis summary

Introducció

Els trastorns psicòtics són complexos en la seva etiologia, ja que involucren factors genètics, epigenètics i ambientals. Aquesta complexitat es tradueix en una gran heterogeneïtat clínica, amb diferents etapes que van des de manifestacions subclíniques fins a l'aparició de símptomes clínics en un primer episodi psicòtic. En els darrers anys, l'accés a grans volums de dades biològiques ha transformat la comprensió d'aquests trastorns, assentant les bases per al futur desenvolupament d'eines per a la medicina de precisió en psiquiatria. Aquestes dades podrien oferir la possibilitat d'identificar individus amb alt risc de desenvolupar psicosi i estratificar-los en funció de la seva simptomatologia i severitat, permetent així millorar la detecció precoç i la intervenció primerenca, amb un impacte positiu en la prognosi a llarg termini del trastorn.

Hipòtesis

Aquesta tesi proposa que les puntuacions de risc poligènic (PRS, per les sigles en anglès) influeixen en l'espectre complet de la psicosi tenen un paper determinant en l'espectre complet de la psicosi, influenciant tant les manifestacions subclíniques com les etapes clíniques primerenques. A més, es planteja que les modificacions epigenètiques induïdes per l'exposició a factors ambiental estan associades amb el desenvolupament i la progressió de la psicosi subclínica. Es considera que aquestes modificacions poden incloure alteracions en els perfils epigenètics relacionats amb

l'envelliment i l'estrès prenatal, els quals poden tenir un impacte significatiu en el desenvolupament del trastorn.

Objectius

Aquesta tesi té com a objectiu investigar com les PRS afecten l'espectre de la psicosi, des de les manifestacions subclíniques fins a les fases clíniques inicials. També es pretén explorar la relació entre les modificacions epigenètiques, derivades de l'exposició a factors ambientals, i la seva influència en el desenvolupament i la progressió de la psicosi subclínica. En particular, es volen identificar les alteracions en els perfils epigenètics associats amb l'edat i l'estrès prenatal que podrien tenir un paper crucial en l'evolució del trastorn.

Mètodes

La recerca es va dur a terme mitjançant l'anàlisi de dues cohorts que representen les etapes inicials dels trastorns psicòtics: la cohort BASYS, que inclou infants i adolescents amb un alt risc familiar de desenvolupar esquizofrènia i trastorn bipolar, i la cohort PEPs, composta per individus que experimenten un primer episodi de psicosi. Ambdues cohorts inclouen un grup control aparellat per edat. Aquests cohorts tenen un disseny multicèntric, naturalístic i longitudinal. Es van calcular PRS que reflecteixen la susceptibilitat genètica als trastorns mentals, rendiment cognitiu, neuroticisme i consum de cànnabis. Les puntuacions epigenètiques van ser utilitzades per estimar l'edat cronològica i fenotípica dels individus, així com l'exposició a estrès prenatal. Les relacions entre aquestes puntuacions es van avaluar utilitzant models estadístics d'associació i de mediació.

Principals resultats

Els resultats de l'estudi van demostrar que la PRS d'esquizofrènia presenta puntuacions més desfavorables en individus amb un primer episodi psicòtic i en poblacions d'alt risc familiar a esquizofrènia, però no semblen influir significativament

en variables clíniques ni subclíniques. En canvi, les PRS de depressió, cognició, neuroticisme i consum de cànnabis sí tenen un impacte en la manifestació clínica. Pel que fa a les modificacions epigenètiques, es va observar que els individus d'alt risc familiar mostren un desfàs entre l'edat cronològica i l'estimada per puntuacions epigenètiques, indicant una desacceleració en el procés d'envelliment epigenètic. A més, aquests individus tenen puntuacions epigenètiques que suggereixen una major exposició a estrès prenatal. Tant l'acceleració de l'edat epigenètica i puntuacions d'estrès prenatal es relacionen amb una major severitat subclínica de la psicosi exclusivament en individus amb alt risc familiar d'esquizofrènia.

Conclusions

La línia d'investigació d'aquesta tesi aporta noves dades per una comprensió més profunda dels factors genètics i epigenètics que influeixen en les etapes inicials dels trastorns psicòtics, aspecte essencial per al desenvolupament de la medicina de precisió. Els resultats obren la possibilitat de considerar factors pleiotròpics que poden contribuir a l'heterogeneïtat clínica de la psicosi, i suggereixen el potencial de les dades genòmiques i epigenòmiques per guiar decisions clíniques en psiquiatria. Aquesta tesi posa de manifest la complexitat de l'arquitectura genètica i epigenètica que subjau en els trastorns psicòtics i la seva variabilitat clínica. La investigació futura haurà de centrar-se en la integració de dades multiòmiques amb informació sociodemogràfica, clínica i neurobiològica per millorar el poder predictiu i ooferir una visió holística dels mecanismes subjacents a aquests trastorns. Aquest enfocament integral podria impulsar avenços en les estratègies diagnòstiques i terapèutiques, promovent una atenció en salut mental més personalitzada i efectiva.

1. Introduction

1.1 Overview of psychotic disorders

1.1.1 Concept and clinical presentation

Psychotic disorders, including schizophrenia, are chronic, severe and debilitating conditions with elevated mortality rates, reducing life expectancy by 10-20 years (1–3). Approximately 3% of the global population will experience a psychotic disorder at some point in their lives (4), highlighting the considerable global burden these conditions place on disability rates.

The clinical presentation of psychotic disorders encompasses a spectrum of alterations in perception, behavior, affect and cognition, profoundly impacting the individual's psychosocial functioning (5). Positive symptoms include hallucinations (altered perceptions), delusions (false beliefs), formal thought disorder (disconnected, fast-shifting and disorganized thoughts) and behaviors such as suspiciousness and grandiosity. These symptoms are often the most noticeable and typically prompt those close to the patients to seek professional help. Negative symptoms reflect an individual's diminished ability to process emotions, manifesting as anhedonia (lack of interest in pleasurable activities), asociality (social withdrawal), blunted affect (decreased expression of emotions), abulia (loss of initiative) and alogia (limited speech). Despite often preceding positive symptoms, negative symptoms can be overlooked due to their more subtle nature.

Cognitive impairment, now recognized as a core and distinct symptom dimension in psychotic disorders, affects various cognitive functions. These include neurocognitive deficits such as poor sustained attention, executive dysfunction, reduced processing speed, difficulties in reasoning and problem-solving and impairments in working memory, verbal learning and visual learning and memory—key processes for daily real-world functioning. Additionally, social cognition is affected, leading to difficulties in processing social information (6,7).

The diagnosis of schizophrenia, the most paradigmatic psychotic disorder, requires a comprehensive assessment of the patient's history and a careful evaluation of their current mental state. This process is guided by the clinical criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (8) and the International Classification of Diseases (ICD) (9), which specify the necessary symptoms and their required duration. Typically, significant signs of disturbance must persist for at least six months, including at least one month of active-phase symptoms. The evaluation also ensures that the symptoms are not attributable to other medical conditions or substance use. **Table 1** provides a detailed description of the diagnostic criteria, offering a structured approach for healthcare professionals to ensure accurate and consistent diagnoses of schizophrenia.

Table 1. Diagnostic criteria for schizophrenia according to DSM-V and ICD-11.

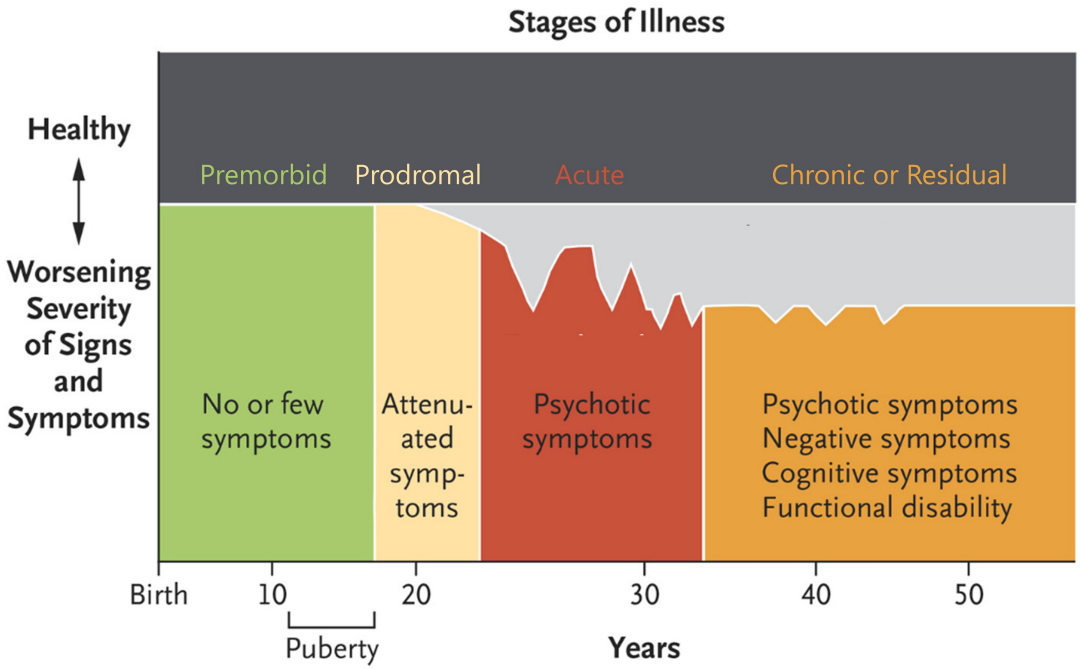
DSM-V	Criterion A: At least two of the following for at least one month: 1. Delusions 2. Halluciations 3. Disorganized speech 4. Grossly disorganized or catatonic behavior 5. Negative symptoms (i.e. diminished emotional expression or avolition) Criterion B: Level of functioning has to be significantly and long term lowered compared to the previously achieved level Criterion C: Continuous signs of the disturbance persist for at least 6 months, must include criterion A symtpotms for at least one month Criterion D: Schzioaffective disorder and depressive or bipolar disorder with psychotic symptoms ruled out Criterion E: The disturbance is not caused by substance use or medical conditions Criterion F: If a patient has a history of autism spectrum or communication disorders from childhood, schizophrenia diagnosis can be made in case of prominent delusions/ hallucinations and other required symptoms of schizophrenia are present for at least 1 month
ICD-11	At least two of the following symptoms must be present most of the time for a period of 1 month or more: 1. Persistent delusions 2. Persistent hallucinations 3. Disorganized thinking 4. Experiences of influence, passivity or control 5. Negative symptoms 6. Grossly disorganized behaviour 7. Psychomotor disturbances, including catatonia The symptoms are not a manifestation of another medical condition and are not due to the effects of a substance or medication on the central nervous system, including withdrawal effects.

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, fifth version; ICD-10: International Classification of Diseases, eleventh version.

1.1.2 Stages of illness

The progression of psychotic disorders typically involves several distinct phases. Initially, the premorbid phase refers to the period before the onset of noticeable symptoms. This is followed by the prodromal phase, which spans from the onset of these initial, subtle changes to the appearance of clear psychotic symptoms. The disorder usually progresses to the acute phase, characterized by the intense expression of most psychotic symptoms. Finally, the disorder may transition to the chronic or residual phase, where positive symptoms may be managed with pharmacological treatment, but negative symptoms, neurocognitive impairments and poor psychosocial functioning often persist (10,11) (**Figure 1**). Throughout the illness, symptoms can vary in type and severity, with periods of exacerbation and symptom remission.

Figure 1. Stages of illness in schizophrenia, the most paradigmatic psychotic disorder.



The progression of psychotic disorders typically involves several distinct phases: premorbid, prodromal, acute and chronic or residual. Symptoms vary in type and severity, with periods of exacerbation and remission. Adapted from Lieberman et al., 2018 (12).

The onset of the acute phase of psychotic disorders is often marked by a first episode of psychosis (FEP), tipically occurring between adolescence and early adulthood (13). While clinical criteria define the boundary between the prodromal and acute phases, the progressive emergence of symptoms suggests that the clinical manifestation of psychotic disorders can be viewed as a continuum, ranging from subtle to pronounced symptoms (14,15).

Studying the early stages of psychosis—including the subclinical, prodromal and FEP—is crucial for understanding the pathophysiological mechanisms underlying psychotic disorders (16). These early phases are particularly valuable for research because they involve fewer confounding effects from prolonged pharmacological treatments, the progresssionof the disorder, or additional health complications. Furthermore, the FEP is critical for prognosis, as numerous factors associated with this phase influence long-term outcomes. Factors such as early onset, prolonged untreated psychosis, low socioeconomic status, more severe negative symptoms and poor response to antipsychotic treatment are linked to prognosis and can significantly affect the course of the disorder (17).

To effectively study the early stages of psychosis, it is essential to recruit samples that reflect these stages accurately. Given the significance of these early phases in understanding psychotic disorders, researchers are increasingly focusing on cohorts of individuals experiencing their FEP. Various methodologies are employed to evaluate these stages, allowing for a nuanced understanding of their development. Since a familial history of psychosis is a well-documented risk factor for FEP (18,19), there is a growing emphasis on including cohorts enriched with individuals at familial high risk (FHR). This approach ensures that the samples better representat populations more likely to develop FEP, thereby enhancing the validity and applicability of the research findings (20).

1.1.3 Etiological factors

Psychotic disorders display a significant clinical heterogeneity at all stages, with symptoms and severity varying widely among individuals. This variability reflects the complex etiology of these disorders, which arises from a combination of genetic, environmental and neurobiological factors (5). Despite extensive research, the precise mechanisms underlying psychotic disorders remain elusive, and no definitive biomarkers have been identified. This underscores the need for early detection and accurate, individualized approaches to diagnosis and treatment, tailored to each patient's unique symptom profile and underlying causes.

1.2 Genetic etiological factors

1.2.1 Common genetic variability and genome-wide approaches

Genetic factors contribute significantly to psychotic disorders, with heritability estimated to be around 80% for schizophrenia (21). However, genetic factors alone are insufficient to cause the disorder; its acute manifestation occurs when the combined effects of genetic and non-genetic influences exceed a hypothetical "threshold of liability" (22).

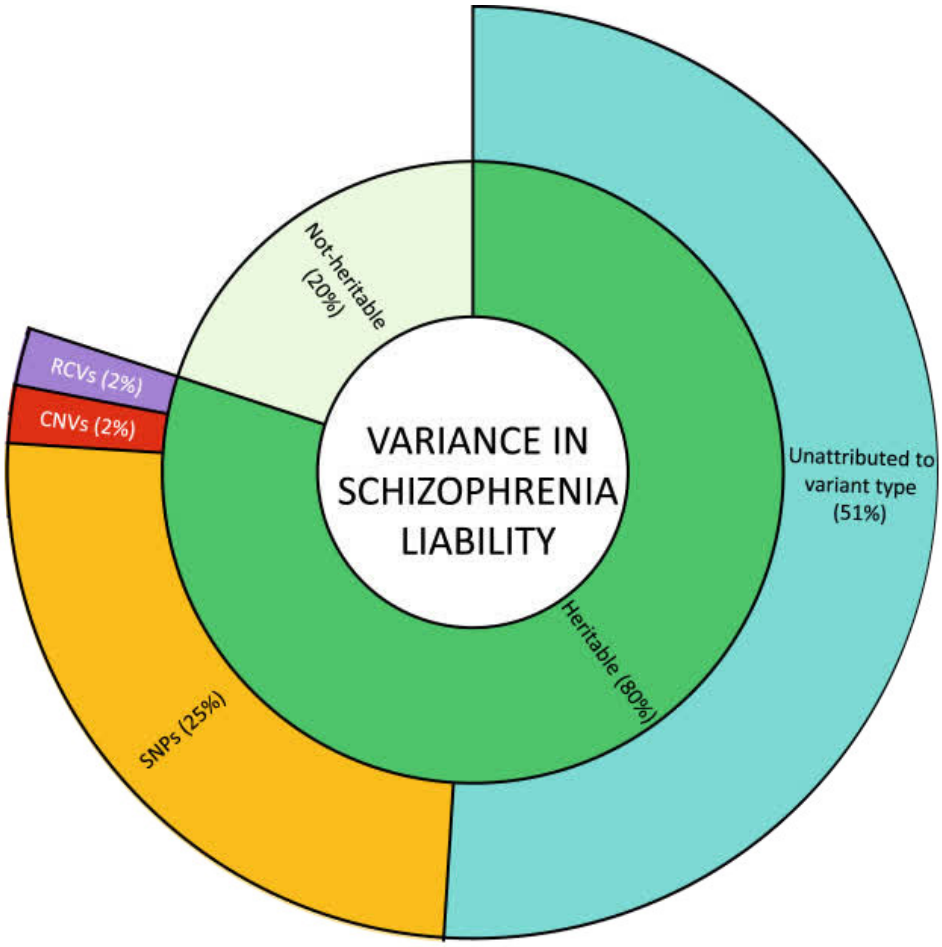
Understanding genetic components is key for elucidating the complex genetic basis of psychiatric disorders. Single nucleotide polymorphisms (SNPs) are common variants, occurring in at least 1% of the population, and generally confer a low risk. In contrast, rare variants, which occur in less than 1% of the population, often have a more substantial impact on disease risk. Additionally, copy number variants (CNVs) involve duplications or deletions of DNA segments affecting multiple nucleotides (23,24).

Genome-wide association studies (GWAS) have transformed our understanding

of the genetic architecture of psychiatric disorders. These studies have identified numerous SNPs associated with schizophrenia, bipolar disorder and major depressive disorder, among others (25–27). However, GWAS findings explain only about 25% of the estimated heritability for schizophrenia, revealing a 'hidden heritability' not captured by common variants (26) (**Figure 2**). This suggests that other genetic factors, such as rare variants, CNVs and gene-gene interactions also contribute significantly to the heritability of schizophrenia. Current genomic approaches, integrating common variants with these additional factors, account for only around 40% of the expected heritability in schizophrenia (28).

Despite the limitations of a SNP-based approach, the agnostic nature of GWAS has expanded the scope of genetic research beyond classical candidate gene studies. Most genome-wide significant SNPs are located in intergenic regions, complicating their biological interpretation. Nevertheless, variations in non-coding regions can still have significant biological effects. These variants may be in strong linkage disequilibrium (LD) with SNPs that have biological functions, interact with other genetic variants or function as expression quantitative trait loci (eQTL), modulating the expression of distal genes (29).

Figure 2. Variance in schizophrenia liability.



SNP: single nucleotide polymorphism; CNV: copy number variants; RCV: rare coding variants

The inner ring represents heritability estimates of schizophrenia, attributed to heritable and non-heritable components, such as environmental factors and de novo mutations. The outer ring represents the contributions to variance from known genetic components including SNPs, CNVs and RCVs, which are rare variants and CNVs that modify the amino acid sequences of proteins. Adapthed from Owen et al., 2023 (28).

1.2.2 Polygenic risk scores in research

Although the specific biological mechanisms associated with each genetic locus remain largely unknown, bioinformatic and statistical approaches have used GWAS data to estimate the cumulative effect of SNPs. Polygenic risk scores (PRS) have

emerged as a powerful tool for the study of the genetic architecture of complex phenotypes, including mental disorders (30,31). PRS summarize an individual's genetic liability by combining genotyping information and reference GWAS results, ultimately relying on the additive effect of the risk conferred by each SNP.

The most successful disorder-specific PRS is for schizophrenia, constructed from the most powerful GWAS available (26). However, this PRS explains only 8.5% of the variability of the disorder, falling short of clinical prediction standards. Schizophrenia and other psychiatric disorder PRS have been utilized to explore susceptibility to psychotic disorders and clinical heterogeneity, including aspects such as treatment response, symptom severity and cognitive function (32,33). Additionally, non-disorder-specific PRS, such as those for cognitive traits or neuroticism, have been studied for their relationship with clinical outcomes in psychosis. **Table 2** provides a summary of the findings of these PRS across various clinical features and different stages of psychotic disorders, including FEP and high-risk cohorts.

Table 2. Summary of PRS findings on psychotic disorders susceptibility and clinical and subclinical features in samples including individuals with chronic, acute and high risk for psychosis as well as young population-based cohorts.

First author	Sample of study (n)	PRS	PRS method	Main findings
Perkins (34)	Psychosis high risk individuals (764), Controls (279)	SZ, BD	p+T	PRS for SZ discriminates psychosis converters from non-converters
Santoro (35)	FEP patients (60), Controls (60)	SZ	p+T	PRS for SZ discriminates FEP from controls, associated with global, depressive and excitement symptoms
Jonas (36)	FEP patients (249), Controls (205)	SZ	p+T	PRS for SZ associated with psychosis, negative symptoms, illness severity, poor cognition
Zhang (37)	FEP patients (5110)	SZ	p+T	PRS for SZ associated with symptoms and treatment response
Murillo-Garcia (38)	FEP patients (122), Unaffected relatives (225), Controls (176)	SZ, IQ	beta shrinkage	PRS for SZ increased in psychotic disorder patients and unaffected relatives compared to controls; PRS for IQ did not differ between groups
He (39)	Individuals at ultra-high risk for psychosis (107)	SZ, CP, SZ resilience	p+T	PRS for SZ, CP and SZ resilience associated with poor cognition; no PRS associated with conversion to psychosis
Richards (40)	SZ patients (3034)	SZ, BD, MDD, EA, IQ	p+T	PRS for IQ and EA associated with cognition
Toulopoulou (41)	SZ patients (416), Unaffected siblings (290), Controls (607)	SZ	p+T	PRS for SZ associated with increased risk, effect partially mediated by cognition
Vassos (42)	SZ patients (445), Controls (265)	SZ	p+T	PRS for SZ associated with increased risk, discriminated SZ from other psychiatric disorders
Wang (43)	SZ patient trios (1130 trios)	SZ	p+T	PRS for SZ associated with increased risk and poorer CP

Zheutlin (44)	SZ patients (106160), Controls (unspecified)	SZ	p+T, beta shrinkage	PRS for SZ associated with increased risk, anxiety, substance use, neurological, personality disorders, suicidal behavior, memory loss, obesity
Calafato (45)	Psychotic disorder patients (1168), Unaffected relatives (552), Controls (1472)	SZ, BD	p+T	PRS for SZ increased in psychotic disorder patients and unaffected relatives compared to controls
Ohi (46)	SZ patients (173), Unaffected relatives (70), Controls (196)	SZ, BD	p+T	PRS for SZ increased in psychotic disorder patients and unaffected relatives compared to controls; PRS for BD increased in psychotic disorder patients compared to controls
Habtewold (47)	SZ patients (1119), Unaffected siblings (1059), Controls (586)	SZ	p+T	PRS for SZ associated with poor cognitive trajectories in all groups
Shafee (48)	Psychotic disorder patients (314), Controls (423)	SZ	p+T	PRS for SZ associated with current cognitive abilities, but only in control group
Werner (49)	Treatment-resistant SZ patients (108), Non-treatment-resistant SZ patients (213)	SZ	p+T	PRS for SZ associated with treatment resistance
Wimberley (50)	Treatment-resistant SZ patients (181), Non-treatment-resistant SZ patients (681)	SZ	p+T	PRS for SZ not associated with treatment resistance
Smigielski (51)	SZ patients (384), Schizoaffective disorder patients (86), BD patients (455), At-risk for psychosis individuals (120), Controls (305)	SZ, BD	beta shrinkage	PRS for SZ and BD increased in groups with overt symptoms compared to control group; PRS for SZ associated with transdiagnostic symptomatology

Hubbard (52)	Young population-based cohort (5109), SZ patients (11466), Controls (6299)	SZ, Cognition	p+T	PRS for SZ associated with cognition; PRS for cognition associated with SZ status
Maxwell (53)	Young population-based cohort (3590)	SZ, BD, MDD, EA, IQ, Neuroticism, ...	beta shrinkage	PRS for EA associated with negative symptoms; PRS for neuroticism with cognitive disorganization; PRS for MDD and neuroticism with paranoia
Neumann (54)	Young population-based cohort (9247)	SZ, BD, MDD, EA, Cognitive ability, Neuroticism, others	p+T	PRS for SZ, MDD, cognitive ability, neuroticism associated with general psychopathology; PRS for SZ, cognitive ability, neuroticism associated with internalizing problems; PRS for cognitive ability associated with externalizing problems
Askeland (55)	Young population-based cohort (15205)	SZ, ADHD, Autism	p+T	PRS for ADHD associated with hyperactivity and inattention; PRS for autism associated with language and motor difficulties, hyperactivity and inattention
Wainberg (56)	Young population-based cohort (9856)	SZ, BD, MDD, ADHD, Anorexia nervosa	p+T	PRS for MDD and ADHD associated with behavioral problems
Scott (57)	Psychotic/mood disorder patients (409), Controls (1064)	SZ, BD, Depression, Neuroticism	beta shrinkage	All PRS increased in psychotic/mood disorder group
Kwong (58)	Young population-based cohort (5317)	SZ, MDD, Depression, Neuroticism, Anxiety	p+T	PRS for MDD, depression, neuroticism associated with depressive symptoms
Ahangari (59)	Psychotic disorder patients (539), Controls (322)	SZ, BD, MDD	beta shrinkage	PRS for SZ associated with negative and disorganized symptoms; PRS for BD associated with manic symptoms

Lencz (60)	SZ patients (5446), Controls (5830)	SZ, Cognitive ability	p+T	PRS for SZ associated with cognitive ability; PRS for cognitive ability associated with increased risk for the disorder
Park (61)	Young population-based cohort (6602)	EA, CP	beta shrinkage	Cognitive PRS associated with IQ
Kämpe (62)	Psychotic disorder patients (10403)	SZ, BD, MDD, EA, IQ, Cannabis use disorder, Alcohol dependence	beta shrinkage	PRS for SZ associated with transition to psychotic disorders to SZ; PRS for SZ and EA associated with hospitalization

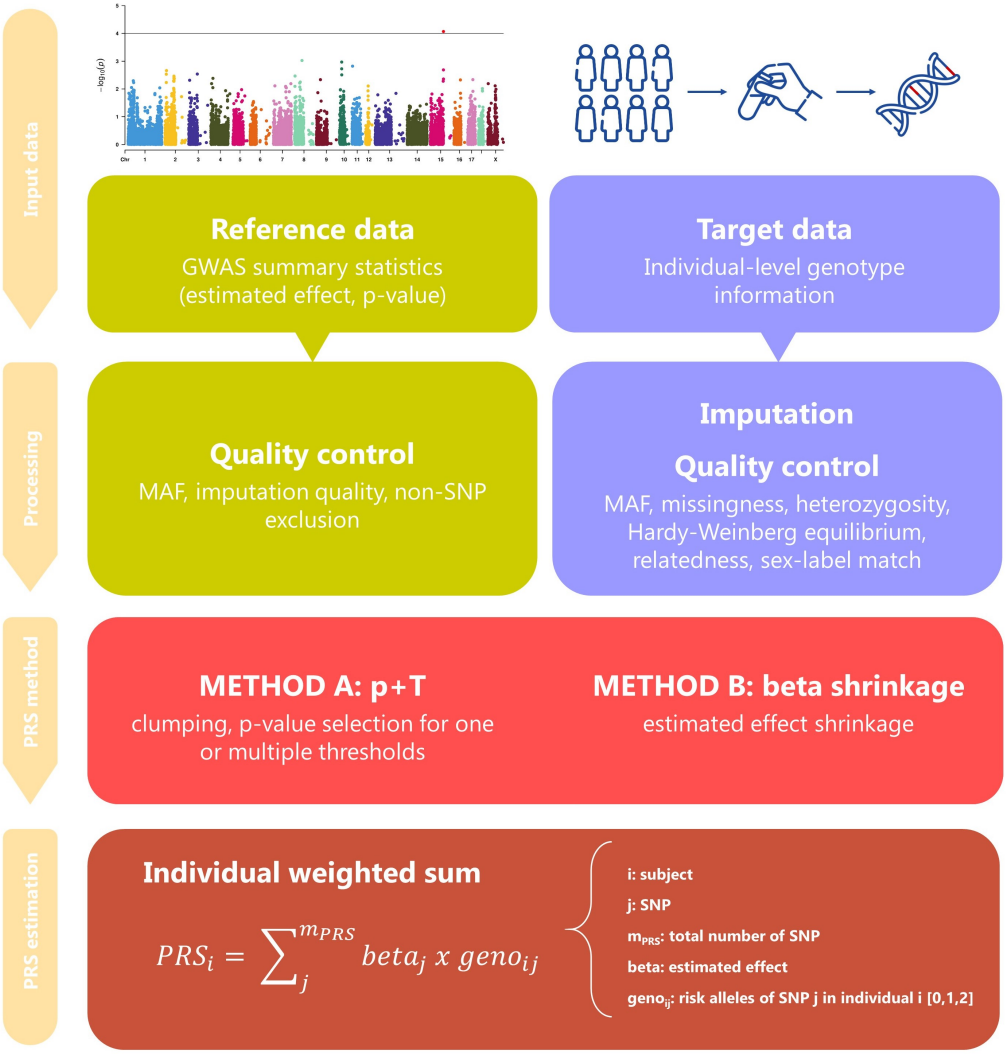
FEP: first episode of psychosis; SZ: schizophrenia; BD: bipolar disorder; MDD: major depressive disorder; ADHD: attention; EA: educational attainment; IQ: intelligence; p+T: p-value-based clumping and thresholding.

The existing literature suggests potential future applications of different types of PRS tailored to specific clinical questions. Depending on the context, PRS might be used to enhance disorder prediction, differentiate between diagnostic categories, stratify patient populations or inform treatment strategies (23).

1.2.3 Polygenic risk scores strategy

The pipeline for constructing PRS has evolved significantly with the advances in public imputation servers and the integration of machine learning techniques, though consensus on a standardized protocol has yet to be established (63). Nonetheless, all PRS calculation pipelines ultimately involve computing a weighted sum of SNPs' estimated effects on a phenotype (**Figure 3**).

Figure 3. Pipeline for PRS calculation. Two sources of input data are processed and combined to estimate an inidivudal PRS. There are two approaches for PRS construction, based on p-value clumping and thresholding (p+T) and beta shrinkage.



PRS: polygenic risk score; GWAS: genome-wide association study; MAF: minor allele frequency; SNP: single nucleotide polymorphism. Original figure.

Two sources of input data, reference data from GWAS summary statistics and target data from individual genotypes, undergo quality control and imputation processes. The PRS can be constructed using two main approaches: Method A (p-value clumping and thresholding) and Method B (beta shrinkage). The final PRS for an individual is calculated as a weighted sum of the estimated effects and genotypes across all SNPs.

A key advancement in PRS calculation is genotype imputation alogrithms, such as the Michigan Imputation Server (64). The imputation pipeline estimates the most likely genotypes based on the genetic information from densely genotyped reference panels, such as the 1000 Genomes Project or the Haplotype Reference Consortium (HRC). This process provides predicted genotypes for SNPs not directly genotyped in a study sample, along with a probability measure indicating the confidence of these estimations. Imputation greatly expands the number of SNPs available for PRS calculation, increasing the number from hundreds of thousands to several million.

Ensuring the reliability of genotyping information requires rigorous quality control (QC). QC processes are crucial for including only high-quality SNPs, thereby avoiding technical and sample-specific biases in the PRS. Tools like PLINK (65) are employed for QC, controlling for parameters linked to methodological issues, such as SNP and individual missingness rates and imputation quality. It also addresses the representativeness of the sample by considering SNP minor allele frequency, heterozygosity and Hardy-Weinberg equilibrium assumption, as well as individual relatedness and chromosome and labelled-sex match. Only SNPs and genotyped individuals meeting stringent QC standards are retained for analysis.

Once a robust number of high-quality SNPs are available, various methods can be used to construct the PRS. Two commonly employed strategies are p-value-based clumping and thresholding (p+T) and beta shrinkage-based methods. p+T methods select the most representative loci of a pre-defined group of significantly associated SNPs, though debates continue about the optimal p-value thresholds. Beta shrinkage-based methods, a more advanced approach, adjust for SNP effects and include all available SNPs without relying on p-value thresholds. These methods leverage advanced statistical models and LD information to enhance prediction accuracy, outperforming p+T methods (66).

As the field progresses, the integration of machine learning techniques, along

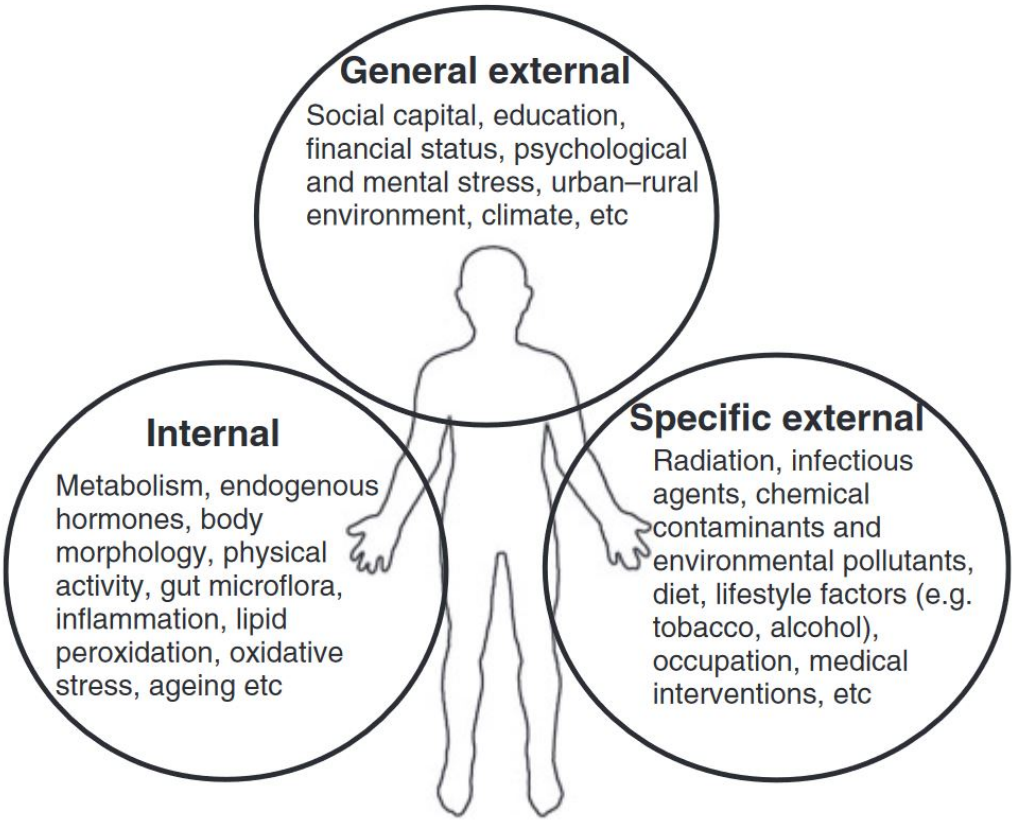
with ongoing improvements in genotype imputation and QC processes, is expected to enhance the accuracy and applicability of PRS in understanding the genetic architecture of complex traits, including psychiatric disorders.

1.3 Environmental etiological factors

1.3.1 Environmental risk factors

Alongside genetic influences, the concept of the 'exposome' encompasses all non-genetic factors affecting an individual from conception onward (67). This framework allows for a comprehensive examination of lifelong exposure to environmental risk factors associated with mental disorders (68). Research into the environmental risk factors has identified various external influences in early development (such as obstetric complications and paternal age), proximal factors (such as social inequity, migration and isolation) and onset factors (including cannabis use and recent traumatic experiences) (69–72). Additionally, the exposome considers speficic internal factors like oxidative stress or inflammation, which can create a particular cellular environment to developing psychotic disorders (73) (**Figure 4**). The study of environmental risk factors emphasizes the complex interplay between these factors and genetic susceptibilities, a phenomenon known as gene-environment interactions (GxE). This interaction may help address the gap in understanding the heritability of these conditions (74,75).

Figure 4. Overview of the exposome and its domains.



The exposome encompasses all non-genetic factors impacting an individual throughout their life. It presents examples within three domains: general external, specific external and internal. From Wild 2012 (73).

Schizophrenia, along with other related conditions such as bipolar and major depressive disorders, are believed to originate from neurodevelopmental alterations that manifest during young adulthood as neurodevelopment completes (76–78). This developmental process is particularly susceptible to environmental stress, especially during critical prenatal stages, which can disrupt typical brain development and increase the risk of psychotic disorders later in life. Obstetric complications, which encompass a range of issues such as abnormal fetal growth and delivery complications, have been consistently linked to increased clinical risk and severity of psychosis, including during FEP (79–82). Understanding how these early-life environmental factors impact neurodevelopmental trajectories is crucial for elucidating the etiology of these psychiatric disorders.

Cannabis use is a prominent environmental risk factor for psychosis and is well-established as a major contributor to the disorder's onset (83). Cannabis has a profound psychoactive effect, particularly on young individuals (84). It impacts the brain's endocannabinoid system, which is essential for mood regulation and cognitive function, potentially leading to poorer outcomes, relapse and treatment resistance (85–88). The frequency of cannabis use is notably hihgher among individuals experiencing a FEP and while medical counseling is recommended for cessation, its effectiveness remains a topic of ongoing debate (89).

1.3.2 Epigenetic scores in research

Assessing patients' sociodemographic contexts, past stressful life events and traumatic experiences typically involves using various scales. However, retrospective assessments often rely on individuals' recollections, which are inherently subjective (90,91). Even though validated scales are designed to minimize data skew, they cannot provide an objective measure of the biological impact of environmental factors.

Epigenetics offers a promising alternative for assessing the biological response to environmental stress (92,93). DNA methylation, a key epigenetic modification, involves the addition of a methyl group to a CpG, typically affecting gene expression without altering the underlying DNA sequence (94). By focusing on methylation changes associated with specific environmental conditions, researchers can identify reliable biological markers of environmental exposure. This approach provides valuable insights into how environmental factors impact biological processes and contribute to the development of complex disorders such as schizophrenia.

Epigenetic scores, akin to PRS, have been developed to capture genome-wide methylation marks associated with environmental factors. The first generation of epigenetic scores aimed to capture methylation patterns of time-dependent CpGs, estimating an individual's 'epigenetic age'. Second-generation epigenetic scores sought to identify CpGs associated with age-related mortality phenotypes, offering a more

nuanced understanding of how epigenetic age correlates with health outcomes. By comparing epigenetic to chronological age, researchers can assess aging asynchronies, providing insights into the impact of environmental exposures and stressors on the aging process and overall health.

The latest advancements in epigenetic scoring involve methylation profile scores (MPS), driven by the rise of epigenome-wide association studies (EWAS). Similar to GWAS, EWAS report precise information of the association between CpG sites and specific environmental exposures or health conditions (95,96). MPS can serve as proxies for the biological impact of these conditions, summarizing the cumulative impact of environmental exposures on the epigenome. These scores offer a promising tool for integrating epigenetic data into individual assessments, enhancing the understanding of how dynamic and complex environmental factors influence the onset and prognosis of psychotic disorders (97). The calculation of epigenetic scores relies on the additive effect of each CpG's estimated impact.

In the study of psychotic disorders, epigenetic scores have revealed distinct alterations in the epigenetic profiles of affected individuals. While some studies show no significant changes or a slight deceleration in epigenetic aging, others indicate an association with epigenetic patterns for mortality-related conditions (98). The specific mechanisms linking psychotic disorders to epigenetic aging remain largely unexplored. Potential origins of slower epigenetic aging may include factors from in utero development and treatments such as antipsychotics and mood stabilizers have been associated with faster epigenetic aging (99). Additionally, these scores are employed to investigate the environmental risk factors associated with the disorder and related traits. Despite the current limitations in predictive capacity, the evidence supports further exploration of DNA methylation as a biomarker for disorder onset and progression. Similar to PRS, epigenetic scores exhibit limited predictive capacity in clinical settings, underscoring the need for ongoing research and refinement in this area (95). **Table 3** summarizes the findings of epigenetic scores on various clin-

ical features in different stages of psychotic disorders, including FEP and high-risk cohorts.

Table 3. Summary of epigenetic scores findings on psychotic disorders susceptibility and clinical features.

First Author	Sample of Study (n)	Epigenetic Score	Estimation	Main Findings
Ori (100)	Schizophrenia patients (1090), Controls (1206)	Horvath, Hannum, Levine	Epigenetic age, phenotypic age	Epigenetic age of all epigenetic clocks was decelerated and phenotypic age was accelerated in SZ patients
Caspi (101)	Psychotic disorders patients (1812), Controls (1753)	DunedinPACE	Epigenetic age	Epigenetic age was accelerated in SZ patients
Liu (102)	Schizophrenia patients (142), ASD patients (post-mortem) (222)	Horvath	Epigenetic age	Epigenetic age was accelerated in older SZ patients
Yusupov (103)	Transdiagnostic patients (429)	Horvath, Hannum, DunedinPACE, Levine, GrimAge	Epigenetic age, phenotypic age	Burden of psychiatric disease was associated with epigenetic age acceleration of DunedinPACE and phenotypic age GrimAge
Li (104)	FEP patients (38), Controls (38)	Horvath, Hannum, Levine	Epigenetic age	Epigenetic age of Horvath was decelerated in drug-naïve FEP patients; epigenetic age of Hannum and phenotypic age Levine was accelerated after risperidone treatment
Dada (105)	Psychotic disorders patients (138)	Horvath, Hannum	Epigenetic age	Psychotic symptoms were associated with epigenetic age acceleration

Zheutlin (44)	SZ patients (106160), Controls (unspecified)	SZ	p+T, beta shrinkage	PRS for SZ associated with increased risk, anxiety, substance use, neurological, personality disorders, suicidal behavior, memory loss, obesity
Calafato (45)	Psychotic disorder patients (1168), Unaffected relatives (552), Controls (1472)	SZ, BD	p+T	PRS for SZ increased in psychotic disorder patients and unaffected relatives compared to controls
Ohi (46)	SZ patients (173), Unaffected relatives (70), Controls (196)	SZ, BD	p+T	PRS for SZ increased in psychotic disorder patients and unaffected relatives compared to controls; PRS for BD increased in psychotic disorder patients compared to controls
Habtewold (47)	SZ patients (1119), Unaffected siblings (1059), Controls (586)	SZ	p+T	PRS for SZ associated with poor cognitive trajectories in all groups
Shafee (48)	Psychotic disorder patients (314), Controls (423)	SZ	p+T	PRS for SZ associated with current cognitive abilities, but only in control group
Werner (49)	Treatment-resistant SZ patients (108), Non-treatment-resistant SZ patients (213)	SZ	p+T	PRS for SZ associated with treatment resistance
Wimberley (50)	Treatment-resistant SZ patients (181), Non-treatment-resistant SZ patients (681)	SZ	p+T	PRS for SZ not associated with treatment resistance
Smigielski (51)	SZ patients (384), Schizoaffective disorder patients (86), BD patients (455), At-risk for psychosis individuals (120), Controls (305)	SZ, BD	beta shrinkage	PRS for SZ and BD increased in groups with overt symptoms compared to control group; PRS for SZ associated with transdiagnostic symptomatology

ASD: autistic spectrum disorder; FEP: first episode of psychosis; MPS: methylation profile score.

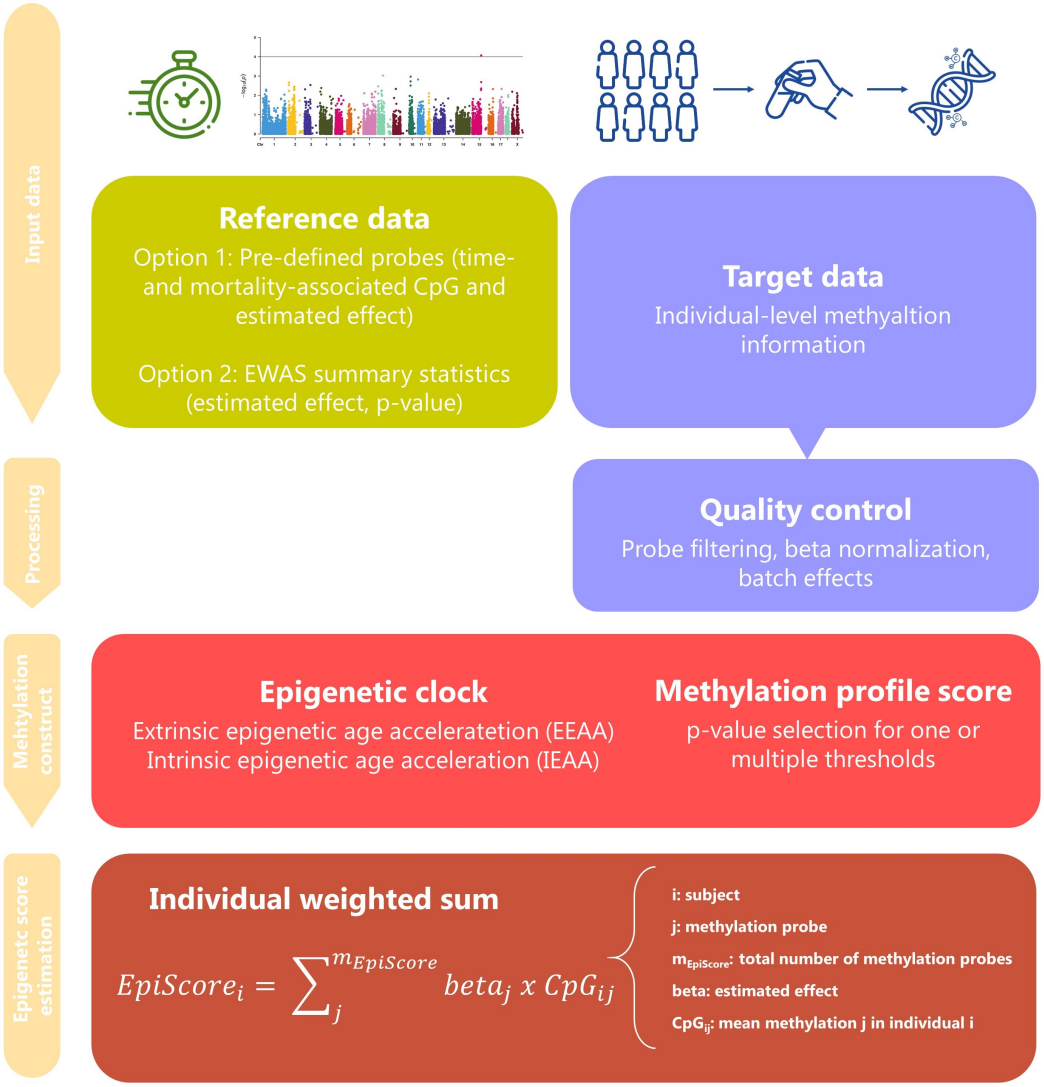
1.3.3 Epigenetic scores strategy

Epigenetic scores present unique challenges that require specific methodological considerations. Much like PRS, epigenetic scores integrate genome-wide information of multiple loci (**Figure 5**). However, constructing and interpreting these scores involves distinct complexities, including issues related to probe selection and the statistical power of EWAS. These factors are crucial for the accuracy and reliability of epigenetic scores but are often less thoroughly addressed in the literature (111,112).

Methylation arrays provide detailed information about methylated CpG sites, with the newest arrays covering up to 930,000 sites. During analysis, bisulfite treatment converts unmethylated cytosines into thymine, allowing for the identification of methylated sites. The resulting analysis pipeline provides the relative proportion of methylated CpG sites across the pool of DNA extracted from the individual (96).

One major challenge is managing substantial batch effects that can arise during data collection and processing. Variations in laboratory conditions, reagents and equipment can introduce considerable noise into the data. The Chip Analysis Methylation Pipeline (ChAMP) Bioconductor package (113) offers various tools for processing raw methylation data from these arrays to ensure data quality. This involved filtering out unreliable probes, normalizing methylation data and correcting for potential technical batch effects. After quality control, the data are presented as a beta value matrix for each CpG site, ranging from 0 to 1, which represents the proportion of cells with that specific methylated probe. This beta matrix is then used for constructing epigenetic scores and conducting other analyses.

Figure 5. Pipeline for epigenetic score calculation.



EWAS: genome-wide association study; EpiScore: epigenetic score.

Two sources of input data, reference data from pre-defined probes or EWAS summary statistics and target data from individual methylation information, undergo quality control processes. The epigenetic score can be constructed using two main approaches: epigenetic clock and methylation profile score. The final epigenetic score for an individual is calculated as a weighted sum of the estimated effects and methylation levels across all probes. Original figure.

Another critical issue is the mismatch between the age and tissue type used to obtain methylation data in EWAS and the study samples. Different cell types exhibit specific epigenetic patterns, and commonly used tissues for methylation extraction, such as blood and saliva, contain heterogeneous cell populations that can obscure statistical associations. Furthermore, discrepancies between the age of the study

sample and the EWAS reference data can mask relationships between environmental factors and clinical outcomes later in life (114).

Despite these challenges, epigenetic scores are increasingly valuable for studying the biological mechanisms underlying mental disorders and have demonstrated promising results (110). Continued refinement in methodologies and careful consideration of these factors are essential for advancing the application of epigenetic scores in both research and clinical settings. Just as with PRS methods, the evolution of epigenetic scoring involves incorporating co-methylation data and other strategies to enhance predictive accuracy by improving the selection and quality of CpGs.

1.4 Towards precision medicine

Psychotic disorders are marked by considerable clinical heterogeneity, which underscores the need for more precise and individualized approaches in clinical practice. The current availability of comprehensive biological data is pivotal for advancing our understanding and management of these disorders. Such data richness enables the development of tools for precision medicine in psychiatry. By incorporating individual differences in genetic, epigenetic and neurobiological markers, clinicians can develop more effective, personalized treatment plans that address the unique needs of each patient (115).

Prevention is a key aspect of managing psychotic disorders effectively. Leveraging the full spectrum of available data allows for the design of targeted preventive measures to identify individuals at high risk, enabling closer monitoring and improving prognosis. Early detection and intervention are key for enhancing long-term outcomes. This proactive approach not only mitigates the severity of symptoms but also helps prevent the progression to full-blown psychosis in those identified as high risk. Advances in predictive analytics and machine learning algorithms are instru-

mental in this regard, as they can process complex datasets to uncover patterns and risk factors that traditional methods might overlook.

Patient stratification is another critical element of precision psychiatry. Tailoring pharmacological treatment to individual patients can minimize side effects and improve treatment response and adherence. Traditional trial-and-error approaches are suboptimal and often result in prolonged periods of inadequate treatment, adversely affecting patient outcomes (34). Pharmacogenomics (PGx) offers a promising alternative by guiding treatment decisions based on genetic variations that influence individual responses to medications This enables clinicians to select the most appropriate drugs and dosages from the beginning, reducing the risk of adverse effects and enhancing the likelihood of therapeutic success (116). Such precision in treatment can significantly enhance the overall quality of life for patients.

Despite ongoing challenges, the integration of genetic and epigenetic findings into clinical practice shows great promise. These efforts strive to create a more efficient, patient-centered healthcare system that leverages biological and non-biological data to improve outcomes for individuals with psychotic disorders. Combining diverse data sources hold the potential to uncover biomarkers for disease progression and treatment response, leading to more dynamic and responsive care strategies (117). The continued evolution of precision psychiatry promises to transform the landscape of mental health care, making it more targeted, effective and responsive to the needs of patients with psychotic disorders. In this framework, PRS epigenetic scores are likely to play a crucial role in bridging the genetic and epigenetic foundations of these disorders with precision medicine, offering a promising path forward.

2. Hypotheses

H1: Polygenic risk scores influence the full spectrum of psychosis, from subclinical manifestations to clinical stages, through its impact on diverse underlying factors.

H1.1: Polygenic risk scores of psychiatric disorders, cognition, cannabis use and neuroticism are associated with the onset and progression of both clinical and subclinical psychosis.

H1.2: Polygenic risk scores influencing the individual's global functioning exert their effects through impacts on psychotic symptoms and cognitive functions.

H2: Epigenetic modifications arising from environmental exposures are linked to the development and progression of subclinical psychosis.

H2.1: Alterations in age-related epigenetic profiles significantly impact the development and manifestation of subclinical psychotic features.

H2.2: Epigenetic alterations due to intrauterine stress contribute to the subclinical development and progression of psychosis.

3. Objectives

O1: To investigate how genetic variability captured in polygenic risk scores impacts the clinical continuum of psychosis from subclinical to clinical stages.

O1.1: To identify and characterize genetic factors associated with the onset and progression of early-stage psychosis, detailing its impact on the broader disease trajectory.

O1.2: To elucidate the mediating roles of psychotic symptoms and cognitive performance on the association of genetic susceptibility and functional outcomes in psychosis.

O2: To explore how epigenetic modifications induced by environmental stressors contribute to the development and progression of subclinical psychotic features.

O2.1: To determine the impact of age-related epigenetic profiles and explore their association with subclinical psychotic features.

O2.2: To investigate the relationship between intrauterine stress-induced epigenetic modifications and their influence on subclinical psychotic features.

4. Material, Methods and Results

Psychological Medicine

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Link between cognitive polygenic risk scores and clinical progression after a first-psychotic episode

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Abstract

Background. Clinical intervention in early stages of psychotic disorders is crucial for the prevention of severe symptomatology trajectories and poor outcomes. Genetic variability is studied as a promising modulator of prognosis, thus novel approaches considering the polygenic nature of these complex phenotypes are required to unravel the mechanisms underlying the early progression of the disorder.

Methods. The sample comprised of 233 first-episode psychosis (FEP) subjects with clinical and cognitive data assessed periodically for a 2-year period and 150 matched controls. Polygenic risk scores (PRSs) for schizophrenia, bipolar disorder, depression, education attainment and cognitive performance were used to assess the genetic risk of FEP and to characterize their association with premorbid, baseline and progression of clinical and cognitive status.

Results. Schizophrenia, bipolar disorder and cognitive performance PRSs were associated with an increased risk of FEP [false discovery rate (FDR) $\leqslant 0.027$]. In FEP patients, increased cognitive PRSs were found for FEP patients with more cognitive reserve (FDR $\leqslant 0.037$). PRSs reflecting a genetic liability for improved cognition were associated with a better course of symptoms, functionality and working memory (FDR $\leqslant 0.039$). Moreover, the PRS of depression was associated with a worse trajectory of the executive function and the general cognitive status (FDR $\leqslant 0.001$).

Conclusions. Our study provides novel evidence of the polygenic bases of psychosis and its clinical manifestation in its first stage. The consistent effect of cognitive PRSs on the early clinical progression suggests that the mechanisms underlying the psychotic episode and its severity could be partially independent.

Introduction

Schizophrenia is one of the most incapacitating psychiatric conditions worldwide (Vos et al., 2015). The usual course of the disorder is marked by psychotic episodes with positive (delusions, hallucinations) and negative symptoms (apathy, social withdrawal, avolition) as well as

cognitive impairment, which results in functional disability for the individual (Millan et al., 2016). It has been well-demonstrated that interventions at early stages of the illness – that is, at the onset of first-episode psychosis (FEP) – can improve subsequent outcomes (Albert & Weibell, 2019). Thus, individuals with an FEP constitute a key group for studying the risk factors linked to the development of schizophrenia and other related disorders and its progression in terms of clinical outcome in later stages (Bernardo et al., 2019).

The accomplishment of symptomatic and functional remission is one of the major objectives in FEP interventions (Andreasen et al., 2005). Although the majority of FEP patients may show an improvement in their symptomatology after antipsychotic (AP) treatment, many continue to have long-term impairments in functioning (Amoretti et al., 2021b; Austin et al., 2013; Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004). Outcomes in FEP can vary on a continuum from complete remission and full recovery to more severe disease progress or worse long-term course of illness (Fusar-Poli, McGorry, & Kane, 2017). A potential reason for this variability is the intrinsic diagnostic instability of patients at FEP (Schwartz, 2000). Cognitive impairment can be found to be pre-existent to the first clinical manifestation. It has been reported that cognitive performance can depend on different factors, such as treatment with second-generation APs *v.* first-generation (Harvey, Rabinowitz, Eerdekens, & Davidson, 2005), APs dose (Ballesteros et al., 2018), the potential effects of AP medications due to excessive dopaminergic blockades (Sakurai et al., 2013) and their associated anticholinergic burden properties (Ballesteros et al., 2018), the symptomatology amelioration (Faber, Smid, van Gool, Wiersma, & van den Bosch, 2012) and/or depending on the stage of the illness (Ballesteros et al., 2018). Cognitive alterations may also persist even during remission periods (Bowie & Harvey, 2006; Chang et al., 2017; Cuesta et al., 2015) and tends to be linked to more severe negative symptomatology and functioning (Milev, Ho, Arndt, & Andreasen, 2005; Puig et al., 2017). Moreover, the cognitive reserve (CR) has become a subject of study in mental disorders, as a resilience factor based on the ability of the brain to cope with psychopathology and offset the harmful effects of the disorder (Stern, 2014). In severe mental illnesses such as schizophrenia, CR has proved to predict clinical, cognitive and functional outcomes (Amoretti et al., 2018). In addition, higher CR has also been considered a protective factor in psychiatric populations (Grande et al., 2017), and has been suggested that in schizophrenia samples, it delays the clinical diagnosis threshold and severity of symptoms (Herrero et al., 2020). Therefore, the early identification of clinical, sociodemographic and biological features may be important to identify subsets of patients with similar characteristics, facilitating personalized treatment approaches (Compton, Kelley, & Ionescu, 2014).

The genetic burden for schizophrenia has been associated with related endophenotypes – i.e. measurable and heritable components linked to the external manifestation of the disorder – in healthy relatives (Greenwood, Shutes-David, & Tsuang, 2019; Seidman et al., 2015), thus evidencing common pathophysiological mechanisms. Approaches using genetic constructs such as the polygenic risk scores (PRSs) allow us to study mental disorders and overcome some limitations of candidate-gene strategies (Assary, Vincent, Keers, & Pluess, 2018; Collins, Kim, Sklar, O'Donovan, & Sullivan, 2012). Previous studies have linked the schizophrenia and bipolar disorder PRSs with symptom severity, comorbid conditions and cognitive functioning (Mistry, Harrison, Smith, Escott-Price, & Zammit, 2018a, 2018b), further evidencing the critical role of a common genetic background between mental disorders and their clinical manifestation.

The aim of this study was to analyze the association of psychopathological and cognitive PRSs in the early progression of the clinical manifestation after an FEP. We hypothesized that PRSs reflecting a greater liability for mental disorders would be associated with psychosis onset and a slower recovery of symptoms and psychosocial functionality after the FEP. Additionally, PRSs reflecting cognitive abilities would be linked to an improved cognitive status and progression after the FEP.

Methods

This study is part of the multicentric project 'Phenotype–genotype interaction: application of a predictive model in first psychotic episodes' (PEPs project). A complete description of the PEPs protocol has been published previously (Bernardo et al., 2013). This longitudinal 2-year prospective follow-up study presents clinical parameters from various assessments/visits: baseline, 2-month, 6-month, 1-year and 2-year follow-up.

Sample

During the recruitment period (2009–2012), 335 subjects who presented an FEP and 253 healthy control subjects were included in the PEPs project. Patients included in the main project met the following inclusion criteria: aged between 7 and 35 years at recruitment; presence of psychotic symptoms of less than 12 months' duration; the ability to speak Spanish correctly and providing written informed consent. The exclusion criteria were: mental retardation according to DSM-IV-TR criteria (American Psychiatric Association, 1994); history of head trauma with loss of consciousness and presence of an organic disease with mental repercussions. Healthy controls were matched with patients according to their age (±10% of flexibility), sex and the parental socio-economic status (SES) (±1 level), determined using the Hollingshead's Two-Factor Index of Social Position, which has five potential levels: high, medium-high, medium, medium-low and low (Hollingshead & Redlich, 2007). Controls also had to be fluent in Spanish and give written informed consent. The exclusion criteria for controls were the same as for the patients, plus the presence of a present or past psychotic disorder or major depression and having a first-degree relative with psychotic disorder history.

For the present study, we identified those subjects from the PEPs cohort who provided blood samples for genetic analysis, passed the genetic quality control (see below), aged ⩾16 years old and had European ancestry. Thus, the final sample comprised of 233 FEP subjects (Table 1) and 145 healthy controls [97 males (66.9%), mean age = 24.5 years (S.D. = 5.4)]. First assessments of clinical and cognitive data were available for a range of 160–232 and complete follow-up data for a range of 89–182 FEP patients. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice and the Hospital Clinic Ethics and Research Board. Informed consent was obtained from all participants or from parents or legal guardians of under-age subjects.

Assessments

Sociodemographic, clinical and pharmacological assessments

The complete assessment of the PEPs project is reported by Bernardo et al. (2013). Within the PEPs project, a complete

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Table 1. Main sociodemographic, pharmacological and clinical features of the FEP sample

Feature		Mean (s.d.) or *n* (%)
Sex	Male	162 (69.5%)
	Female	71 (30.5%)
Age at FEP		24.6 (5.7)
Psychosis type	Non-affective	196 (84.1%)
	Affective	37 (15.9%)
Main AP medication at basal point	Olanzapine	78 (34.9%)
	Risperidone	66 (29.6%)
	Aripiprazole	30 (13.5%)
	Paliperidone	18 (8.1%)
	Quetiapine	13 (5.8%)
	Amisulpride	8 (3.6%)
	Clozapine	5 (2.2%)
	Haloperidol	3 (1.3%)
	Ziprasidone	1 (0.4%)
	Zuclopenthixol	1 (0.4%)
Other medication at basal point	Anxiolytic	99 (43.6%)
	Antidepressant	29 (12.8%)
	Antiepileptic	21 (9.3%)
	Lithium	15 (6.6%)
AP CEDD (12 months)		133.9 (140.8)
AP CEDD (24 months)		89.7 (95.9)
PAS		44.8 (23.9)
CR		76.7 (12.1)

AP, antipsychotic; PAS, Premorbid Adjustment Scale; CR, cognitive reserve; CEDD, chlorpromazine equivalent daily doses.

psychopathological assessment was carried out during the 2 years of follow-up. For the present study, due to the potential loss of sample at 2 years, we focused on symptomatology and functional data for a period of 1 year.

General sociodemographic data and clinical assessment: Sex, age and age at the onset of the illness were collected along with the duration of the untreated psychosis and the parental SES (Hollingshead & Redlich, 2007). The diagnosis was confirmed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) (SCID-I and -II) (First, Gibbon, Spitzer, Williams, & Benjamin, 1997; González-Pinto et al., 2008) according to DSM-IV criteria. The psychopathological assessment was carried out with the Spanish versions of the different scales. Symptomatology was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987; Peralta & Cuesta, 1994). Higher scores on this scale indicate greater severity. Regarding the psychosocial functioning assessment, the overall functional outcome was assessed by means of the Functioning Assessment Short Test (FAST) (Amoretti et al., 2021a; Rosa et al., 2007). The FAST scale comprises six specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. Higher scores indicate worse functioning. The Premorbid Adjustment Scale (PAS) (Cannon-Spoor, Potkin, & Jed Wyatt, 1982) was applied retrospectively to assess premorbid adjustment. The PAS was completed based on information from patients and parents and/or close relatives. Higher scores indicate worse premorbid adjustment.

Pharmacological assessment: Pharmacological treatment was also collected at each visit. Chlorpromazine equivalents, expressed as chlorpromazine equivalent daily dose (CEDD), based on international consensus (Gardner, Murphy, O'Donnell, Centorrino, & Baldessarini, 2010) were calculated for AP medication. As this was a naturalistic study, there were no specific guidelines for treatment, so patients received pharmacological treatment based on the clinician's decision. Prior treatment with APs did not exceed 12 months at study entry (Bioque et al., 2016). For this study, the dose of AP was calculated as the mean CEDD.

Cognitive assessment

In the PEPs project, the cognitive assessment at baseline was performed in the second month after inclusion in order to ensure the clinical stability of patients after the FEP and was repeated at 2-year follow-up (Cuesta et al., 2015).

The neuropsychological battery measured the following cognitive domains: (1) sustained attention, assessed with different variables from the Continuous Performance Test-II (CPT-II) (Conners, Epstein, Angold, & Klaric, 2003), version 5; (2) verbal learning and memory, evaluated with the Verbal Learning Test Spain Complutense for adults (TAVEC) (Benedet, Christiansen, & Goodglass, 1998); (3) working memory, based on the Digit Span Subtest and the Letter-Number Sequencing Subtest of the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997) and (4) executive functioning, evaluated using the Wisconsin Card Sorting Test (WCST) (Heaton, 1993), corrected by age and educational level. Following our previous work, a principal component analysis (PCA) was performed between 10 neuropsychological variables from the battery tests aforementioned identifying the four cognitive domains described above (see online Supplementary Table S1) (Amoretti et al., 2020). Higher scores corresponded to better performance in all the cognitive domains except for attention. Additionally, a global cognitive score was obtained from the aforementioned cognitive domains (Amoretti et al., 2020). All the tests and measures used for domain summary scores are described elsewhere (Bernardo et al., 2013; Cabrera et al., 2016; Cuesta et al., 2015). To assess CR we used a 'Cognitive reserve score' conducted by Amoretti et al. in previous works and also framed in the PEPs project (Amoretti et al., 2016, 2018). To create this 'Cognitive reserve score', the three most commonly proposed proxy indicators of CR were used (Amoretti et al., 2016, 2018; Barnett, Salmond, Jones, & Sahakian, 2006; de la Serna et al., 2013; González-Ortega et al., 2019). These include IQ, education and participation in leisure, social and physical activities. Higher scores in this proxy correspond to better performance.

In the PEPs project, all clinical assessments were administered by expert clinicians after done an extensive training in each scale, except for those that were self-administered. Those who failed the first evaluation were reassessed. In the cognitive assessment, to evaluate the differences between raters, an interrater reliability study was also conducted among different neuropsychologists at each center. A good to excellent inter-rater reliability among

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psychologists was indicated by intraclass correlation coefficients >0.80 in two of the tests of the battery: the WAIS Vocabulary subtest and WCST, in which the final score may partially depend on the judgment of the psychologist administering and correcting the test. The complete method and the results found in the PEPs project have already been described in a specific work (Cuesta et al., 2015).

Blood samples and genotyping

Blood samples were collected in K2EDTA BD Vacutainer EDTA tubes (Becton Dickinson, Franklin Lakes, New Jersey), stored at −20°C and sent to the central laboratory. DNA was extracted with the MagNA Pure LC DNA isolation kit – large volume and MagNA Pure LC 2.0 Instrument (Roche Diagnostics GmbH, Mannheim, Germany). DNA concentration was determined by absorbance (ND1000, NanoDrop, Wilmington, Delaware). A total of 2.5 µg of genomic DNA was sent for genotyping at the Spanish National Genotyping Centre (CeGen) using Axiom™ Spain Biobank Array (developed in the University of Santiago de Compostela, Spain).

PRS calculation

Genotyping data were submitted to the Michigan Imputation Server (Das et al., 2016), following the standard pipeline for Minimac4 software and setting a European population reference from build GRCh37/hg19, reference panel HRC 1.1 2016 and Eagle v2.4 phasing.

For the PRS calculation, genome-wide association study (GWAS) summary results from multiple repositories (Psychiatric Genomics Consortium and SSGAC). The selected PRSs were: schizophrenia (PRS_{SZ}; 69 369 cases and 236 642 controls) (Ripke, Walters, & O'Donovan, 2020), bipolar disorder (PRS_{BD}; 41 917 cases; 371 549 controls) (Mullins et al., 2021), depression (PRS_{DEP}; 246 363 cases; 561 190 controls) (Howard et al., 2019), education attainment and cognitive performance (PRS_{EA} and PRS_{CP}; 1 131 881 and 257 841 individuals; respectively) (Lee et al., 2018). Higher psychopathological PRSs reflect a greater liability for the disorder and higher cognitive scores a better cognitive performance; duplicated and unknown strand GWAS summary single-nucleotide polymorphisms (SNPs) were excluded.

The aforementioned PRSs were selected for this study according to multiple criteria. The psychopathological PRSs (PRS_{SZ}, PRS_{BD}, PRS_{DEP}) were chosen for their clinical proximity to an FEP and the shared genetic background among the disorders (Lee et al., 2019). On the other hand, while PRS_{CP} captures more specific cognitive abilities, PRS_{EA} also includes other personal and social abilities that reflect the academic success.

The quality control was performed with PLINK v1.07 (Purcell et al., 2007). Inclusion criteria for SNPs were minor allele frequency >0.1, Hardy–Weinberg equilibrium $p > 10^{-6}$, marker missingness <0.01 and imputation INFO > 0.8. Pruning was done using a window/step size of 200/50 kb and $r^2 > 0.25$. Sample quality control included individuals with heterozygosity values within three standard deviations (S.D.) from the mean, a missingness rate <0.01, matching chromosomal and database-labeled sex, relatedness π-hat < 0.125 and self-reported European ancestry. PRS's capacity to discriminate cases from controls and predictivity has been highly correlated with ancestry, since most reference GWAS participants are European (Perkins et al., 2020; Vassos et al., 2017).

PRSs were constructed using PRSice-2 v2.3.3 software (Choi & O'Reilly, 2019), with clumping parameters at 250 kb and $r^2 > 0.1$ and using the odds ratio (OR) or beta values of SNPs in the reference GWAS data that had $p < 0.05$. This p value was used as the default threshold for the five PRSs to avoid the genetic noise of weakly associated SNPs in the reference GWAS and model overfitting (Choi, Mak, & O'Reilly, 2020). Further information about the constructed PRSs can be found in online Supplementary Fig. S1.

Statistical analysis

All the analyses were performed with R (R Core Team, 2017). To avoid false-positive results, the false discovery rate (FDR) method was applied and the significance threshold was set at 0.05. A genetic PCA was performed to control population stratification (Patterson, Price, & Reich, 2006) by means of the SNPRelate package, and the first 10 components were used as covariates in the statistical analyses.

All PRSs were dichotomized into high risk PRS (above the highest 75% score quartile) and mid-to-low risk PRS (below the highest 75% score quartiles). This procedure was performed using the whole sample to better capture the effect of high genetic risk and avoid putative intermediate and low scores masking effect (Lin et al., 2018; Mas et al., 2020; Vassos et al., 2017; Wang et al., 2018).

The comparison of sociodemographic, pharmacological, clinical and cognitive variables between the whole FEP sample (n = 335) and the present study FEP sample (n = 233) as well as sex and age differences between FEP and controls were performed by means of chi-square and t tests.

The risk of the PRSs for an FEP was assessed by a chi-square test and the associated ORs. The association between basal PRS and different clinical outcomes – in terms of psychopathological symptoms, psychosocial functioning and cognitive status – was evaluated with generalized linear models corrected by sex, age, previous AP treatment days and the first 10 components of the genetic PCA. For those individuals with complete data at all assessment points, linear mixed-effects modeling was used for longitudinal analyses, considering the month of assessment as a random effect and the PRS as the fixed effect, corrected by sex, age, previous AP days, AP dose (1 year AP CEDD mean for symptomatology and functionality and 2 years AP CEDD mean for cognitive status) and the first 10 components of the genetic PCA. For linear mixed-effects models with a significant between-subject difference, post-hoc analyses were performed to characterize the effect of the PRSs at each assessment point. These analyses were performed by means of generalized linear models including sex, age, previous AP treatment days and the first 10 components of the genetic PCA as covariates.

Results

Descriptive statistics

The FEP sample of the present study (n = 233) was compared to the total FEP sample of the PEPs project (n = 335). The sample of the study was found representative, only different for the mean age (the sample study was 23.6 years and the total PEPs 24.6 years, p = 0.046) (online Supplementary Table S2). The main features of the FEP sample of the study at study entry and premorbid status are reported in Table 1 and the symptomatology,

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psychosocial functioning and cognitive measurements for the assessments during the follow-up in Table 2. The dropout rate of the FEP patients ranged from 19.8% to 38.4%.

FEP risk

There were no age or sex differences in the FEP individuals and controls ($p = 0.908$, $p = 0.637$; respectively). All PRSs were used to assess their association with the risk of suffering an FEP in our cohort. There was a higher proportion of high risk PRS_{SZ} [31.8% *v.* 15.2%, FDR = 0.004, OR (95% CI) = 2.60 (1.53–4.42)] and PRS_{BD} [29.2% *v.* 17.2%, FDR = 0.028, OR (95% CI) = 1.98 (1.18–3.31)] and a lower proportion of high risk PRS_{CP} [20.2% *v.* 32.4%, FDR = 0.034, OR (95% CI) = 0.53 (0.33–0.85)] in FEP individuals (online Supplementary Table S1). Thus, high scores PRS_{SZ} and PRS_{BD} conferred an increased risk of FEP and high scores for PRS_{CP} had a protective effect.

Baseline analysis

Symptomatology, psychosocial functionality and cognitive status were evaluated at baseline for the FEP patients. No significant effects of the PRSs were found for the baseline measurement of symptoms and functionality. As for the cognitive status, higher PRS_{DEP} was found to be associated with decreased executive function (FDR = 0.019), higher PRS_{EA} and PRS_{CP} with an increased working memory (FDR = 0.039, FDR = 0.024; respectively) and with an increased CR (FDR = 0.037, FDR = 0.001; respectively) (Table 3). Baseline association analyses of clinical status and PRSs constructed with different p value thresholds can be found in online Supplementary Table S4.

Longitudinal analysis

Follow-up clinical data were used for the longitudinal analyses. Increased PRS_{EA} was associated with trajectories reflecting the manifestation of less positive and total PANSS symptoms (FDR = 0.019, FDR = 0.026; respectively), but no post-hoc differences were found, thus showing no significant effect of the PRS_{EA} on symptom severity at any discreet assessment point. Additionally, a trend of an association of PRS_{CP} and positive symptom progression was found (FDR = 0.051) (Fig. 1a; Table 4).

Regarding the psychosocial functionality progression, higher PRS_{EA} was associated with trajectories reflecting an increased autonomy, cognitive functioning and a lower total score (FDR = 0.010, FDR = 0.006, FDR = 0.039; respectively). A trend of an association of PRS_{EA} and the financial issues was found (FDR = 0.055). Higher PRS_{SZ} was associated with a worse progression of the leisure time domain (FDR = 0.029). Post-hoc differences were found for PRS_{EA} and cognitive functioning at month 6 (FDR = 0.029) (Fig. 1b; Table 4).

Cognitive measurements were also used for longitudinal assessment. Higher PRS_{EA} and PRS_{CP} were associated with trajectories reflecting an increased working memory (FDR = 0.001, FDR = 0.030; respectively) and higher PRS_{DEP} with a decrement of the executive function and the composite score (FDR = 1.08×10^{-4}, FDR = 0.001; respectively). Post-hoc differences were found for PRS_{CP} and working memory at month 24 (FDR = 0.024) and for PRS_{DEP} and the executive function at baseline and month 24 (FDR = 0.006, FDR = 0.007; respectively) and for the composite score at baseline and month 24 (FDR = 0.025, FDR = 0.003; respectively) (Fig. 1c; Table 4). Longitudinal association analyses of clinical status and PRSs constructed with different p value thresholds can be found in online Supplementary Table S5.

Discussion

Main findings

Early intervention at the initial manifestation of severe mental disorders is critical to prevent poor outcomes, and therefore the characterization of factors associated with the prognosis such as genetics are key to understand the underlying mechanisms. The present study aimed to investigate the role of the genetic burden for psychopathological disorders and cognitive features in the clinical progression after an FEP. The PRS reflecting the cognitive performance was associated with the CR. Moreover, educational attainment, cognitive performance and depression PRSs were associated with the course of symptoms, psychosocial functioning and the cognitive status after the psychosis onset. It is noteworthy that increased PRSs for schizophrenia and bipolar disorder conferred an increased risk of suffering an FEP but did not influence symptomatologic or cognitive parameters, providing evidence that early symptom improvement might be partially independent from the psychopathological mechanisms that determine the onset of psychosis.

Schizophrenia PRS

PRSs calculated with schizophrenia GWAS have been widely associated with risk of psychopathology development in chronic and FEP samples (Perkins et al., 2020; Santoro et al., 2018; Sørensen et al., 2018; Toulopoulou et al., 2019; Vassos et al., 2017; Wang et al., 2018; Zheutlin et al., 2019). To the best of our knowledge, this is the first study to replicate these previous findings using PRSs constructed with the third and largest wave of the Psychiatric Genomics Consortium (Ripke et al., 2020). Previous findings report inconsistent associations with clinical features such as symptom severity, neurocognitive performance and treatment resistance (Chen et al., 2018; Jonas et al., 2019; Ohi et al., 2018; Perkins et al., 2020; Richards et al., 2020; Santoro et al., 2018; Shafee et al., 2018; Sørensen et al., 2018; Werner et al., 2020; Wimberley et al., 2017; Zhang et al., 2019), possibly due to the heterogeneity of samples in terms of schizophrenia progression and AP treatment consequences. Considering the lack of association of PRS_{SZ} with clinical or cognitive features in our FEP sample (only with the recovery of leisure time functionality domain) and otherwise positive associations in the literature, we cannot rule out the possibility that this PRS could have a role for some specific clinical manifestations – e.g. a greater number of psychotic episodes, an earlier age at onset or worse response to treatment – that lead to a debilitating and chronic course, recognizable in latter stages several years after the onset of the disorder.

Bipolar disorder PRS

The effect of bipolar disorder PRSs in schizophrenia has been described in multiple studies (Mistry et al., 2018a), but no previous information about its role on FEP risk can be found in the literature. Here, we report for the first time the risk of PRS_{BD} to develop an FEP. Similarly to the PRS_{SZ}, we could not find any effect of PRS_{BD} on the clinical and cognitive status, in accordance

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Table 2. Clinical and cognitive assessments during the follow-up

	Basal		2-month		6-months		12-months		24-months		Available sample for longitudinal analyses
	n	Mean (s.d.)	*n*	Mean (s.d.)	*n*	Mean (s.d.)	*n*	Mean (s.d.)	*n*	Mean (s.d.)	
Symptomatology											
Positive	232	18.5 (8.2)	223	18.8 (5.3)	207	10.5 (4.3)	186	10.1 (4.6)	–	–	182
Negative	232	18.3 (7.9)	223	16.7 (6.8)	207	15.3 (6.4)	186	14.7 (6.5)	–	–	182
General	232	37.4 (12.6)	223	30.0 (10.4)	207	26.9 (8.7)	186	26.0 (9.6)	–	–	182
Total	232	74.2 (24.1)	223	58.5 (20.2)	207	52.7 (17.0)	186	50.8 (18.4)	–	–	182
Functionality											
Autonomy	226	4.3 (3.5)	213	3.54 (3.1)	200	3.25 (2.9)	177	2.86 (2.9)	–		158
Occupational functioning	226	7.9 (5.5)	213	7.1 (5.2)	200	6.1 (5.2)	177	5.6 (5.2)	–	–	158
Cognitive functioning	226	5.8 (3.9)	213	4.8 (3.7)	200	3.8 (3.3)	177	3.6 (3.4)	–		158
Financial issues	226	1.5 (1.8)	213	1.2 (1.6)	200	0.9 (1.4)	177	0.9 (1.4)	–	–	158
Interpersonal relationships	226	6.7 (4.9)	213	5.6 (4.5)	200	4.9 (4.3)	177	4.5 (4.3)	–	–	158
Leisure time	226	2.1 (1.8)	213	2.0 (1.8)	200	1.8 (1.7)	177	1.7 (1.6)	–	–	158
Total	226	28.0 (16.4)	213	24.2 (15.3)	200	20.8 (14.8)	177	19.1 (14.5)	–	–	158
Cognitive status											
Attention	–	–	166	88.6 (8.9)	–	–	–	–	104	86.0 (9.5)	93
Working memory	–	–	188	79.8 (16.0)	–	–	–	–	115	84.1 (15.7)	114
Verbal memory	–	–	181	134.0 (50.4)	–	–	–	–	112	159.0 (47.7)	107
Executive function	–	–	177	126.0 (43.7)	–	–	–	–	109	150.0 (41.6)	102
Composite score	–	–	160	294.0 (50.2)	–	–	–	–	99	330.0 (49.0)	89

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Table 3. Basal association of PRSs with clinical scales, cognitive status and premorbid adjustment

	PRS_{SZ}				PRS_{BD}				PRS_{DEP}				PRS_{EA}				PRS_{CP}			
	Estimate	*t*	R^2	FDR	Estimate	*t*	R^2	FDR	Estimate	*t*	R^2	FDR	Estimate	*t*	R^2	FDR	Estimate	*t*	R^2	FDR
Symptomatology																				
Positive	0.451	0.330	0.061	0.742	−1.098	−0.782	0.063	1.000	0.919	0.657	0.062	0.768	1.985	1.457	0.070	0.147	2.332	1.684	0.074	0.188
Negative	−0.512	−0.384	0.051	0.832	0.409	0.298	0.051	0.967	−1.160	−0.852	0.053	1.000	1.625	1.222	0.059	0.357	1.557	1.150	0.058	0.222
General	0.647	0.317	0.061	1.000	−0.541	−0.256	0.060	1.000	−0.375	−0.179	0.059	0.945	3.817	1.869	0.072	0.206	3.112	1.485	0.065	0.267
Total	0.786	0.195	0.050	1.000	−1.995	−0.482	0.050	1.000	−0.568	−0.138	0.049	0.975	6.643	1.659	0.065	0.152	6.009	1.473	0.061	0.124
Functionality																				
Autonomy	0.125	0.208	0.035	0.835	1.154	1.909	0.054	0.173	−0.477	−0.774	0.038	0.660	0.714	1.202	0.043	0.462	0.499	0.822	0.039	0.412
Occupational functioning	0.131	0.144	0.078	0.886	0.695	0.750	0.081	1.000	−0.667	−0.713	0.081	0.715	−0.791	−0.875	0.082	0.765	−0.138	−0.150	0.078	0.881
Cognitive functioning	1.045	1.519	0.033	0.392	0.545	0.778	0.024	0.656	0.029	0.041	0.021	0.967	0.842	1.234	0.029	0.438	0.828	1.191	0.028	0.235
Financial issues	0.425	1.670	0.053	0.353	0.178	0.691	0.050	0.370	−0.050	−0.186	0.055	0.541	0.026	0.103	0.046	0.844	0.375	1.443	0.049	0.881
Interpersonal relationships	1.082	1.267	0.032	0.625	0.904	1.058	0.040	0.546	−0.460	−0.527	0.035	0.628	0.264	0.316	0.033	1.000	0.666	0.776	0.033	0.554
Leisure time	−0.543	−1.791	0.073	0.248	0.328	1.054	0.065	0.518	−0.470	−1.507	0.079	0.216	0.644	2.128	0.075	0.246	0.250	0.817	0.067	0.357
Total	1.675	0.587	0.046	0.558	4.062	1.411	0.054	0.480	−2.838	−0.974	0.049	0.497	1.837	0.650	0.046	0.516	2.244	0.780	0.047	0.872
PAS	−2.022	−0.525	0.139	0.544	3.795	0.953	0.142	0.440	−6.333	−1.565	0.148	0.372	7.278	1.868	0.156	0.081	7.084	1.791	0.149	0.105
Cognitive status																				
Attention	−2.082	−1.343	0.182	0.629	0.810	0.524	0.173	0.698	−0.523	−0.307	0.175	0.814	2.040	1.310	0.174	0.627	3.469	2.227	0.195	0.115
Working memory	2.768	1.022	0.196	0.925	−2.444	−0.880	0.194	0.571	2.022	0.691	0.193	0.490	−5.680	−2.087	0.213	0.039	−6.936	−2.546	0.223	0.024
Verbal memory	8.978	0.984	0.115	0.490	−5.716	−0.620	0.111	0.536	16.350	1.691	0.126	0.279	−8.302	−0.896	0.114	0.372	−9.842	−1.063	0.116	0.579
Executive function	2.841	0.348	0.108	0.893	2.326	0.280	0.108	1.000	25.468	3.064	0.153	0.019	−1.599	−0.201	0.108	0.967	−4.188	−0.510	0.111	0.978
Composite score	0.409	0.469	0.175	0.645	1.156	1.313	0.179	0.565	−0.654	−0.726	0.206	0.075	0.610	0.703	0.176	0.554	0.590	0.668	0.180	0.634
CR	1.641	0.822	0.186	0.425	−2.103	−1.022	0.192	0.380	1.611	0.752	0.183	0.440	−4.654	−2.329	0.203	0.037	−6.652	−3.342	0.247	0.001

SZ, schizophrenia; BD, bipolar disorder; DEP, depression; EA, education attainment; CP, cognitive performance; PAS, Premorbid Adjustment Scale; CR, cognitive reserve.
Significant results are marked in bold.
Corrected by sex, age, previous AP treatment days and first 10 components of genetic PCA.

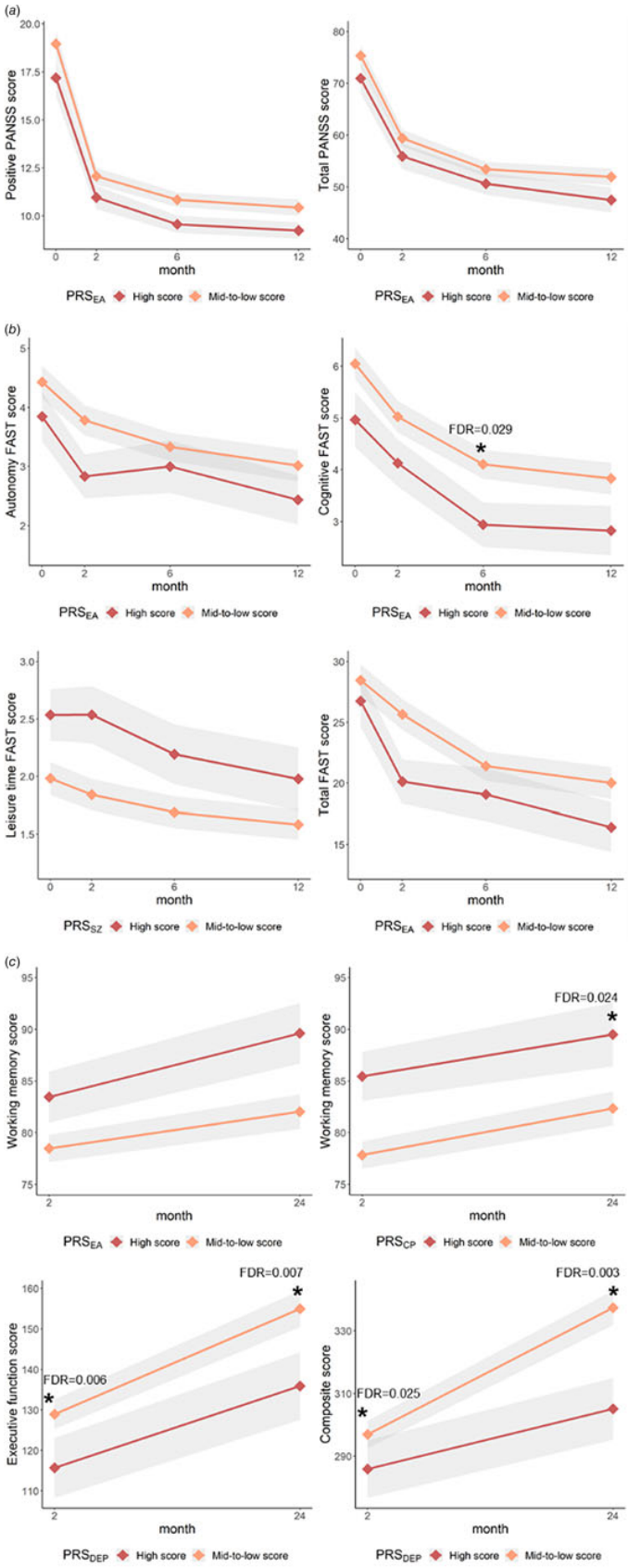

Fig. 1. Summary of the progression of clinical measures during follow-up. The plots show the mean of each clinical measurement and standard error range for each month of assessment. (a) Symptomatology progression, (b) psychosocial functionality progression and (c) cognitive progression. Significant post-hoc analyses are marked with an asterisk. DEP, Depression; EA, education attainment; CP, cognitive performance.

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Table 4. Longitudinal association of PRSs with clinical scales and cognitive status

	PRS_{SZ}				PRS_{BD}				PRS_{DEP}				PRS_{EA}				PRS_{CP}			
	Estimate	*t*	R^2	FDR	Estimate	*t*	R^2	FDR	Estimate	*t*	R^2	FDR	Estimate	*t*	R^2	FDR	Estimate	*t*	R^2	FDR
Symptomatology																				
Positive	−0.304	−0.360	0.282	1.000	−0.958	−1.100	0.284	0.820	−0.195	−0.217	0.281	0.829	2.231	2.636	0.299	0.019	1.723	1.970	0.291	0.051
Negative	0.200	0.188	0.119	0.851	0.718	0.652	0.120	0.773	−1.028	−0.908	0.121	1.000	1.951	1.809	0.130	0.145	1.738	1.573	0.127	0.118
General	0.253	0.158	0.216	0.874	−1.854	−1.128	0.220	0.784	−0.637	−0.375	0.216	1.000	3.512	2.184	0.231	0.061	2.498	1.506	0.223	0.134
Total	0.156	0.051	0.242	0.959	−2.090	−0.661	0.243	1.000	−1.848	−0.567	0.243	0.857	7.703	2.509	0.261	0.026	5.973	1.886	0.253	0.061
Functionality																				
Autonomy	−0.269	−0.553	0.081	0.871	0.481	0.960	0.083	1.000	−0.220	−0.426	0.081	0.671	1.382	2.852	0.110	0.010	0.854	1.700	0.091	0.091
Occupational functioning	−0.219	−0.277	0.100	0.782	0.557	0.681	0.101	1.000	0.386	0.460	0.100	0.969	0.044	0.054	0.099	0.957	0.190	0.230	0.099	1.000
Cognitive functioning	0.115	0.225	0.103	1.000	−0.024	−0.046	0.103	0.964	0.139	0.257	0.103	1.000	1.526	3.017	0.130	0.006	0.895	1.694	0.112	0.092
Financial issues	−0.031	−0.127	0.088	0.899	0.217	0.857	0.091	1.000	−0.182	−0.699	0.090	0.728	0.517	2.087	0.103	0.077	0.343	1.347	0.094	0.180
Interpersonal relationships	−0.769	−1.091	0.090	0.831	−0.130	−0.178	0.086	0.859	−0.663	−0.884	0.088	0.568	1.585	2.227	0.104	0.055	0.449	0.609	0.087	0.544
Leisure time	−0.636	−2.621	0.099	0.029	0.086	0.334	0.077	1.000	0.002	0.008	0.077	0.994	0.468	1.859	0.088	0.130	0.323	1.250	0.082	0.213
Total	−1.763	−0.765	0.124	1.000	1.199	0.501	0.122	0.925	−0.527	−0.215	0.122	0.830	5.476	2.359	0.142	0.039	3.073	1.281	0.127	0.202
Cognitive status																				
Attention	−2.551	−1.622	0.258	0.323	1.790	1.109	0.254	0.270	−2.185	−1.200	0.255	0.349	2.966	1.863	0.264	0.130	1.725	1.052	0.251	0.295
Working memory	3.380	1.218	0.181	0.677	−3.012	−1.050	0.180	0.444	1.408	0.454	0.175	0.444	−9.931	−3.693	0.242	0.001	−6.216	−2.203	0.197	0.030
Verbal memory	11.851	1.283	0.139	0.303	−8.943	−0.936	0.137	0.351	20.324	2.019	0.155	0.137	−13.414	−1.435	0.136	0.308	−9.492	−0.997	0.162	0.321
Executive function	2.277	0.280	0.162	0.780	−3.274	−0.397	0.163	1.000	35.197	4.295	0.247	1.08×10^{-4}	10.113	1.266	0.169	0.416	0.053	0.006	0.162	0.995
Composite score	7.960	0.806	0.232	0.422	−13.191	−1.325	0.242	0.282	40.301	3.799	0.302	0.001	−7.818	−0.790	0.233	0.863	−7.294	−0.729	0.233	0.468

SZ, schizophrenia; BD, bipolar disorder; DEP, depression; EA, education attainment; CP, cognitive performance.
Significant results are marked in bold.
Corrected by sex, age, previous AP days and AP dose (1 year AP CEDD mean for symptomatology and functionality and 2 years AP CEDD mean for cognitive status) and first 10 components of genetic PCA.

with the study of Richards et al. (2020). On the other hand, no association of PRS_{DEP} with FEP risk could be found. Yet, worse scores of this PRS were linked to impaired cognitive status after an FEP. Our findings could be capturing the defective cognitive functionality associated with the impaired dysfunctional goal-directed decision-making processes and reward maximization found in mood disorders (Saperia et al., 2019).

Cognitive PRSs

Impaired cognitive functions of schizophrenia patients can be found before illness onset and therefore they are not entirely a consequence of the psychotic (Ayesa-Arriola et al., 2021). This places abnormal neurodevelopment as a core component in the onset of schizophrenia (Kobayashi et al., 2014) while also suggesting a genetic etiology (Dickinson et al., 2020). In order to delve into the genetic foundations of the clinical and cognitive manifestation of our FEP sample, two scores reflecting the cognitive performance of the general population were calculated. While PRS_{CP} specifically captures the genetic basis for neurocognitive capacities, PRS_{EA} – based on the years of schooling and comprising >1.1 million individuals – also relates to social, economic and health outcomes (Lee et al., 2018). For the first time we are able to describe a protective effect of the genetics underlying cognitive features in the early progression of clinical manifestation after an FEP. At study entry, the effect of cognitive PRSs could only be detected on the cognitive status. Nonetheless, the role of PRS_{EA} on the evolution of symptom severity and functionality suggests that the protective factor of the cognitive PRS may have a more relevant role in symptom and functionality regain. Regarding the cognitive progression, the protective effect of cognitive PRSs on the working memory domain agrees with the work of Richards and colleagues, in which a very strong link between the cognitive PRSs and the general intelligence factor is reported (Richards et al., 2020).

Cognitive reserve

The premorbid cognitive status (measured as CR) has been proposed as a mediator between the clinical manifestation and the final psychosocial functioning, possibly acting as a coping mechanism for the long-term effects on patients (Amoretti et al., 2020). CR has been consistently identified as baseline and 2-year mediator of symptomatology, functionality and cognition in previous studies of the PEPs project (Amoretti et al., 2016, 2018, 2020; González-Ortega et al., 2019). In the present work, the PRS_{CP} was associated with a better cognitive progression, higher FEP risk as well as with an increased CR. Moreover, it has been demonstrated in our previous studies that having a high CR and better premorbid adjustment may confer a better prognosis (Amoretti et al., 2021b). If the role of CR as mediator of symptomatology, functionality and cognition is confirmed and the association of cognitive PRSs with CR is replicated in independent cohorts, it could be considered that individuals with increased a genetic basis for a better cognition would be more resilient to the distressful effects of the psychotic episode and have a better prognosis.

Limitations and strengths

Some limitations of the present work should be taken into consideration. First, sample size is moderately limited in the longitudinal follow-up due to patient drop-out and therefore the statistical analysis might be underpowered to detect small effects. In addition, due to constraints associated with the PANSS (Blanchard, Kring, Horan, & Gur, 2011), another limitation of the study has been the absence of a specific scale to assess negative symptomatology, such as the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011; Mané et al., 2014) or a specific tool to assess the CR, as at the time that the PEPs project was developed (2009–2012) there was no validated instrument to measure the CR as the Cognitive Reserve Assessment Scale in Health (CRASH) (Amoretti et al., 2019) and the BNSS was under development. However, this study comprises one of the largest and best characterized FEP samples in the literature, with a naturalistic design and thus representative of the psychiatric population without the confounding effect of prolonged AP treatment, medical comorbidities or chronicity. The subsample used for the present study is comparable with the total PEPs sample, with the exception of a small difference of mean age (most probably due to age restriction criteria). The PRSs have been calculated with the largest GWAS from international consortiums and thus the comprised genetic variants have a great capacity to capture the genetic susceptibility of the phenotypes. Strict quality control of genetic data and multiple test significance thresholding have been implemented to prevent methodological artifacts and statistical errors in the results.

Conclusions

Novel genetic approaches considering the polygenic etiology of psychotic disorders are crucial to disentangle the molecular basis of the pathophysiological mechanisms underlying the onset and progression of schizophrenia. Cognitive rather than psychopathological polygenic scores were found widely associated to premorbid cognitive status and symptom recovery, suggesting that the underlying mechanisms mediating the emergence of the psychotic episode and its severity could be partially independent. Further research on this topic is essential to unravel the etiopathogenic processes of schizophrenia to ultimately prompt early intervention protocols for high-risk individuals and provide personalized attention – both pharmacological and psychological – to prevent severe forms of the disorder.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722001544

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Conflict of interest. M. 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. MBi has received honoraria from talks and consultancy of Adamed, has received honoraria from consultancy of Ferrer, has received research support and honoraria from talks and consultancy of Janssen-Cilag, has received honoraria from talks and consultancy of

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Ethical standards. 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 2008.

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The role of cognitive reserve and clinical symptoms in the association between genetic liability for educational attainment and functioning in first-episode psychosis: a mediation analysis

RUNNING TITLE: Educational attainment and functioning in FEP

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Abstract

Background: Polygenic risk scores for educational attainment (PRS_{EA}), cognitive reserve (CR), and clinical symptoms are associated with psychosocial functioning in first-episode psychosis (FEP). Nevertheless, the mechanisms underlying their complex interaction is yet to be explored. This study aimed to assess the mediating role of CR and clinical symptoms, both negative (NS) and positive (PS), on the interrelationship between PRS_{EA} and functionality, one year after a FEP.

Methods: A total of 162 FEP patients underwent clinical, functional, and genetic assessments. Using genome-wide association study (GWAS) summary results, PRS_{EA} were constructed for each individual. Two mediation models were explored. The parallel mediation model explored the relationship of PRS_{EA} with functionality through CR and clinical symptoms, NS, and PS. The serial mediation model tested a causal chain of the three mediators: CR, NS and PS. Mediation analysis was performed using the PROCESS function V.4.1 in SPSS V.22.

Results: A serial mediation model revealed a causal chain for PRS_{EA} > CR > NS > Functionality (β=-0.35, 95%CI [-0.85, -0.04], $p<0.05$). The model fit the data satisfactorily (CFI=1.00; RMSEA=0.00; SRMR=$7.2x10^{-7}$). Conversely, in a parallel mediation, none of the three mediators significantly mediated the relationship between PRS_{EA} and functionality and the model poorly fit the data (CFI=0.30; RMSEA=0.25; SRMR=0.11).

Conclusions: Both CR and NS mediate the relationship between PRS_{EA} and functionality at one-year follow-up, using serial mediation analysis. This may be relevant for prevention and personalized early intervention to reduce illness impact and improve functional outcomes in FEP patients.

Key words: first-episode psychosis, polygenic risk score, functioning, cognitive reserve, negative symptoms

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Introduction

First-episode psychosis (FEP) is characterised by functional impairments in social, occupational, and independent living activities and is a crucial period for early intervention to improve long-term prognosis (1,2). Achieving functional remission in FEP is a core clinical objective (3), yet recovery rates vary over the course of the illness (4–6), with long-term functioning impairments present even in patients in clinical remission (7–9). Several factors are believed to influence functioning in FEP patients, including genetic variability (2), negative symptoms (10–12), cognitive performance (13,14) and cognitive reserve (CR)(15,16).

Genetic variability is a potential modulator of prognosis in FEP (2) and is understood using polygenic risk scores (PRSs) (17). PRSs aggregate the effects of many genetic variants across the human genome into a single score and are used to predict the genetic disposition for developing a given disease, including mental disorders (18), while also overcoming certain limitations of candidate-gene strategies (2). In fact, PRSs demonstrated good discriminative ability of case-control status in FEP individuals (2,19). Schizophrenia and bipolar disorder PRSs have been linked to symptom severity, comorbid disorders, and cognitive impairments (20). A significant positive correlation between PRS and the Positive and Negative Syndrome Scale (PANSS) but not overall functioning was found in a sample of FEP individuals (21). Another study (22) failed to find an association between schizophrenia PRSs and functioning. In both studies, the inclusion of patients at different illness stages with varying symptomatology and small sample sizes may have reduced power to identify small effects. The PRS for educational attainment (PRS_{EA}) is based on the completed years of schooling and captures associated social, economic, and health outcomes (23). Lower educational attainment is associated with higher schizophrenia PRSs (24) and an overall higher frequency of copy number variants (CNVs) which are considered high risk for psychiatric disorders (25). Importantly, a higher PRS_{EA} was associated with lower symptom severity and better functionality suggesting increased

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autonomy and better cognitive functioning (2), thus highlighting the potential protective properties of PRS_{EA}.

Cognitive reserve (CR) has also been considered a protective factor and is understood as the brain's ability to cope in response to pathology and delay the onset of the associated clinical, cognitive, and functional symptoms (26–30). In various psychiatric populations, including FEP, higher CR has been associated with later onset age, greater insight, and reduced illness severity in terms of symptoms, particularly negative symptoms, better cognitive performance, and functioning (15,31–34). Individual differences in CR could explain why people with similar disorders differ in their levels of functioning (30,35–38). .

Research exploring PRSs and their associations with CR, clinical symptoms, and functioning following a FEP remains limited. Understanding the factors contributing to functional performance in FEP may contribute to early personalized intervention and person-focused therapy. The aim of this study was to investigate the mediating role of CR and clinical symptoms (negative and positive) on the interrelationship between genetic liability for educational attainment and functionality one-year post-FEP. We hypothesise that patients with higher PRS_{EA} will have higher CR and less clinical symptoms, thus better overall functionality at one-year follow-up.

Methods

Sample

335 FEP patients participated in the 'Phenotype-Genotype Interaction: Application of a Predictive Model in First Psychotic Episodes' (PEPs based on Spanish acronym) (39,40), a collaborative project between various members of the Spanish Research Network on Mental

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Health (CIBERSAM) (41). This was a multicentre, naturalistic, prospective, longitudinal study. For comprehensive information regarding medication and sample diagnosis see Bioque et al. (42).

The PEPS study inclusion criteria were: 1) between 7 and 35 years at first evaluation; 2) < 12 months history of psychotic symptoms; 3) fluent Spanish, and 4) provide written informed consent. Exclusion criteria were: 1) intellectual disability according to DSM-IV-TR criteria; 2) history of head trauma with loss of consciousness, and 3) organic disease with mental repercussions.

Patients who provided blood samples for genetic analysis, passed the genetic quality control (see section: blood samples and genotyping), completed all assessments at one-year follow-up, were aged ⩾16 years old (chosen cut-off point as this is the age at which most scales report adolescent-adulthood results), had self-reported European ancestry, belonged to the non-affective psychotic disorder diagnostic category and, additionally, had all the information needed to calculate CR, were included. To control for the potential loss of sample, we focused on symptomatology and functional data for a period of 1 year. **Supplementary Figure 1** depicts the selection process of the 162 patients with FEP.

The PEPs Project was approved by the Clinical Research Ethics Committee of all participating centres and was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice.

Written informed consent was obtained from all participants prior to inclusion in the study.

Assessments

Clinical, pharmacological and sociodemographic assessment. Relevant sociodemographic, clinical, and pharmacological data were collected for all participants. Sociodemographic data included age, sex, and education. Pharmacological treatment was based on international

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consensus (43) and measured using chlorpromazine equivalents (CPZ). To calculate the duration of untreated psychosis (DUP), the number of days between the time taken from the initial onset of psychotic symptoms to beginning treatment for psychosis was calculated. The onset of psychotic symptoms was assessed with the Symptom Onset in Schizophrenia (SOS) scale (39,44), explored via interviews with the patient, medical records, and interviews with relatives.

Diagnoses were established using the Structured Clinical Interview for DSM (SCID-I-II) (45,46) according to DSM-IV criteria. The PANSS scale (47) was administered for the psychopathology assessment. Higher scores indicate greater symptom severity.

Although the PANSS is one of the most widely used measures of negative symptom severity, it has several limitations as it was not designed to evaluate negative symptoms exclusively (48). Thus, we also used the PANSS-Marder Factor Scores (49) as it has more restrictive criteria to assess positive and negative symptomatology. For the present study, the PANSS was solely used to understand the role of positive and negative symptoms in the sample as the literature has shown that cognitive reserve is highly associated with negative symptoms only (50), whereas functionality has been linked to both positive and negative symptoms (51). The sum of the following items of the PANSS were used to calculate the Positive Symptom Factor (PS): delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6), stereotyped thinking (N7), somatic concerns (G1), unusual thought content (G9) and lack of judgment and insight (G12); and for the Negative Symptom Factor (NS): blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity and conversation flow (N6), motor retardation (G7) and active social avoidance (G16).

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Functional assessment. The Functioning Assessment Short Test (FAST) (52) evaluated overall functioning across the following six areas: autonomy, occupational functioning, cognitive functioning, management of personal finances, interpersonal relationships and leisure time. Higher scores indicate poorer functioning.

The Premorbid Adjustment Scale (PAS) (53) evaluates the achievement of developmental goals prior to the onset of psychotic symptoms and was administered retrospectively to assess premorbid adjustment. Information was obtained from the patients themselves and parents/close relatives. All participants completed the childhood and adolescence elements of this scale. Higher scores indicate worse premorbid adjustment.

Cognitive reserve assessment. Premorbid intelligence quotient (IQ), educational attainment level, and lifetime participation in leisure, social, and physical activities are the three most commonly proposed proxy indicators of CR in psychiatry, particularly in FEP (31,33,35,36,38) and were used to assess CR in this study. Estimated premorbid IQ was evaluated with the Vocabulary subtest of the Wechsler Adult Intelligence Scale-III (54) as a measure of crystallised intelligence. The total number of participants' completed years in education, as well as parents' educational level, were used to assess educational attainment level. The scholastic performance domain of the PAS scale was used to evaluate lifetime participation in leisure, social, and physical activities and by enquiring about involvement in social activities, their self-rated capacity to take part in physical activities and satisfaction with hobbies. Higher scores indicate better performance. A "Cognitive Reserve Score" was created via a Principal Components Analysis (PCA) for each subject with completed data for the three core proxy indicators.

Blood samples and genotyping. K2EDTA BD Vacutainer EDTA tubes (Becton Dickinson, Franklin Lakes, New Jersey) were used to collect blood samples, which were subsequently stored at -

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20°C prior to shipment to the central laboratory for further analysis. The MagNA Pure LC DNA isolation kit – large volume and MagNA Pure LC 2.0 Instrument (Roche Diagnostics GmbH, Mannheim, Germany) supported DNA extraction and DNA concentration was determined by absorbance (ND1000, NanoDrop, Wilmington, Delaware). Specifically, 2.5 µg of genomic DNA was sent for genotyping at the Spanish National Genotyping Centre (CeGen) using Axiom™ Spain Biobank Array (developed in the University of Santiago de Compostela, Spain).

PRS calculation. Genotyping data were submitted to the Michigan Imputation Server (55), following the standard pipeline for Minimac4 software and setting a European population reference from build GRCh37/hg19, reference panel HRC 1.1 2016 and Eagle v2.4 phasing.

For PRS calculation, GWAS summary results from the Social Science Genetic Association Consortium were obtained. Based on our previous study (2) we selected the PRS_{EA} (1,131,881 individuals) (23), measured as the number of years of schooling that individuals completed. Higher scores reflect the genetic liability for higher educational attainment. Duplicated and unknown strand GWAS summary single-nucleotide polymorphisms (SNPs) were excluded.

Quality control was performed with PLINK v1.07 (56). Inclusion criteria for SNPs were minor allele frequency > 0.01, Hardy-Weinberg equilibrium $p > 10^{-6}$, marker missingness < 0.01 and imputation INFO > 0.8. Pruning was done using a window/step size of 200/50 kb and $r^2 > 0.25$. Sample quality control included individuals with heterozygosity values within three standard deviations (SD) from the mean, a missingness rate of < 0.01, matching chromosomal and database-labeled sex and relatedness π-hat < 0.125.

The PRS were constructed using PRS-CS, a method that implements a high-dimensional Bayesian regression to perform a continuous shrinkage of SNP effect sizes using GWAS summary statistics and an external linkage disequilibrium (LD) reference panel (57). The LD

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reference panel was constructed using a European subsample of the UK Biobank (58). For the remaining parameters, the default options as implemented in PRS-CS were adopted.

A genetic principal component analysis (PCA) was performed to control population stratification (59)by means of the SNPRelate package, and the first 10 components were used as covariates in the statistical analyses including PRS.

Statistical Analysis

Normality of continuous variables was tested using the Kolmogorov–Smirnov and Shapiro–Wilk tests. The confounding effect on functionality of discrete variables was analyzed using a t-test and Pearson's correlation coefficient was used for continuous variables. Before testing the mediation hypothesis, we tested the relationship between mediators and the outcome variable using Pearson's correlation coefficient.

Mediation analysis tested whether the effect of a causal variable (PRS_{EA}) on an outcome variable (functionality, FAST scale score) is affected by one or more mediator variables (CR, NS, PS, and Marder PANSS Factor Scores) at one-year follow-up. The relationship between variables is described by three effects: (1) Total effect (c), the association between causal variable and outcome variable; (2) Direct effect (c'), the effect of the causal variable on the outcome variable, when controlling for the mediator variables; and (3) Indirect effect, the effect of the causal variable on the outcome variable via the mediator variable (60). Two mediation models were explored. A parallel mediation model explored the relationship of PRS_{EA} with functionality through CR, NS and PS. A serial mediation model tested a causal chain of the three mediators: CR, NS and PS. Based on clinical knowledge, we propose that genetic predisposition for educational attainment may be linked to higher CR, which in turn decreases clinical symptomatology and therefore increases functionality (PRS_{EA} > CR > Clinical symptoms > Functionality) (2,10,38). For each model we obtained the total effect, the direct effect, and

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the total indirect effect of all mediator variables, as well as the indirect effect of each individual mediator or serial path.

The statistical significance of the indirect effect was tested with a nonparametric bootstrapping approach (5000 iterations) to obtain 95% confidence intervals. In these analyses, mediation is considered significant if the 95% bias corrected for the indirect effect does not include 0.

Analysis was performed using the PROCESS function V.4.1 in SPSS V.22. The model 4 (model as a parameter in the PROCESS function) was used for the parallel mediation model, and model 6 for the serial mediation models. To control for population stratification, all models were fitted by the first ten principal components of the PCA analysis. Model fit statistics were also reported using the following: a Comparative Fit Index (CFI) (satisfactory>0.90), a Root Mean Square Error of Approximation (RMSEA) (satisfactory<0.05), and a Standardized Root Mean Square Residual (SRMR) (satisfactory<0.08) (61). The fit indices were derived using the R package *lavaan* (62).

Results

Table 1 shows the characteristics of the sample with 70% male and a mean age of 24.7 (SD=5.4). The mean dose of antipsychotic medication was equivalent to 577.8 (SD=489.5) mg/day of CPZ, and the mean DUP was 98.7 (SD=128.2) days (14 weeks approximately).

Functionality, measured using the FAST total score, was negatively correlated with PRS_{EA} (r=-0.21, p=0.004) and CR (r=-0.23, p=0.003), and positively correlated with NS (r=0.69, p<0.001) and PS (r=0.56, p<0.001), indicating that higher PRS_{EA} and CR are associated with better functional outcome. In contrast, higher levels of NS and PS are correlated with worse functional outcome. As these correlations were significant, the conditions required to perform mediation analysis were fulfilled.

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The total effect of PRS_{EA} on functionality was significant (β=-3.27, 95%CI [-5.62, -0.93], p=0.006). In the parallel mediation model (**Figure 1**), the direct effect was not significant (p=0.077), and a total indirect effect was present (β=-1.74, 95%CI [-3.27, -0.18], p<0.05) (**Table 2**). None of the three mediators significantly mediated the relationship between PRS_{EA} and functionality. Fitting indices also demonstrated that the model poorly fit the data (CFI=0.30; RMSEA=0.25; SRMR=0.11).

The serial mediation model hypothesizes a causal chain linking the three mediators in a specified order and direction flow. We propose that PRS_{EA} may be linked to higher CR, which in turn decreases clinical symptomatology and therefore increases functionality (**Figure 2**). Results show that the three mediators in the abovementioned causal order fully mediate the relationship between PRS_{EA} and functionality, as no direct effect was observed whereas the total indirect effect was significant (**Table 2**). Among the seven paths that could be inferred from the model, only the path including CR and NS as mediators was significant according to 5000 bootstrapped samples. Fitting indices indicated that the model fits the data satisfactorily (CFI=1.00; RMSEA=0.00; SRMR=$7.2x10^{-7}$).

Discussion

The main finding of this study is that the serial mediation model demonstrated that CR and clinical symptoms, more specifically NS, mediate the relationship between PRS_{EA} and functionality at one-year follow-up. To the best of our knowledge, this is the first statistical model describing this causal chain of events, improving our understanding of previously observed clinical findings. Based on this causal relationship between variables, a parallel mediation model poorly fit the data. Our results provide evidence for the role of genetic liability in the cognitive and clinical aspects of FEP, further supporting findings for the association between PRS_{EA} (and not psychological PRSs) and cognition, illness course, and

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functioning (2). In our serial model, a causal chain (PRS_{EA} > CR > Clinical symptoms > Functionality) was found.

In terms of CR, results indicate its potential genetic component. Genetic and environmental factors are both important in CR. Genetics determine individual aspects of functional brain processes, which can be influenced by the interaction of innate individual factors (e.g., in utero or genetically determined) as well as lifetime exposures. Conversely, environmental elements such as education, occupation, physical exercise, leisure activities, and social interaction are also influential (63–65). In this context, the protective effect of the genetics underlying cognitive features in the early progression of clinical manifestation after a FEP has been recently reported (2). As such, FEP individuals with an increased genetic predisposition for better cognitive functioning could be more resilient to the stressful effects of the psychotic episode and have a better prognosis (2). Equally, environmental factors are currently addressed in specific interventions enhancing CR in FEP and high-risk populations (66). Therefore, our results add to the previous research demonstrating the mediating effects of CR, while also including the genetic component and its influence in the relationship with clinical symptoms and functioning.

Regarding clinical aspects, different studies have shown that CR is closely linked with negative symptoms (50,67) and only one study (51) has found a relationship between CR and positive symptomatology; the authors described that CR partially mediates the relationship between positive symptoms and functioning. Notably, negative and cognitive symptoms are indeed the primary predictors of functioning at different stages of psychotic disorders (68,69), and appear to have a greater impact on functioning than positive symptoms (70,71). Several studies of the PEPs project have established the role of CR as a mediator of clinical and cognitive symptoms, as well as functionality (31,35,38,72). Amoretti et al. (15) found that higher levels of CR predict a better prognosis following a FEP and reiterates the need to consider the genetic component

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of this disorder. Nevertheless, in this study, CR alone did not predict functionality. This may be due to its complex interplay with NS and PS which are believed to have a more direct impact upon functionality (10). Hence, CR may have a strong genetic basis which influences NS, PS, and functionality. Specifically, findings suggest that PRS_{EA} may lead to higher CR which in turn is linked to lower NS and therefore better functionality following a FEP (e.g., PRS_{EA} > CR > NS > Functionality). This finding is relevant for the application of PRS in personalised medicine which aims to improve early disease detection, as well as early prevention (73) and personalised intervention methods (74).

Certain limitations in the present study must be considered. Firstly, several constraints are associated with the use of the PANSS as it was not designed with the purpose of solely measuring negative symptoms (75). To account for this, we used the PANSS-Marder Factor Scores (48) which applies stricter criteria for assessing positive and negative symptomatology. Future studies may include specific scales to assess negative symptoms such as the Brief Negative Symptom Scale (BNSS) (76,77) to address this drawback. A similar limitation is seen in all studies measuring CR in psychiatric populations as at the time of conducting this study there were no validated tools to evaluate CR. The Cognitive Reserve Assessment Scale in Health (CRASH)(78) for adult population, and Cognitive Reserve Questionnaire for Adolescents (CoRe-A) (79) have since been designed and should be administered accordingly. Secondly, the limited sample size may increase the risk of reducing statistical power and the ability to detect small effects. As such, further research with larger sample sizes is required. Finally, the short follow-up period is a potential limitation in this study. Nonetheless, the present study is a naturalistic and multicentric study from the entire Spanish population and comprises the largest and best characterized first-episode sample of the country. Additionally, the PRSs were calculated with the largest GWAS from international consortiums ergo the genetic variants have a greater capacity to capture the genetic susceptibility of the phenotypes explored.

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Furthermore, the specific PRS-CS method implemented ensures that the shrinkage of variant effect sizes allows the inclusion of all available SNPs in the PRSs and therefore avoids p-value thresholding.

Conclusions

This study provides a potential clinical explanation for the association between genetic predisposition for educational attainment and functional outcomes. We identified an influence of CR on NS in mediating the relationship between PRSEA and functioning in individuals with FEP. These results highlight the suitability and applicability of mediation models to explore the relationship between genetic and clinical data. Additionally, these results may be of significant clinical importance for two primary reasons. Firstly, we provide a clinical framework for clinicians by identifying a potential causal chain of events which can be part of the ongoing development of PRSs in precision psychiatry to further advance towards personalized interventions. Secondly, and based on these insights, the use of cognitive interventions could be recommended to enhance CR by focusing on mental stimulation (e.g., cognitive tasks), physical exercise, leisure activities, and social skills training (66, 80). This is clinically relevant given the importance of functional outcomes during the first years after a first-episode. To prevent severe forms of the disorder and a poorer prognosis, rapid identification, timing of treatment, and early interventions in first-episode patients are key factors in determining their prognoses and functional outcomes.

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Conflicts of interest

E. Vieta has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda.

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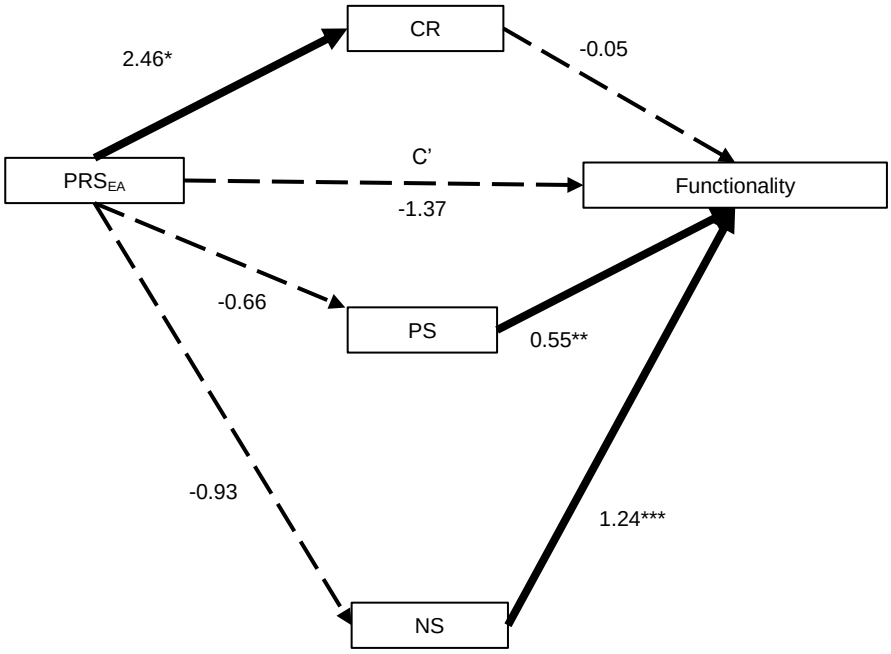
Ethical standards

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 2008.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding authors.

Figure 1. Parallel mediation model. The mediating effect of three mediators (CR, PS and NS) in the relationship between PRS_{EA} and functionality.



All presented effects are unstandardized. C' is the direct effect of PRS_{EA} on functionality. *p<0.05, **p<0.01, ***p<0.001. Continuous lines denoted significant regression.

Abbreviations: CR=Cognitive Reserve; PS=Positive Symptoms; NS=Negative Symptoms; PRS_{EA}=Polygenic risk score for educational attainment

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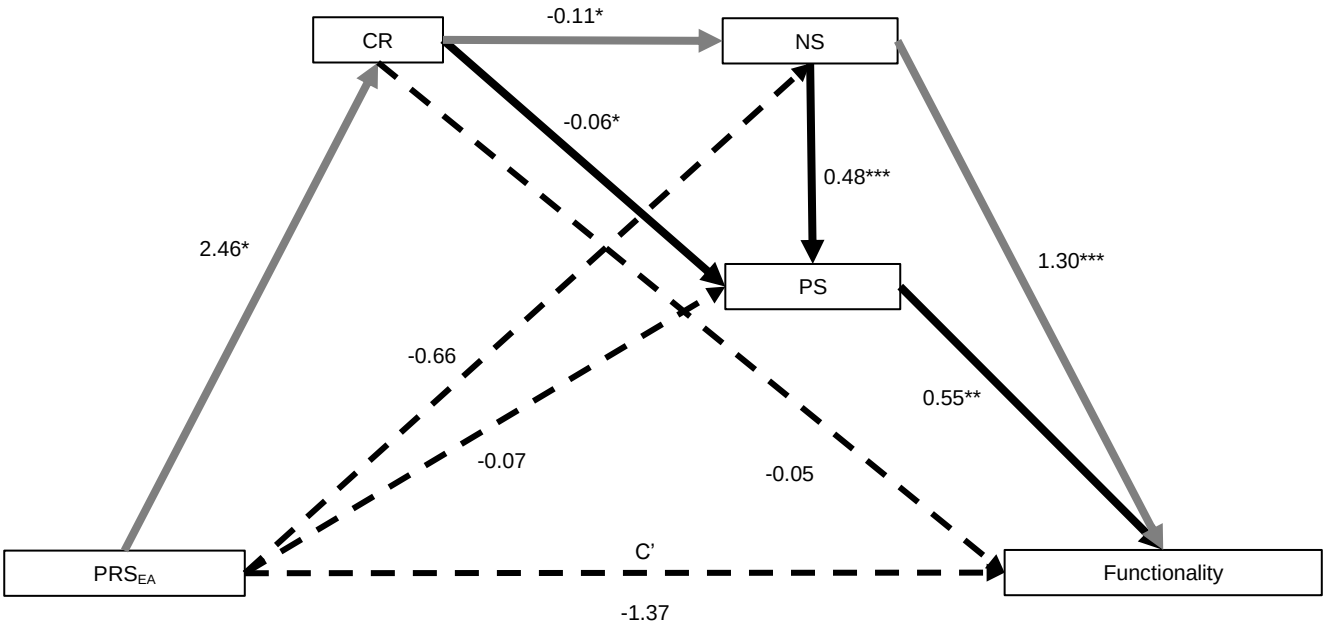
Figure 2. The serial mediating effect of CR, PS and NS in the relationship between PRS_{EA} and functionality.



All presented effects are unstandardized. C' is the direct effect of PRS_{EA} on functionality. *p<0.05, **p<0.01, ***p<0.001. Continuous lines denoted significant regression. Grey lines represent path with significant indirect effect.

Abbreviations: CR=Cognitive Reserve; PS=Positive Symptoms; NS=Negative Symptoms; PRS_{EA}=Polygenic risk score for educational attainment

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Table 1. Main sociodemographic, functional and clinical features of the FEP sample at study entry (N = 162)

Sociodemographic variables (Mean±SD or n (%))	
Sex (Male/Female)	113(70)/49(30)
Age (years)	24.7±5.4
Age at onset (years)	24.6±5.4
Duration of untreated psychosis (days)	98.7±128.2
Educational level	
No education	1 (0.6)
Primary education	27 (16.7)
Lower secondary education	63 (38.9)
Upper secondary and non-tertiary education	41 (25.3)
University	29 (17.9)
Others	1 (0.6)
Chlorpromazine equivalents	577.8±489.5
Cannabis (yes)	73(44)
Tobacco (yes)	116(69)
Clinical and functional variables at baseline (Mean±SD)	
Positive Marder PANSS Factor	20.8±8.4
Negative Marder PANSS Factor	18.2±8.0
Functionality (FAST)	27.7±16.3
Cognitive Reserve	75.9±11.8
Clinical and functional variables at one-year follow-up (Mean±SD)	
Positive Marder PANSS Factor	12.4±5.3
Negative Marder PANSS Factor	14.1±6.4
Functionality (FAST)	18.2±14.9

Abbreviations: FAST= Functioning Assessment Short Test. PANSS = Positive and Negative Syndrome Scale.

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Table 2. Non-standardized total, direct and indirect effects (total and of each individual mediator or path) of the two mediation models.

	β	[95% CI]	p-value
1. Parallel Mediation Model			
Total Effect	-3.08	[-5.34, -0.74]	**0.008**
Direct Effect	-1.37	[-3.22, 0.48]	0.145
Total Indirect Effect	-1.71	[-3.35, -0.07]	**<0.05**
CR Indirect Effect	-0.13	[-0.59, 0.22]	>0.05
PS Indirect Effect	-0.7	[-0.97, 0.12]	>0.05
NS Indirect Effect	-1.21	[-2.77, 0.13]	>0.05
2. Serial Mediation Model			
Total Effect	-3.08	[-5.34, -0.74]	**0.008**
Direct Effect	-1.37	[-3.22, 0.48]	0.145
Total Indirect Effect	-1.71	[-3.35, -0.07]	**<0.05**
PRS_{EA} >CR >Functionality	-0.13	[-0.59, 0.23]	>0.05
PRS_{EA} >PS>Functionality	-0.09	[-0.57, 0.51]	>0.05
PRS_{EA} >NS >Functionality	-0.86	[-2.42, 0.52]	>0.05
PRS_{EA} >CR >PS>Functionality	-0.08	[-0.24, 0.01]	>0.05
PRS_{EA} >CR>NS >Functionality	-0.35	[-0.85, -0.04]	**<0.05**
PRS_{EA} > NS>PS>Functionality	-0.18	[-0.55, 0.14]	>0.05
PRS_{EA} >CR>NS>PS>Functionality	-0.07	[-0.21, 0.00]	>0.05

Abbreviations: CI= Confidence interval; CR= Cognitive Reserve; PS= Positive Symptoms; NS= Negative Symptoms; PRS_{EA} = polygenic risk score for educational attainment

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Exploration of cannabis use and polygenic risk scores on the psychotic symptom progression of a FEP cohort

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ABSTRACT

Cannabis use is highly prevalent in first-episode psychosis (FEP) and plays a critical role in its onset and prognosis, but the genetic underpinnings promoting both conditions are poorly understood. Current treatment strategies for cannabis cessation in FEP are clearly inefficacious. Here, we aimed to characterize the association between cannabis-related polygenic risk scores (PRS) on cannabis use and clinical course after a FEP. A cohort of 249 FEP individuals were evaluated during 12 months. Symptom severity was measured with the Positive and Negative Severity Scale and cannabis use with the EuropASI scale. Individual PRS for lifetime cannabis initiation (PRS_{CI}) and cannabis use disorder (PRS_{CUD}) were constructed. Current cannabis use was associated with increased positive symptoms. Cannabis initiation at younger ages conditioned the 12-month symptom progression. FEP patients with higher cannabis PRS_{CUD} reported increased baseline cannabis use. PRS_{CI} was associated with the course of negative and general symptomatology over follow-up. Cannabis use and symptom progression

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after a FEP were modulated by cannabis PRS, suggesting that lifetime initiation and use disorders may have partially independent genetic factors. These exploratory results may be the first step to identify those FEP patients more vulnerable to cannabis use and worse outcomes to ultimately develop tailored treatments.

1. Introduction

Schizophrenia is a complex mental disorder, with highly heterogeneous course patterns and closely related to increased use of cannabis (Moore et al., 2007), particularly at early stages (Barbeito et al., 2013). It is estimated that approximately 50% of first-episode psychosis (FEP) individuals are cannabis users at onset (Arranz et al., 2020; González-Pinto et al., 2008). Cannabis has a remarkable effect on FEP development and outcome (Di Forti et al., 2019; Schoeler et al., 2016). Specifically, cannabis use is associated to earlier age at psychosis onset (di Forti et al., 2014; González-Pinto et al., 2008; Sugranyes et al., 2009), treatment resistance (Patel et al., 2016), more relapses (Bioque et al., 2022) and poor every-day functioning (Harrison et al., 2008). Notwithstanding the severe consequences, a high percentage of FEP patients continue using cannabis and have severe difficulties in achieving abstinence (Hiemstra et al., 2018).

The role of genetics in the co-occurrence of cannabis use and mental disorders is poorly understood, but some studies have characterized a partially overlapped genetic liability (Johnson et al., 2021, 2020; Pasman et al., 2018). Numerous genetic variants and chromosomic regions have been reported as shared risk variants (Caspi et al., 2005; Johnson et al., 2020; Müller-Vahl and Emrich, 2008; Pasman et al., 2018). A polymorphism in the *FAAH* gene was found to confer a ten-fold risk of FEP onset in cannabis consumers in the FEP sample used for the present study (Bioque et al., 2019). However, the relationship between cannabis use and psychosis is far more complex. Some authors have suggested that cannabis could also be used as a form of self-medication to deal with psychotic, depressive and anxiety (Ferdinand et al., 2005; Mané et al., 2015; Radhakrishnan et al., 2022). Both cannabis use and schizophrenia have a complex genetic architecture, associated with numerous genetic variants conferring small effects. The genome-wide genetic susceptibility measured with polygenic risk scores (PRS) has confirmed the overlap between cannabis use and schizophrenia (Johnson et al., 2021; Pasman et al., 2018). The PRS for cannabis use disorder was found associated with schizophrenia, even when accounting for smoking and cannabis ever-use (Johnson et al., 2021) and the PRS for schizophrenia with cannabis use (Hiemstra et al., 2018). Genetic predisposition to cannabis use could have an effect on cannabis use and also to some specific symptoms that would in turn be associated to cannabis use and the later onset of psychosis. If confirmed, this common genetic susceptibility could elucidate some of the biological mechanisms underlying cannabis use, its self-medication effect and psychosis.

As previously remarked, cannabis use is widely reported as a risk factor for psychosis and worse clinical outcomes. This study aims to further characterize its effect after the onset of the FEP on the psychotic symptomatology and its trajectory during 12 months. To explore the genetic underpinnings of both cannabis use and symptom severity, cannabis initiation and use disorder PRS were constructed for each participant. We expected that FEP patients with increased PRS would report increased cannabis use as well as more severe symptoms and a slower 12-month progression to recovery.

2. Methods

This study is part of the multicentric project 'Phenotype–genotype interaction: application of a predictive model in first psychotic episodes' (PEPs Project). A complete description of the PEPs protocol has been published previously (Bernardo et al., 2019, 2013).

2.1. Sample

During the recruitment period (2009–2012), 335 subjects who presented a FEP were included in the PEPs Project. Patients included met the following inclusion criteria: aged 7–35 years old at recruitment; presence of psychotic symptoms of less than 12 months' duration; ability to speak Spanish correctly and providing written informed consent. The exclusion criteria were: presenting intellectual disability according to DSM-IV criteria (American Psychiatric Association, 1994); history of head trauma with loss of consciousness and presence of an organic disease with mental repercussions.

For the present study, we included those subjects who provided blood samples for genetic analysis, passed the genetic quality control (see below), were $\geq$ 16 years old (21 individuals excluded) and had European ancestry (51 individuals excluded). The final sample comprised 249 FEP subjects. This study was conducted under the ethical principles of the Declaration of Helsinki and Good Clinical Practice and the Hospital Clinic Ethics and Research Board. Informed consent was obtained from all participants or from parents or legal guardians of under-age subjects.

2.2. Assessments

Sociodemographic and premorbid data were collected at enrollment, including age, gender, years of education and age at FEP. For the present study, we focused on cannabis use, age of FEP onset and clinical data for a period of 12 months.

Diagnoses were assessed with the Structured Clinical Interview for DSM-IV Disorders (SCID-IV). After that, diagnoses were dichotomized into affective (Bipolar Disorder, Major Depressive Disorder, Schizoaffective Disorder) and non-affective psychosis (Unspecified Psychosis, Schizophreniform Disorder, Schizophrenia, Brief Psychotic Episode).

Symptomatology related to schizophrenia was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The items of the scale can be subdivided in positive, negative and general psychotic symptoms. Higher scores on this scale indicate greater severity.

Substance use was assessed with the European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence (EuropASI) (Kokkevi and Hartgers, 1995). For the present study included in the analyses information about the proportion of cannabis users, monthly cannabis use (number of times cannabis was used) and age of cannabis initiation.

2.3. Blood samples and genotyping

Blood samples were collected in K2EDTA BD Vacutainer EDTA tubes (Becton Dickinson, Franklin Lakes, New Jersey), stored at −20 °C and sent to the central laboratory. DNA was extracted with the MagNA Pure LC DNA isolation Kit – Large volume and MagNA Pure LC 2.0 Instrument (Roche Diagnostics GmbH, Mannheim, Germany). DNA concentration was determined by absorbance (ND1000, NanoDrop, Wilmington, Delaware). A total of 2.5 μg of genomic DNA was sent for genotyping at the Spanish National Genotyping Centre (CeGen) using Axiom™ Spain Biobank Array.

2.4. PRS calculation

Genotyping data was submitted to the Michigan Imputation Server (Das et al., 2016), following the standard pipeline and pre-imputation

quality control required for Minimac4 software and setting a European population reference from build GRCh37/hg19, reference panel HRC 1.1 2016 and Eagle v2.4 phasing.

The PRS were constructed using PRS-CS, a method that implements a high-dimensional Bayesian regression to perform a continuous shrinkage of SNP effect sizes using GWAS summary statistics and an external linkage disequilibrium (LD) reference panel (Ge et al., 2019). Here, two GWAS summary statistics were used to calculate individual PRS conferring risk for lifetime cannabis initiation (PRS_{CI}) (Pasman et al., 2018) and cannabis use disorder (PRS_{CUD}) (Johnson et al., 2020). The LD reference panel was constructed using a European subsample of the UK Biobank (Bycroft et al., 2018). For the remaining parameters, the default options as implemented in PRS-CS were adopted.

A genetic quality control was performed with PLINK v1.07 (Purcell et al., 2007). Inclusion criteria for SNPs were minor allele frequency (MAF) > 0.01, Hardy-Weinberg equilibrium $p > 10^{-6}$, SNP missingness < 0.01 and imputation INFO > 0.8. Pruning was performed using a window/step size of 200/50 kb and $r^2 > 0.25$ prior to the heterozygosity and relatedness check. Sample quality control included individuals with heterozygosity values $\pm$ 3SD from the mean, individual missingness $<$ 0.01, matching chromosomal and database-labeled sex, relatedness π-hat < 0.125 and self-reported European ancestry.

2.5. Statistical analysis

All the analyses were performed with R v4.1.2 ("R Core Team," 2017). A genetic principal component analysis (PCA) was performed to control population stratification (Patterson et al., 2006) by means of the *SNPRelate* package, and the first 10 components were used as covariates in the statistical analyses including PRS. Multiple testing correction was applied in all the analyses by means of the FDR method, and the threshold of significance of the adjusted *p* value (p.adj) was set at $\alpha <$ 0.05.

The association between cannabis use, age of cannabis initiation, age at FEP onset, symptom severity and PRS at baseline was evaluated with generalized linear models and corrected by sex, age and diagnostic. Linear mixed-effects modeling was used for longitudinal analyses, considering month of assessment as a random effect and the PRS and time as fixed effect and corrected by sex, age and diagnostic.

3. Results

3.1. Description of the sample

The sample consisted of 249 FEP individuals, 74 (29.7%) females, with a mean age of 24.5 years (SD = 5.7 years). Forty-two patients (16.9%) were diagnosed with affective psychosis. The mean age of cannabis use initiation was 16.1 years (SD = 2.9 years). Table 1 shows cannabis use pattern and psychotic symptoms of the sample at each assessment point during the 12-month follow-up.

Table 1
Cannabis use and psychotic symptoms measures during the 12-month follow-up.

Assessment	Baseline n(%) or mean(SD)	2-month n(%) or mean(SD)	6-month n(%) or mean(SD)	12-month n(%) or mean(SD)
Cannabis users	114(46.2%)	50(21.3%)	49(22.5%)	41(20.7%)
Monthly cannabis use (joints)	34.0(68.6)	5.6(25.3)	3.7(15.4)	1.9(8.6)
Total symptoms (PANSS score)	73.7(24.4)	57.1(20.4)	52.3(17.1)	50.2(18.2)
Positive symptoms (PANSS score)	18.4(8.3)	11.7(5.3)	10.4(4.4)	9.9(4.5)
Negative symptoms (PANSS score)	18.0(7.9)	16.5(6.9)	15.1(6.3)	14.5(6.5)
General symptoms (PANSS score)	37.3(12.7)	29.8(10.5)	26.8(8.8)	25.7(9.5)

3.2. Cannabis use and FEP severity

Individuals reporting an earlier cannabis initiation age had their FEP at younger ages ($t = 7.044$; $R^2 = 0.281$; p.adj $= 2.85 \times 10^{-10}$). Cannabis use at baseline was also associated with FEP age, but the result did not survive multiple testing correction ($t = -2.091$; $R^2 = 0.025$; p.adj = 0.056).

The effect of cannabis use on the psychotic symptomatology was tested at baseline and for the 12-month progression. Table 2 shows the association of positive symptoms with cannabis use (p.adj = 0.002) and a trend with monthly cannabis use (p.adj = 0.056) at baseline. Only cannabis initiation age was associated with the 12-month symptom course. Individuals initiating cannabis use at younger ages reported a worse overall progression of symptoms (p.adj = 0.014), including positive (p.adj = 0.018), negative (p.adj= 0.023) and general (p.adj=0.030) subscales.

3.3. Cannabis PRS and cannabis use

To assess the role of genetics in the cannabis use pattern, the PRS capturing the genetic liability for cannabis initiation (PRS_{CI}) and cannabis use disorder (PRS_{CUD}) were included in the analyses. No PRS was associated with the age of cannabis initiation (p.adj > 0.05 for all analyses). Table 3 shows that greater PRS_{CUD} was associated with cannabis use and a monthly use at baseline (p.adj $= 2.61 \times 10^{-4}$; p.adj = 0.014). No associations were found for PRS_{CI} and cannabis use pattern.

3.4. Cannabis PRS and FEP severity

The PRS were not associated with the age at FEP (p.adj > 0.05 for all analyses). The baseline symptomatology was not associated with the PRS, but a trend was found for PRS_{CI} and the negative subscale (p.adj = 0.052). The 12-month progression of total, negative and general symptoms was associated with PRS_{CI} (p. adj = 0.017, p.adj = 0.035, p.adj = 0.024; respectively). No associations were found for PRS_{CUD} (Table 4).

4. Discussion

This prospective study explored the relationship between cannabis use, psychotic symptoms and cannabis PRS in a FEP sample longitudinally. Cannabis initiation was linked to earlier FEP onset and the progression of psychotic symptoms. Cannabis use pattern at study entry was associated with the cannabis use disorder PRS, while PRS reflecting the genetic proneness for lifetime cannabis initiation was found to have an effect on symptom progression. The present study characterizes the impact of cannabis use and the role of the genetic susceptibility underlying cannabis use in the clinical evolution after a first psychotic episode. The findings of this exploratory study establish a foundational understanding of the genetic architecture of cannabis use and its relationship with the clinical outcome in the first stages of psychotic disorders.

Earlier FEP onset was associated with cannabis initiation age and use, although the latter did not survive multiple testing correction. We replicated results found in other subsets of the present sample (Amoretti et al., 2022; Mané et al., 2017) and reported in the literature (di Forti et al., 2014; González-Blanco et al., 2021; Sugranyes et al., 2009). Additionally, we detected an effect of current cannabis use in the positive symptoms similar to the associations previously described in this FEP sample (Amoretti et al., 2022; González-Blanco et al., 2021). A statistical trend suggests a dose-dependent relationship, but increased sample sizes are needed to confirm this result. The most recent metanalysis reveals a small increase of positive symptomatology in schizophrenia patients reporting current cannabis use (Sabe et al., 2020). The effect was more conspicuous in the previous metanalysis, which included FEP samples (Large et al., 2014). The only cannabis use

Table 2
Cannabis use and psychotic symptom severity at study entry and 12-month follow-up. Significant results are marked in bold.

Cannabis use	Psychotic symptoms	Baseline			12-month		
		t	R^2	p.adj	t	R^2	p.adj
Cannabis user	Total	1.615	0.015	0.143	0.898	0.014	0.397
	Positive	3.561	0.051	**0.002**	1.398	0.010	0.998
	Negative	−1.588	0.033	0.113	−1.123	0.035	0.421
	General	1.820	0.016	0.140	1.132	0.008	0.591
Monthly cannabis use	Total	1.084	0.009	0.559	1.577	0.009	0.576
	Positive	2.481	0.031	0.056	0.799	0.003	0.662
	Negative	−0.322	0.024	0.748	0.531	0.028	0.602
	General	0.698	0.009	0.648	1.217	0.006	0.448
Cannabis use initiation age	Total	−0.676	0.009	0.667	−3.855	0.054	**0.014**
	Positive	−0.707	0.005	0.962	−3.634	0.032	**0.018**
	Negative	0.032	0.023	0.974	−2.949	0.050	**0.023**
	General	−0.844	0.011	1.000	−3.998	0.052	**0.030**

Table 3
PRS association with cannabis use pattern at study entry and during the 12-month follow-up. Significant results are marked in bold.

PRS	Cannabis use	Baseline			12-month		
		t	R^2	p.adj	t	R^2	p.adj
PRS_{CI}	Cannabis user	0.429	0.101	0.669	−0.062	0.032	0.952
	Monthly cannabis use	0.354	0.075	0.724	0.390	0.018	0.705
PRS_{CUD}	Cannabis user	3.888	0.151	**2.61E−04**	2.837	0.051	0.079
	Monthly cannabis use	2.734	0.104	**0.014**	1.497	0.029	0.422

Table 4
PRS association with psychotic symptoms at baseline and during the 12-month follow-up. Significant results are marked in bold.

PRS	Psychotic symptoms	Baseline			12-month		
		t	R^2	p.adj	t	R^2	p.adj
PRS_{CI}	Total	2.153	0.047	0.065	2.914	0.049	**0.017**
	Positive	0.887	0.025	0.376	1.582	0.017	0.121
	Negative	2.075	0.095	0.052	2.738	0.087	**0.035**
	General	2.282	0.046	0.093	3.033	0.041	**0.024**
PRS_{CUD}	Total	−0.884	0.032	0.504	−0.881	0.042	0.397
	Positive	−1.131	0.027	0.518	−1.223	0.016	0.501
	Negative	0.421	0.080	0.674	0.872	0.080	0.520
	General	−1.217	0.032	0.900	−1.530	0.034	0.609

feature linked to psychotic symptoms was initiation age. Considering that almost 50% of cannabis users achieved cessation and monthly intake was severely reduced during the 12-month follow-up, these results suggest that the – possibly dose-dependent – effect of current cannabis use on positive symptoms may be reversible. Previous longitudinal studies have described better outcomes in FEP patients who stop using cannabis (González-Pinto et al., 2011; Schoeler et al., 2016). Thus, the development of preventive tools is decisive to hinder the effect of cannabis in younger individuals at critical stages of brain development (Bara et al., 2021; Penzel et al., 2021; Schneider, 2008), that may have major impact on the clinical outcomes.

Individuals with increased PRS_{CUD} were more prone to use cannabis, as previously demonstrated in non-psychotic samples (Johnson et al., 2019; Meyers et al., 2019). This effect was not statistically significant for the 12-month progression analyses, thus implying that despite an increased genetic liability for cannabis abuse and dependency, cessation can be achieved after FEP onset. These results are particularly meaningful since cannabis use after FEP onset is associated with poor outcomes (Baeza et al., 2009; Bioque et al., 2022; González-Pinto et al., 2016, 2011; Marconi et al., 2016; Marino et al., 2020; Wisdom et al., 2011). However, the current treatment strategies for cannabis cessation are insufficient for a considerable number of FEP patients (McDonell and Oluwoye, 2019). The present results suggest that other factors might contribute to consumption persistence, which may be considered for the development of novel treatment strategies for cannabis use in FEP.

The influence of PRS_{CI} on cannabis use was not detected, but individuals with increased scores reported a worse progression of negative and general symptoms. These findings could be explained by the nature of the reference GWAS, which captures the genetic variability of lifetime cannabis use in the general population. Cannabis initiation is a complex process, and therefore the multiple genetic and environmental factors that trigger the consumption may operate differently in individuals at high clinical risk. Intriguingly, the association of PRS_{CI} with non-positive symptoms implies that the captured genetic susceptibility may also reflect the proneness for affective, depressive and other unspecific symptoms. Considering the effect of cannabis on the dopaminergic neurotransmission associated to negative symptoms (Awad and Voruganti, 2015; Howes and Kapur, 2009; Peters et al., 2021), it could be hypothesized that individuals with this genetic proneness could initiate cannabis consumption as self-medication to mitigate the symptoms. However, cannabis use would trigger the psychotic episode and a more severe manifestation of these symptoms (di Forti et al., 2014; Harrison et al., 2008) and thus its putative self-medication effect could rebound after sustained substance use (Diana, 2011; Sabe et al., 2020). Consistent with this hypothesis, some authors have shown that cannabis use, anxiety and depressive symptoms have shown to have a bidirectional association with psychotic experiences (Radhakrishnan et al., 2022).

Some limitations of the present work should be taken into consideration. Firstly, the sample size is moderately limited in the longitudinal follow-up due to patient drop-out and therefore the statistical analysis might be underpowered to detect small effects. Secondly, cannabis use pattern was not assessed through biochemical quantification of cannabinoids concentration. Instead, cannabis use pattern was obtained by the

self-reported data of EuropASI scale which may not be completely accurate. Furthermore, EuropASI does not provide quantitative objective method to assess specific cannabinoids (mainly tetrahydrocannabinol and cannabidiol), which have different clinical effects (Hahn, 2018). Subjects included in the analyses are exclusively of European ancestry, and therefore the implications of the present findings may not be generalizable to other ancestries. However, this study comprises one of the largest and best characterized FEP samples in the literature, with a naturalistic design and thus representative of the psychiatric population. Exhaustive assessment during a considerably long follow-up period enables a complete exploration of the association between cannabis use and symptom evolution after the FEP and cannabis PRS. Furthermore, these PRS have been calculated with large GWAS from international consortiums and thus the comprised genetic variants have a great capacity to capture the genetic susceptibility of the phenotypes.

In the present study, cannabis initiation was linked to earlier FEP onset and the progression of positive psychotic symptoms. Interestingly, the genetic liability for cannabis use disorder was linked to the pattern of consumption at baseline, but not at follow-up, opening the door to new strategies for cannabis use cessation in FEP. Intriguingly, the genetic susceptibility for lifetime cannabis initiation were not associated with its use but with the progression of general (anxious and depressive) and negative symptoms. If confirmed, these findings on general and negative symptoms would contribute to personalized intervention since FEP onset.

Author statement

The results presented here are part of a broader project, the PEPs study. MB is the coordinator of the PEPs study and JSR is the coordinator of the biological module. AGS and AM performed the statistical analysis and wrote the first draft of the manuscript, and both authors contributed equally to this work. LP and NR performed the sample isolation and preparation and participated in the statistical analysis.GM, SA, ARB, EJ, TL participated in the coordination of the sample shipment, the maintenance of the database and in the recruitment and assessment of the sample. MJC, EV, AL, AGP, CMDC, IB 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 PEPs group authors listed in the acronym, contributed to the final draft of the manuscript.

Declaration of Competing Interest

C. De-la-Camara received financial support to attend scientific meetings from Janssen-Cilag, Almirall, Eli Lilly, Lundbeck, Rovi, Esteve, Novartis, and Astrazeneca.

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Epigenetic age deacceleration in youth at familial risk for schizophrenia and bipolar disorder

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Epigenetic modifications occur sequentially during the lifespan, but their pace can be altered by external stimuli. The onset of schizophrenia and bipolar disorder is critically modulated by stressors that may alter the epigenetic pattern, a putative signature marker of exposure to environmental risk factors. In this study, we estimated the age-related epigenetic modifications to assess the differences between young individuals at familial high risk (FHR) and controls and their association with environmental stressors. The sample included 117 individuals (6–17 years) at FHR (45%) and a control group (55%). Blood and saliva samples were used estimate the epigenetic age with six epigenetic clocks through methylation data. Environmental risk was measured with obstetric complications, socioeconomic statuses and recent stressful life events data. Epigenetic age was correlated with chronological age. FHR individuals showed epigenetic age deacceleration of Horvath and Hannum epigenetic clocks compared to controls. No effect of the environmental risk factors on the epigenetic age acceleration could be detected. Epigenetic age acceleration adjusted by cell counts showed that the FHR group was deaccelerated also with the PedBE epigenetic clock. Epigenetic age asynchronicities were found in the young at high risk, suggesting that offspring of affected parents follow a slower pace of biological aging than the control group. It still remains unclear which environmental stressors orchestrate the changes in the methylation pattern. Further studies are needed to better characterize the molecular impact of environmental stressors before illness onset, which could be critical in the development of tools for personalized psychiatry.

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INTRODUCTION

Schizophrenia and bipolar disorder are impairing conditions that have differential diagnostic criteria. However, their familial aggregation and overlapping clinical and genetic features do not fully correlate with their nosological boundaries, pointing towards a partially shared etiology [1–4]. The individuals at familial high risk (FHR) have a two- to fourfold increase in the risk of developing a psychiatric disorder, for which the exposure to environmental stressors have a critical role [5].

Schizophrenia and bipolar disorder are associated with a shorter lifespan, which has been linked to age-related biomarkers and physiological conditions such as increased inflammation and oxidative stress, a shorter telomere length and metabolic disruption [6–13], suggesting that patients suffer from the effects of accelerated aging. Epigenetic modifications (changes in chromatin structure, primarily measured by assessing the methylation of CpG dinucleotides) have been closely related to gene expression, driving cell senescence and affecting their function [14]. Methylation patterns change throughout the lifespan, following a specific timing. Epigenetic clocks measure the methylation of specific sets of CpGs for the estimation the epigenetic age in years, a proxy of the biological age of the individual. Epigenetic age correlations with chronological ages of schizophrenia patients and the direction of these are inconsistent and vary across epigenetic clocks [15, 16].

Schizophrenia and bipolar disorder prediction models perform best when including polygenic constructs, multiple environmental factors and their interaction [17]. The characterization of risk factors encompasses multiple sorts of environmental impacts occurring throughout all stages of life [18, 19], which can lead to an acceleration the epigenetic age [16]. Obstetric complications, including maternal and perinatal infections that drive immune responses in the offspring, are thought to cause a neurodevelopmental disruption [20, 21]. Early life adversity (ranging from explicit violence to subtle forms of emotional negligence) has been associated with more severe manifestations of the disorders and suicidal behaviors [22–24]. Moreover, recent traumatic events may also be a substantial risk factor for disorder onset [25, 26]. Young individuals experiencing migration processes, lower socioeconomic statuses and urbanicity—linked to social exclusion and

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isolation—are also at a higher risk of developing schizophrenia [27–29].

In this study, we examined the epigenetic age of a sample consisting of FHR individuals and a control group. Blood and saliva samples were used to estimate their epigenetic age using six epigenetic clocks. We expected that the FHR group would report greater asynchronicities between their epigenetic and chronological age than the control group. Furthermore, we believed that these differences would be associated with the exposure to environmental stressors.

METHODS

The present study is part of the Bipolar and Schizophrenia Young Offspring Study (BASYS), which is a multicenter, longitudinal, naturalistic study that aims to compare the clinical, neuropsychological, neuroimaging, genetic and epigenetic characteristics of the child and adolescent offspring of patients diagnosed with SZ or BD and of a community control group. This study was conducted in the child and adolescent psychiatry units of two hospitals in Spain: the Hospital Clinic in Barcelona and Hospital Gregorio Marañón in Madrid. The methodology as well as the clinical and cognitive characteristics of the sample have been described previously in detail [30].

Sample characteristics

The individuals at FHR were offspring of patients with schizophrenia or bipolar disorder, recruited by psychiatrists from the adult psychiatry units of both hospitals. The inclusion criteria were: (a) age between 6 and 17 years, and (b) a parent diagnosed with schizophrenia or bipolar disorder. The exclusion criteria were: (a) intellectual disability with an impact on functioning, and (b) significant head injury or a current medical or neurological condition. The only inclusion criterion for the offspring of the community controls was an age between 6 and 17 years, while the exclusion criteria were exactly the same as those for the FHR group plus a family history of psychotic disorders in first- or second-degree relatives. As this study focused on epigenetic data, only the individuals who had provided biological samples for DNA methylation analysis (53 FHR and 64 controls) were assessed.

Ethical considerations

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 2008. Written informed consent was obtained from one of the parents, having the other parent been informed, together with written assent from the participant if aged 12 and above.

Clinical and environmental assessment

A trained psychiatrist or psychologist performed a mental health assessment of all the parents using the Spanish version of the Structured Clinical Interview for DSM-IV Disorders (SCID-I) [31, 32]. Parents or primary caregivers were also interviewed about their children. The study participants were assessed directly by trained child psychiatrists or psychologists who were blind to their parental diagnoses, using the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL) [33, 34].

Information about obstetric complications was collected using the Lewis-Murray scale [35]. This scale rates 15 obstetric complications as absent or definitely present, while 9 of the exposures can also be rated as equivocally present. For this study, history of obstetric complications was considered positive if at least one complication was definitely present.

The socioeconomic status was calculated according to the Hollingshead and Redlich scale [36]. The higher socioeconomic level between each set of parents was considered. The higher socioeconomic level between each set of parents was considered. Lower scores indicate a low socioeconomic status.

The occurrence of recent stressful events was determined using the Stressful Life Events Schedule (SLES), child-reported version [37, 38]. The SLES evaluates the presence/absence of a list of potentially stressful, age-adapted events in the last 12 months and rates their potential impact on a scale of 1 (not at all) to 4 (a lot). The SLES provides two scores: the number of stressful life events (SLEs) in the previous year and the score for the total cumulative impact of the SLEs.

Biological samples

Blood samples were collected in EDTA tubes (K2EDTA BD Vacutainer EDTA tubes; Becton Dickinson, Franklin Lakes, NJ, 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). Saliva samples were collected using the Oragene DNA Saliva Collection Kit (OG-500, DNA Self-Collection Kit, Genotek, Ottawa, ON, Canada) and DNA was extracted according to the manufacturer's instructions. DNA concentration and quality were measured spectrophotometrically using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Epsom, Surrey, UK). DNA methylation β-values were obtained at GenomeScan using the Illumina Infinium MethylationEPIC BeadChip Kit.

Methylation data collection

Raw intensity data (.IDAT) files were received and parallel bioinformatics processes were conducted in-house using the Chip Analysis Methylation Pipeline (ChAMP) Bioconductor package [39], which were performed separately for the methylation data obtained from blood samples ($n = 79$) and saliva samples ($n = 38$). Raw .IDAT files were used to load the data into the R environment with the *champ.load* function, which also enabled the simultaneous undertaking of the probe QC and removal steps. Probes with weak signals ($p < 0.01$), cross-reactive probes, non-CpG probes, probes with < 3 beads in at least 5% of the samples per probe, probes that bound to SNP sites, and sex chromosomes were all considered problematic for the accurate detection of downstream methylation and were therefore removed. β-values were then 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 slide and array (significant components detected by the SVD method).

Epigenetic clock construction

The *methylclock* R package [40] was used to construct six epigenetic clocks. Horvath is a multi-tissue-based epigenetic clock designed to predict chronological age in individuals along the whole lifespan [41]. Similarly, Hannum and Wu epigenetic clocks estimate the epigenetic patterns linked to chronological age in blood tissues in adults and children, respectively [42, 43]. PedBE epigenetic clock was constructed for saliva samples in children [44]. Levine epigenetic clock captures the methylation patterns of "phenotypic aging", mortality and morbidity epigenetic patterns rather than with chronological age [45]. CpGs located in telomeric regions can also be measured to estimate telomere length (TL), a well-established biomarker of health conditions associated with aging. The TL estimation by means of epigenetic markers used in this study was constructed with blood samples of adults [46].

Briefly, from normalized and batch-corrected methylation data, the package extracts the methylation levels of the available CpGs included in each clock. Subsequently, the coefficients obtained through an elastic net in the prediction models of each of the clocks in the original studies are used to predict the epigenetic age. Several studies have demonstrated that the epigenetic clocks are resistant to the CpG site missingness from the MethylationEPIC BeadChip Kit [47]. For each clock, we obtained the epigenetic age in years. Epigenetic age acceleration for every epigenetic clock was obtained after regressing chronological age on the epigenetic age. Cell-adjusted epigenetic age acceleration was obtained after regressing epigenetic age acceleration by seven cell-type proportions known to change throughout the lifespan, estimated differently for the blood [48] and saliva [49] samples.

Statistical analysis

All the analyses were performed with R v4.1.2 [50]. Multiple testing correction was applied in all the analyses by means of the FDR method, and the threshold of significance of the two-sided adjusted p value (p.adj) was set at $\alpha < 0.05$.

Group differences in sociodemographic features and environmental risk factors were calculated by linear mixed-effects models for continuous variables, using family relatedness as a random effect, and by chi square tests for categorical variables.

The correlation between epigenetic and chronological age was tested using Pearson's product-moment correlation. The analysis was performed for the entire sample and stratified by tissue used for epigenetic age estimation (blood or saliva).

Table 1. Summary and group comparison of the sociodemographic and diagnostic features of the sample ($n = 117$).

Feature	All ($n = 117$)	FHR (n = 53)	Control ($n = 64$)	Comparison	
	n (%) or mean (SD)			*t* or χ^2	p.adj
Age	11.9 (3.2)	11.8 (3.1)	12.0 (3.2)	−0.275	0.784
Sex—female	64 (54.7%)	28 (52.8%)	36 (56.2%)	0.033	0.071
Obstetric complications	30 (25.6%)	20 (37.7%)	10 (15.6%)	6.320	**0.036**
Socioeconomic status	51.4 (12.6)	48.2 (14.1)	53.9 (10.8)	−2.211	0.058
Recent stressful life events—number (z-score)	−0.1 (0.9)	−0.2 (0.9)	−0.1 (0.9)	−1.005	0.476
Recent stressful life events—impact (z-score)	0.0 (0.9)	−0.1 (0.9)	0.1 (0.9)	−0.999	0.384

Significant differences are marked in bold.
FHR familial high risk.

To assess the epigenetic age acceleration differences between the FHR and controls linear mixed-effects models were used, considering the FHR status as a dependent variable, epigenetic age acceleration as a fixed effect and family relatedness as a random effect. The analyses performed with the entire sample were corrected by sex and tissue used for epigenetic age estimation. The analyses stratified by tissue used for epigenetic age estimation were corrected by sex.

The effect of environmental factors (obstetric complications, socioeconomic statuses and recent stressful life events) on the epigenetic age acceleration was assessed using a linear mixed-effects model corrected for sex and the tissue used for the epigenetic age estimation, with family relatedness as a random effect.

Follow-up analysis using cell-adjusted epigenetic age acceleration estimates were performed. Therefore, similar linear mixed-effects models were constructed to evaluate differences between FHR and control groups and the effect of environmental factors.

RESULTS

Sample description

One hundred seventeen children and adolescents aged 6–17 years (54.7% females) were included in this study, 53 of whom were at FHR (45.3%) and 64 were controls (54.7%). The main sociodemographic of the study sample and the differences between the FHR individuals and controls are shown in Table 1. Only the proportion of FHR individuals reporting an obstetric complication was found significantly increased (p.adj = 0.036). Age distribution of FHR and control individuals is shown in Supplementary Fig. 1.

Epigenetic age correlation with chronological age

The chronological age of the sample was consistently correlated with the estimated epigenetic ages calculated with the epigenetic clocks, and inversely correlated with the estimated TL (p.adj < 0.005 for all analyses) (Fig. 1A). Significant correlations were obtained after the stratification of the sample by tissue used for epigenetic age estimation (p.adj < 0.005 for all analyses) (Fig. 1B, C; Supplementary Table 1).

Epigenetic age acceleration and FHR

Epigenetic age acceleration differences between FHR and control groups were assessed for all the epigenetic clocks. The analyses showed that FHR individuals had a deceleration in the epigenetic ages estimated by three epigenetic clocks, although only two of them survived multiple testing correction. Specifically, the FHR individuals reported epigenetic age negative acceleration for the Horvath and Hannum epigenetic clocks (p.adj = 0.004, p.adj = 0.005) and a trend was found for PedBE (p.adj = 0.086) (Fig. 2). To check for tissue-specific differences between the FHR and control groups, the analyses were stratified by blood and saliva tissues. No epigenetic age acceleration was found different for any of the tissues (p.adj > 0.05 for all analyses) (Supplementary Table 2).

Environmental risk effect on the epigenetic age acceleration

The effect of obstetric complications, the socioeconomic statuses and recent stressful life events on the epigenetic age acceleration was assessed. No significant effect of the environmental factors was found to be associated with the epigenetic age acceleration (p.adj > 0.05 for all the analyses) (Table 2).

Cell-adjusted epigenetic age acceleration analyses

Differences between FHR and control groups and environmental risk effect on epigenetic age acceleration were assessed with the cell-adjusted epigenetic age acceleration measures. FHR individuals reported epigenetic age negative acceleration for the Horvath, Hannum and PedBE epigenetic clocks (p.adj = 0.013, p.adj = 0.020, p.adj = 0.035; respectively). No environmental risk factors had a significant effect on any epigenetic clock (p.adj > 0.05 for all analyses) (Supplementary Table 3).

DISCUSSION

The early stages of psychiatric disorders play a critical role in prognosis and outcome. Thus, the identification and characterization of risk factors and their molecular repercussion are key to understanding the mechanisms underlying psychopathology [51]. In this study, we characterized the epigenetic age of the young offspring of patients with schizophrenia and bipolar disorder. Compared to the offspring of control individuals, the FHR individuals reported a deacceleration of their epigenetic age relative to their chronological age for the Horvath and Hannum epigenetic clocks and no differences for the PedBE, Levine, Wu and TL clocks. None of the environmental stressors included could be associated with this phenomenon. Our results suggest that individuals at high risk may present epigenetic decelerated aging, which is in accordance to previous findings but may conflict with the accelerated aging hypothesis in schizophrenia.

Methylation data were extracted from blood and saliva samples. Although Horvath epigenetic clock can estimate the epigenetic age accurately in most tissues, the rest of epigenetic clocks perform best in either blood or saliva samples. The consistent correlation of epigenetic and chronological ages in the whole sample and in both tissues separately implies that in this particular case, variation generated by the DNA source used for methylation does not have a great impact. Yet, all analyses were performed using methylation tissue as a covariate to minimize any possible effect.

Positive acceleration of the epigenetic age reflects premature cellular aging, while negative acceleration—i.e. deacceleration—denotes a slower pace of cellular aging. We identified epigenetic deacceleration in the FHR individuals for the Horvath, Hannum and PedBE epigenetic clocks, although the latter did not survive multiple testing correction. No tissue-specific differences in epigenetic age acceleration were found, possibly due to the

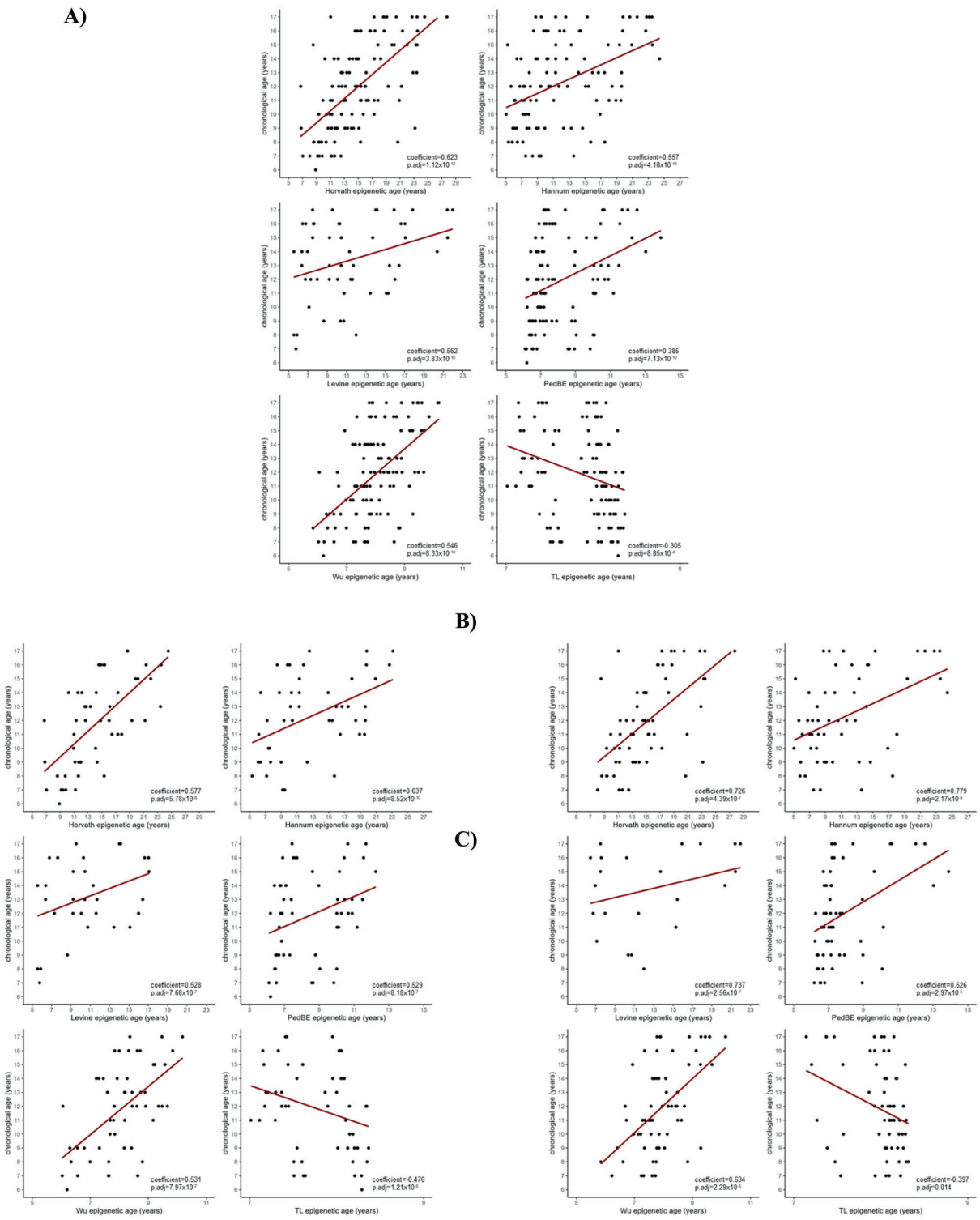

Fig. 1 Linear correlation between chronological and epigenetic age. Epigenetic age estimated with the 6 epigenetic clocks was significantly correlated with correlated age in **A** the whole sample, **B** the individuals who provided blood and **C** the individuals who provided saliva for methylation analysis. Correlation was assessed with Pearson's correation coefficient.

sample size reduction and subsequent loss of statistical power. We found trends towards signification for Horvath and Hannum epigenetic clocks in blood and saliva analyses, suggesting that the tissue used for epigenetic age estimation was not a critical factor.

Previous studies in schizophrenia and bipolar disorder adult samples using epigenetic clocks based on age-related methylation markers—i.e. Horvath, Hannum, PedBE and Wu—have found inconsistent results. Four studies reported epigenetic

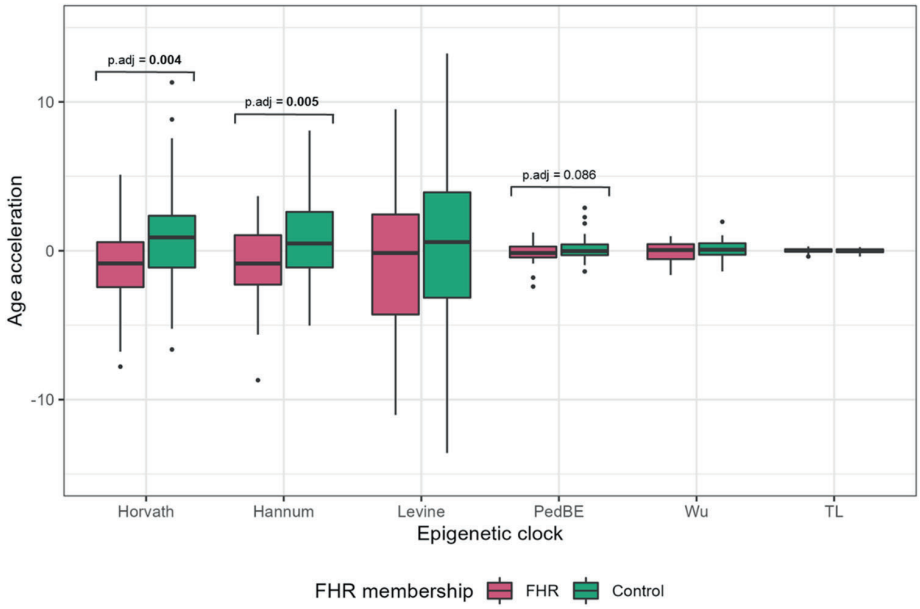

Fig. 2 Boxplots showing epigenetic age acceleration differences between FHR and control individuals. TL telomere length, FHR familial high risk.

Table 2. Effects of obstetric complications, socioeconomic status and recent stressful life events on the epigenetic age acceleration.

Epigenetic age acceleration	Obstetric complications			Socioeconomic status			Recent stressful life events (number)			Recent stressful life events (impact)		
	t	R^2	p.adj	*t*	R^2	p.adj	*t*	R^2	p.adj	*t*	R^2	p.adj
Horvath	0.286	0.001	1.000	−0.476	0.002	1.000	−0.438	0.004	0.994	−0.211	0.002	0.953
Hannum	1.012	0.009	0.837	0.029	0.004	0.977	−0.515	0.000	1.000	−0.235	0.010	1.000
Levine	1.582	0.021	1.000	−1.453	0.022	1.000	−1.263	0.017	1.000	−1.174	0.015	0.834
PedBE	0.197	0.000	0.921	1.000	0.000	0.767	−0.559	0.004	1.000	−0.396	0.002	0.978
Wu	1.777	0.026	1.000	−0.483	0.003	1.000	−1.024	0.009	0.925	−0.718	0.004	1.000
TL	0.046	0.000	1.000	−0.221	−0.001	0.991	1.193	0.013	0.943	1.224	0.014	1.000

TL telomere length.

deacceleration for at least one of the clocks included in the analyses [52–54]—one only in schizophrenia males treated with clozapine [9]—, four did not detect significant differences for epigenetic age acceleration [9, 55–60] and two detected epigenetic age acceleration only in older bipolar disorder patients [61] and a small acceleration in schizophrenia patients [9]. As for the Levine clock/phenotypic age, accelerated epigenetic aging [9, 59] and no differences with chronological age [60] have been found, providing no conclusive distinction between chronologic and phenotypic age epigenetic clocks. The epigenetic clock for TL found shorter lengths—thus implying aging acceleration—in schizophrenia patients [9]. Two studies analyzed longitudinally the effect of first-episode psychosis on epigenetic age acceleration measured with Horvath clock, reporting deaccelerated epigenetic ages before psychosis onset and increased acceleration rates after the psychotic episode and the exposition to antipsychotic medication [62, 63]. Therefore, these previous findings suggest that each epigenetic clock could reflect diverse aspects of aging and that the pace of epigenetic aging could be irregular along the lifespan, reporting more pronounced deviations from chronological age in certain stages of life [9, 61] and due to psychosis onset or exposition to pharmacological treatment. Thus, disorder stages—including the ones preceding the onset—have to be considered to establish the epigenetic age dysregulation as a molecular predictor on mental illness.

The exposition to environmental stressors has been thoroughly considered as a mediator of biological aging. Lifestyle, diet, substance use, education, economic income, psychosocial stress, disease and many other factors have been found to alter biological aging [64–67]. Biological aging has also been found to be affected by the prenatal environment and early life adversity [68–77]. Our results could not confirm the association of environmental stress exposure with a dysregulation of time-dependent methylation pattern. Several reasons may explain the lack of association between environmental stressors and the epigenetic age in our sample. The present sample was recruited at a very young age, making it difficult to detect the cumulative impact of environmental stressors. We lacked a measure covering all environmental stressors, and the use of discreet indexes may have limited our capacity to detect small changes. Moreover, our sample had a low frequency of obstetric complications and showed high homogeneity in the sociodemographic status and frequency of recent stressful life events. Further studies with larger samples and more refined tools for prospectively measuring the effect of environmental insults are required to define their role as

mediators of epigenetic changes and to understand their contribution to psychopathology.

The analyses performed with cell-adjusted epigenetic age acceleration estimates in the entire sample reported identical results in FHR/control group differences (in exception of the PedBE epigenetic clock surviving multiple testing correction) and on the effect of environmental risk factors. The similarity of results suggests that the FHR condition or any of the studied environmental risk factors had a critical effect on blood/saliva cell proportions.

Some limitations of the present work should be taken into consideration. Firstly, the sample size was limited. Therefore, the statistical analysis may have been underpowered to detect small effects. Epigenetic characterization was conducted using heterogeneous biological samples, but parallel data processing was performed for the blood and saliva samples and all the analyses were corrected for tissue type. The study lacked the assessment of alcohol and tobacco use during pregnancy, a putatively confounding variable in epigenetic studies. Participants were recruited based on their family history of either schizophrenia or bipolar disorder, which could have contributed additional heterogeneity in terms of determinants of risk. Finally, the young age of the participants impeded the categorization of the subjects based on their conversion to bipolar disorder or schizophrenia, a presumably more homogeneous phenotype. Nonetheless, the current definition based on familial risk has so far proven to be valid for detecting differences in psychopathology as well as in neuropsychological and brain imaging features [30, 78–84].

Molecular mechanisms driven by epigenetic changes in early stages of life may be critical for the onset of severe mental disorders and their clinical course. The epigenetic age asynchronicities found in the young at high risk provide novel evidence to advance towards the characterization of the molecular signature driven by environmental stressors. The effects of a discordant pace in biological aging could be critical to understand the underlying mechanisms of illness onset and the age-associated conditions detected in schizophrenia and bipolar disorder. Further studies are required to identify the relevance, causality and interaction of internal and external elements that define the clinical manifestation of severe mental disorders to ultimately develop novel tools for personalized psychiatry.

DATA AVAILABILITY

According to the permiss ions of the informed consent, clinical and biological data of the participants of the studies cannot be accessed through public repositories. Epigenetic data results, such as epigenetic age estimation, can be shared upon request. The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. *methylclock* R package documentation can be found at https://github.com/isglobal-brge/methylclock. For cell count estimation, publicly available data were used for blood [48] and saliva [49] tissues.

CODE AVAILABILITY

The code for methylation data preparation, epigenetic clock construction and statistical analysis is not publicly available and can be obtained upon request.

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AUTHOR CONTRIBUTIONS

AGS performed the statistical analysis and wrote the first draft of the manuscript. EdlS participated in the coordination of the sample shipment, the maintenance of the database and in the recruitment and assessment of the sample. GS, IB, IV, CDC, NM and DMM participated in the recruitment and assessment of the sample. PG and NF performed the sample isolation and preparation and participated in the statistical analysis. SM designed, supervised and performed the statistical analysis, performed the interpretation of the results and wrote the first draft of the manuscript. JCF is the coordinator of the project and funding manager.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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Polygenic risk scores mediating functioning outcomes through cognitive and clinical features in youth at family risk and controls

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ABSTRACT

Schizophrenia and bipolar disorder exhibit substantial clinical overlap, particularly in individuals at familial high risk, who frequently present sub-threshold symptoms before the onset of illness. Severe mental disorders are highly polygenic traits, but their impact on the stages preceding the manifestation of mental disorders remains relatively unexplored. Our study aimed to examine the influence of polygenic risk scores (PRS) on sub-clinical outcomes over a 2-year period in youth at familial high risk for schizophrenia and bipolar disorder and controls. The sample included 222 children and adolescents, comprising offspring of parents with schizophrenia (n = 38), bipolar disorder (n = 80), and community controls (n = 104). We calculated PRS for psychiatric disorders, neuroticism and cognition using the PRS-CS method. Linear mixed-effects models were employed to investigate the association between PRS and cognition, symptom severity and functioning. Mediation analyses were conducted to explore whether clinical features acted as intermediaries in the impact of PRS on functioning outcomes. SZoff exhibited elevated PRS for schizophrenia. In the entire sample, PRS for depression, neuroticism, and cognitive traits showed associations with sub-clinical features. The effect of PRS for neuroticism and general intelligence on functioning outcomes were mediated by cognition and symptoms severity, respectively. This study delves into the interplay among genetics, the emergence of sub-clinical symptoms and functioning outcomes, providing novel evidence on mechanisms underpinning the continuum from sub-threshold features to the onset of mental disorders. The findings underscore the interplay of genetics, cognition, and clinical features, providing insights for personalized early interventions.

During the preparation of this work the authors used ChatGPT in order for grammar checking the final versions of the draft. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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1. Introduction

Schizophrenia and bipolar disorder are considered distinct diagnostic entities, but their notable clinical features largely overlap (Sandstrom et al., 2019; Yamada et al., 2020). Familial antecedents, as indicated by studies (Rasic et al., 2014; Sullivan et al., 2003), significantly enhance the risk of illness onset in offspring born to affected parents, emphasizing the key role of genetic predisposition in family aggregation and the substantial genetic correlation between disorders (Cardno and Owen, 2014; Cross-Disorder Group, 2013; Lu et al., 2021). The implementation of genome-wide association studies (GWAS) has established that numerous common variants with small effects contribute to the emergence of psychotic and mood disorders (Smoller et al., 2019; The International Schizophrenia Consortium, 2009). Polygenic risk scores (PRS) are constructs based on the results of highly powered GWAS that estimate the individual genetic liability for complex phenotypes. An extensive body of literature on PRS, reflecting genetic liability not only for mental disorders but also for related phenotypes, highlights their significance in understanding the underlying mechanisms of schizophrenia and bipolar disorder. Studies have reported more unfavorable psychiatric disorders, personality, and cognitive PRS in individuals with severe mental disorders (Mistry et al., 2018a, 2018b; Perkins et al., 2020). Furthermore, these PRS are associated with poorer clinical outcomes, such as more severe psychotic and depressive symptoms (Kwong et al., 2021; Maxwell et al., 2023) and reduced cognitive performance (Habtewold et al., 2020; He et al., 2021; Ohi et al., 2022).

The diagnosis of psychotic spectrum disorders typically occurs during late adolescence and early adulthood, but the onset of the illness is often preceded by a sub-threshold phase. This is characterized by the emergence of disruptions in cognitive performance attenuated symptoms and global functioning that are either less frequent or less severe than those observed at illness onset. These sub-threshold features are observed in the general population as a continuum, ranging from subtle subclinical signs to overt clinical alterations (Cochrane et al., 2012; Oeztuerk et al., 2022; van Os, 2000). Sub-threshold features in non-clinical populations may be triggered by individual biological susceptibility and external stressful stimuli, and have been associated with the subsequent transition to psychosis (van Os et al., 2009). Hence, characterization of the sub-threshold phase and the cross-talk between biological factors and environmental factors can contribute to discern individuals at high risk and prompt preemptive clinical interventions, which can have a major impact on the course of the disorder (Albert and Weibell, 2019; Lieberman et al., 2019).

Previous findings in the sample of this study have demonstrated higher rates of psychopathology (De la Serna et al., 2021; Noguera et al., 2018; Sánchez-Gutiérrez et al., 2020) and deaccelerated epigenetic aging (Segura et al., 2023) in children and adolescents at familial high risk for schizophrenia and bipolar disorder. In this study, we aimed to evaluate the role of psychiatric disorders, neuroticism and cognitive PRS on cognition, symptom severity and functioning over a 2-year period in a cohort comprised of youth at familial high risk for schizophrenia and bipolar disorder, as well as in a control group. We hypothesized that offspring at high familial risk would report less favorable psychiatric disorders, cognitive and personality PRS. Furthermore, we also proposed that the cognitive impairment and poorer clinical outcomes observed in this sample could be influenced by the PRS. Specifically, we believed that any unfavorable PRS associated with familial high risk groups could underlie the manifestation of sub-threshold clinical features.

2. Methods

The present study is part of the Bipolar and Schizophrenia Young Offspring Study (BASYS), which is a multicenter, longitudinal, naturalistic study that aims to compare the clinical, neuropsychological, neuroimaging, genetic and epigenetic characteristics of child and adolescent offspring of patients diagnosed with schizophrenia or bipolar disorder and of a community control group. This study was conducted in the child and adolescent psychiatry units of two hospitals in Spain: the Hospital Clinic in Barcelona and the Hospital Gregorio Marañón in Madrid. The methodology and the clinical and cognitive characteristics of the sample have been described previously in detail (Sanchez-Gistau et al., 2015).

2.1. Sample

The individuals at familial high risk were recruited from the adult psychiatry units of both hospitals. The inclusion criteria were: (a) age between 6 and 17 years, and (b) a parent diagnosed with schizophrenia or bipolar disorder. The exclusion criteria were: (a) intellectual disability with an impact on functioning, and (b) significant head injury or a current medical or neurological condition. Community control parents were recruited through advertisements posted in primary health care centers and other community locations in the same geographical area as the patients. The only inclusion criterion for the offspring of the community controls was an age between 6 and 17 years, while the exclusion criteria were the same as those for the offspring of schizophrenia or bipolar disorder patients plus a family history of psychotic disorders in first- or second-degree relatives. At baseline, BASYS included 41 offspring of parents with schizophrenia (SZoff), 90 offspring of parents with bipolar disorder (BDoff) and 107 offspring of community controls (CCoff). Given the focus on genetic data in this study, we included only the 222 individuals who had provided biological samples for DNA genotyping and passed the genetic quality control (38 SZoff, 80 BDoff and 104 CCoff). Cognitive and clinical assessments were conducted at study entry and after a 2-year follow-up period.

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. The study was approved by the Ethical Review Board of each participating hospital. Written informed consent was obtained from one of the parents or legal guardians, having the other parent been informed, together with written assent from the participant if 12 years of age or older.

2.2. Assessments

2.2.1. Cognitive assessment

The intelligence quotient was assessed using the Spanish version of the Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV) (Wechsler, 2003), which evaluates intellectual abilities in children and adolescents aged between 6 and 16 years. The WISC-IV provides four composite scores: the Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index and the Processing Speed Index. Previous research has shown that the WMI and PSI may be impaired in SZoff (Niemi et al., 2003) and BDoff (Duffy et al., 2009; Gotlib et al., 2005). To avoid the influence of each of these indexes on the full-scale IQ, the General Ability Index (GAI), derived from the VCI and PRI, was used as an index of cognition (Flanagan and Kaufman, 2009).

2.2.2. Clinical assessment

A trained psychiatrist or psychologist performed a mental health assessment of all the parents using the Spanish version of the Structured Clinical Interview for DSM-IV Disorders (SCID-I) (First et al., 1997, 1999). Parents or primary caregivers were also interviewed about their children.

Participants were assessed at each visit with the Scale of Prodromal Symptoms (SOPS) within the Structured Interview for Prodromal Symptoms (Miller et al., 2003). The reliability of SOPS was calculated by the team members who performed the clinical assessments (Kappa statistic for both SOPS total score and subscales > 0.8). The SOPS is a 19-item scale that contains four subscales for positive, negative,

disorganization and general symptom constructs. For this study, the total SOPS score was included in the analyses.

The Clinical Global Impressions (CGI) scale assesses global disease, independently of questionnaire ratings (Guy, 1976). The CGI rates functioning at the time of assessment, taking into account the clinical history, psychosocial circumstances, symptoms, behavior and the impact of symptoms on functioning (Busner and Targum, 2007). Higher scores indicate a higher impact of the illness on functioning.

Measures of global functioning capture the severity of psychotic symptoms and the level of occupational and social functioning. Participants under 18 years were assessed with the Children's Global Assessment Scale (Shaffer, 1983) and participants aged 18 years were assessed with the Global Assessment of Functioning Scale (Endicott, 1976). Both functioning measurements consist of a scale of 1–100, evaluated by the clinician. Higher scores indicate better global functioning.

2.3. 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). Saliva samples were collected using the Oragene DNA Saliva Collection Kit (OG-500, DNA Self-Collection Kit, Genotek, Ottawa, Ontario, Canada) and DNA was extracted according to the manufacturer's instructions. DNA concentration and quality were measured spectrophotometrically using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Epsom, Surrey, UK). A total of 2.5 μg of genomic DNA was sent for genotyping at the Spanish National Genotyping Center (CeGen) using the Axiom Spain Biobank Array (developed at the University of Santiago de Compostela, Spain).

2.4. PRS construction

Genotyping data were submitted to the Michigan Imputation Server (Das et al., 2016). The standard pipeline and pre-imputation quality control required for Minimac4 software was followed and the European population reference from build GRCh37/hg19, the reference panel HRC 1.1 2016 and Eagle v2.4 phasing were used.

For the PRS calculation, GWAS summary results were obtained from the Psychiatric Genomics Consortium and the Science Genetic Association Consortium. The PRS were constructed for schizophrenia (PRS_{SZ}; 69,396 cases and 236,642 controls) (Trubetskoy et al., 2022), bipolar disorder (PRS_{BD}; 41,917 cases and 371,549 controls) (Mullins et al., 2020), major depressive disorder (MDD) (PRS_{MDD}; 246,363 cases and 561,190 controls) (Howard et al., 2019), neuroticism (PRS_{Neu}; 390,278 individuals) (Werme et al., 2021), intelligence (PRS_{IQ}; 269,867 individuals) (Savage et al., 2018), educational attainment (PRS_{EA}; 1131, 881 individuals) (Lee et al., 2018) and cognitive performance (PRS_{CP}; 257,841 individuals) (Lee et al., 2018). Higher PRS_{SZ}, PRS_{BD} and PRS_{MDD} and PRS_{Neu} reflect greater liability for the phenotype and higher PRS_{IQ}, PRS_{EA} and PRS_{CP} reflect better cognitive performance. The PRS were converted into a z-score by subtracting the mean and dividing by the standard deviation (SD).

The quality control was performed with PLINK v1.07 (Purcell et al., 2007). Inclusion criteria for SNPs were minor allele frequency (MAF) $>$ 0.01, Hardy-Weinberg equilibrium p value $> 10^{-6}$, marker missingness $\langle$ 0.01 and imputation score INFO $\rangle$ 0.8. The sample quality control included individuals with heterozygosity values within three SD from the mean, a missingness rate $\langle$ 0.01, matching chromosomal and database-labelled sex and self-reported European ancestry. Pruning was performed using a window/step size of 200/50 kb and $r^2\rangle$ 0.25 prior to the heterozygosity check.

The PRS were constructed using PRS-CS, a method that implements a high-dimensional Bayesian regression to perform a continuous shrinkage of SNP effect sizes using GWAS summary statistics and an external linkage disequilibrium (LD) reference panel. The LD reference panel was constructed using a European subsample of the UK Biobank. For the remaining parameters, the default options as implemented in PRS-CS were adopted.

2.5. Statistical analyses

A genetic principal component analysis (PCA) was performed to control for population stratification (Price et al., 2006) by means of the *SNPRelate* package, and the first 10 components were used as covariates in the statistical analyses including PRS.

Familial risk group differences in sociodemographic, cognitive, prodromal psychotic symptoms and functioning scales at study entry were calculated by generalized linear mixed-effects models, using family ID as a random effect (FHR group membership ~ independent variable + (1|family ID)). Any differences due to the recruitment center were assessed by generalized linear mixed-effects models (recruitment centre ~ independent variable + (1 | family ID). The correlation between PRS was tested using Pearson's product-moment correlation.

The assessment of PRS differences between the familial risk groups was performed with linear mixed-effect models, considering family ID as a random effect and corrected by the 10 first components of the genetic PCA (PRS ~ FHR group membership + PCA components1–10 + (1 | family ID)).

The association between the PRS and the 2-year measures of cognition, prodromal psychotic symptoms and functioning was evaluated with independent linear mixed-effects models using family ID, month of assessment and familial high risk group membership as random effects and corrected by sex, age and the 10 first components of the genetic PCA (dependent variable ~ PRS + sex + age + PCA components1–10 + (1 + family ID + FHR group membership | month of assessment).

Mediation analysis tested whether the effect of a causal variable (PRS) on an outcome variable (global disease and functioning) was affected by one or more mediator variables (cognition, prodromal psychotic symptoms). The relationship between variables is described by three effects: (1) Total effect, the association between causal variable and outcome variable; (2) average causal mediation effect (ACME), the effect of the causal variable on the outcome variable, when controlling for the mediator variable; and (3) average direct effect (ADE), the effect of the causal variable on the outcome variable via the mediator variable (Hayes and Rockwood, 2017). The quasi-Bayesian Monte Carlo method based on normal approximation was used to perform 1000 simulations, from which the p value of total effect, ACME and ADE was extracted. For the sake of simplicity, baseline measures of cognitive, prodromal psychotic symptoms and functioning measures were used in the mediator models. In cases where the models showed no significant total effect, the mediating role of the cognitive and clinical scales was not assessed. For those models with significant total effects, the mediation was categorized as follows: partial mediation when both ACME and ADE were significant, total mediation when only ACME was significant, and no mediation when only ADE was significant.

All the analyses were performed in RStudio environment (RStudio Team, 2017) with R programming language. The variance explained as the marginal pseudo-R^2 (R^2) was estimated with the r.squared GLMM command of the *MuMIn* package. The reported R^2 values reflect the variance of the PRS on the outcome variable, and were calculated as the difference between the R^2 of the full model (including the PRS and the covariates) minus the model excluding the PRS. Multiple testing correction was applied in all the analyses by means of the FDR method, and the threshold of significance of the adjusted p value (p.adj) was set at $\alpha < 0.05$.

Table 1
Sociodemographic data, cognitive, symptom severity and functioning measures and familial risk group comparison.

Feature		SZoff mean (SD) or n(%)	BDoff mean (SD) or n(%)	CCoff mean (SD) or n(%)	comparison*
Age		10.2 (3.3)	12.1 (3.1)	12.0 (3.3)	
Sex - female		16(42.1 %)	36(45.0 %)	63(60.6 %)	
Cognition	Baseline	96.9 (12.8)	107.0 (12.7)	108.0 (12.6)	SZoff < BDoff; SZoff < CCoff
	2-year	101.0 (15.5)	110.0 (11.6)	109.0 (12.2)	
Prodromal psychotic symptoms	Baseline	6.8(8.6)	3.6(6.9)	1.5/ (2.2)	SZoff > CCoff
	2-year	5.9(7.0)	4.1(7.1)	2.5(3.6)	SZoff > CCoff
Global disease	Baseline	1.2(1.2)	0.7(0.9)	0.3(0.7)	
	2-year	1.5(1.3)	0.9(1.1)	0.4(0.8)	SZoff > BDoff; SZoff > CCoff
Global functioning	Baseline	75.4 (18.0)	81.9 (11.7)	86.0 (7.7)	SZoff > CCoff
	2-year	73.5 (19.0)	78.5 (20.5)	87.3 (7.6)	SZoff < CCoff; BDoff < CCoff

*p.adj<0.05; detailed results provided in Table S1.
Offspring of schizophrenia patients (SZoff); offspring of bipolar disorder patients (BDoff); offspring of community controls (CCoff).

3. Results

3.1. Descriptive statistics

The sample consisted of 222 children and adolescents, 38 SZoff (17.1 %), 80 BDoff (30.0 %) and 104 CCoff (46.9 %). Table 1 provides information on sociodemographic, cognitive, prodromal psychotic symptoms and functioning features at both assessment points, along with familial risk group differences. In general, the SZoff reported the most pronounced cognitive impairments and poorer subclinical features, BDoff exhibited intermediate scores across various scales, while CCoff reported the highest levels of cognitive performance and the most favorable subclinical outcomes. Additional information of these analysis can be found in Table S1. No differences were found between recruitment center (data not shown).

The PRS correlation analyses revealed positive correlations within the psychiatric disorders PRS and negative correlations with the cognitive PRS, with the exception of a positive correlation between PRS_{BD} and PRS_{EA}. Likewise, the cognitive PRS exhibited correlations with each. PRS_{Neu} showed positive correlated with PRS_{SZ} and PRS_{MDD} (Fig. S1, see online).

The SZoff group reported higher PRS_{SZ} compared to the controls (p.adj = 0.001), while no other PRS showed significant differences between the SZoff, BDoff or CCoff groups (Table 2).

3.2. PRS association with cognitive, prodromal psychotic symptoms and functioning measures

The PRS were tested for their association with cognitive, prodromal psychotic symptoms and functioning measures over time in the entire sample. The analyses showed that individuals with more disadvantageous PRS_{IQ} and PRS_{EA} exhibited poorer cognitive performance (p.adj $\leq 3.64 \times 10^{-5}$). Higher global disease scores were associated with PRS_{IQ}, PRS_{EA}, PRS_{CP} and PRS_{Neu} (p.adj $\leq$ 0.016), while prodromal psychotic symptoms with PRS_{MDD} and PRS_{Neu} (p.adj $\leq$ 0.014). Additionally, improved global functioning was negatively associated with PRS_{MDD} and PRS_{Neu} (p.adj $\leq$ 0.004). Notably, PRS_{SZ} and PRS_{BD} were not associated with any scale (Table 3).

3.3. Cognitive and clinical mediation of the association of PRS with functioning outcomes

Mediation analyses were performed to further investigate the relationship between PRS and the cognitive, prodromal psychotic symptoms and functioning measures. Building on the previous results, we examined whether the cognition and prodromal psychotic symptoms mediated the association of PRS_{MDD}, PRS_{Neu}, PRS_{IQ} and PRS_{CP} with global disease and functioning.

Fig. 1 provides a summary of the mediation analysis results. The effect of PRS_{MDD} on global functioning was not mediated by prodromal psychotic symptoms (ACME $p = 0.092$; ADE $p = 0.016$). Prodromal psychotic symptoms reported total mediation for the effects of PRS_{Neu} on global disease (ACME $p = 0.002$; ADE $p = 1.000$) and functioning (ACME $p < 2 \times 10^{-16}$; ADE $p = 0.150$). Cognition reported total mediation for the effects of PRS_{IQ} on global disease (ACME $p = 0.004$; ADE $p = 1.374$). For the remaining mediation models, no significant total effect of the PRS on the functioning measures was observed. Further details of the mediation analysis results can be found on Table S2.

4. Discussion

4.1. Main findings

This study assessed the genetic liability for psychiatric disorders, neuroticism and cognition in a sample of child and adolescents, including individuals at familial high risk for schizophrenia and bipolar disorder. Our first hypothesis proposed differences in PRS among the FHR groups. Among all the PRS included in this study, only PRS_{SZ} was elevated in SZoff. Our findings indicate that the observed cognitive impairment and poorer clinical outcomes in this sample are influenced by the PRS, aligning with our second hypothesis. Interestingly, our observations do not align with the third hypothesis, as we did not find evidence that unfavorable PRS_{SZ} underlies the manifestation of subthreshold clinical features measured over a 2-year follow-up. Notably, the effect sizes of these associations were relatively small. This outcome aligns with the prevailing trend in the literature, wherein PRS often demonstrate limited explanatory power, either on their own or in

Table 2
Linear mixed-effect models assessing the differences of PRS between familial risk groups. Significant results are marked in bold.

PRS	SZoff vs CCoff				BDoff vs CCoff				SZoff vs BDoff			
	beta	t	R^2	p.adj	beta	t	R^2	p.adj	beta	t	R^2	p.adj
PRS_{SZ}	−0.730	−4.158	0.013	0.001	−0.145	−0.932	0.002	0.635	0.502	2.588	0.003	0.082
PRS_{BD}	−0.449	−1.890	0.004	0.145	−0.187	−1.008	0.000	0.635	0.237	0.957	0.002	0.774
PRS_{MDD}	−0.224	−1.051	0.004	0.518	−0.089	−0.521	0.005	0.763	0.078	0.341	0.008	0.912
PRS_{Neu}	−0.063	−0.277	0.004	0.943	−0.060	−0.348	0.005	0.763	−0.045	−0.177	0.004	0.912
PRS_{IQ}	0.047	0.198	0.002	0.943	0.055	0.302	0.003	0.763	0.177	0.772	0.006	0.774
PRS_{EA}	0.399	1.953	0.001	0.145	0.209	1.329	0.003	0.635	−0.026	−0.111	0.002	0.912
PRS_{CP}	0.017	0.071	0.002	0.943	0.164	0.914	0.002	0.635	0.337	1.489	0.006	0.492

Schizophrenia (SZ); bipolar disorder (BD); major depressive disorder (MDD); neuroticism (Neu); general intelligence (IQ); educational attainment (EA); cognitive performance (CP); offspring of schizophrenia patients (SZoff); offspring of bipolar disorder patients (BDoff); offspring of community controls (CCoff).

Table 3
PRS association with cognitive, symptom severity and functioning measures assessed by means of linear mixed-effect models. Significant results are marked in bold.

PRS	Cognition				Prodromal psychotic symptoms				Global disease				Global functioning			
	beta	t	R^2	p.adj	beta	t	R^2	p.adj	beta	t	R^2	p.adj	beta	t	R^2	p.adj
PRS_{SZ}	0.221	0.277	0.035	0.782	0.243	0.696	−0.294	0.487	0.054	0.934	0.114	0.351	−1.006	−1.290	0.035	0.231
PRS_{BD}	−0.382	−0.566	−0.181	0.690	−0.604	−1.983	−0.109	0.112	−0.086	−1.731	0.195	0.118	0.057	0.083	0.033	0.934
PRS_{MDD}	0.516	0.737	−0.090	0.690	0.955	3.016	−0.044	**0.010**	0.082	1.593	0.146	0.131	−2.434	−3.541	0.003	**0.003**
PRS_{Neu}	−0.375	−0.537	−0.033	0.690	1.153	3.795	−0.066	**0.001**	0.149	2.998	0.326	**0.012**	−2.258	−3.332	0.135	**0.003**
PRS_{IQ}	3.630	5.574	0.016	**3.37E-07**	−0.420	−1.426	−0.243	0.209	−0.135	−2.806	0.338	**0.012**	1.396	2.121	0.152	0.060
PRS_{EA}	1.038	1.500	−0.214	0.314	−0.485	−1.600	0.069	0.194	−0.146	−2.889	0.233	**0.012**	1.213	1.766	0.052	0.109
PRS_{CP}	2.871	4.259	0.059	**9.17E-05**	−0.404	−1.346	−0.298	0.209	−0.130	−2.625	0.227	**0.016**	1.466	2.182	0.056	0.060

Schizophrenia (SZ); bipolar disorder (BD); major depressive disorder (MDD); neuroticism (Neu); general intelligence (IQ); educational attainment (EA); cognitive performance (CP); neuroticism (Neu).

interaction with environmental risk factors (Agerbo et al., 2015; Woolway et al., 2022). Mediation analyses revealed that the effects of PRS_{Neu} and PRS_{IQ} on functioning were mediated by prodromal psychotic symptoms and cognition, respectively. Overall, the findings suggest that the inherited polygenic risk for schizophrenia is not a critical factor for the emergence of early sub-threshold features. Instead, the genetic liability for depression, neuroticism and cognition may play a more preeminent role on the emergence of early sub-threshold features in young individuals.

4.2. PRS differences between familial risk groups

In this study, only the offspring of individuals with schizophrenia reported a higher genetic susceptibility to the disorder. Neither PRS_{BD} nor PRS_{MDD} showed increased values in any high familial risk group, nor PRS_{SZ} in BDoff, thus failing to detect genetic factors related to the predisposition to mood disorders or cross-disorder susceptibility (Cardno and Owen, 2014; Cross-Disorder Group, 2013; Lu et al., 2021). These findings underscore the predominant genetic load in the offspring of schizophrenia patients, as widely acknowledged in the literature (Santoro et al., 2018; Sørensen et al., 2018; Toulopoulou et al., 2019; Vassos et al., 2017; Wang et al., 2018; Zheutlin et al., 2019) and suggest that the genetic liability for mood disorders, neurotic personality and cognitive abilities may exhibit a more homogeneous distribution across various types familial risk for severe mental illness.

4.3. Schizophrenia PRS does not modulate sub-clinical outcomes

Previous studies using this sample have detected overall increased psychopathological features in individuals at familial high risk (De la Serna et al., 2021; Noguera et al., 2018; Sánchez-Gutiérrez et al., 2020). Given the increased PRS_{SZ} in the SZoff group, our initial hypothesis was that schizophrenia genetic susceptibility would modulate sub-threshold clinical features. However, our analyses did not establish a link between PRS_{SZ} and the cognitive, prodromal psychotic symptoms and functioning measures, suggesting that the genetic load inherited by SZoff may not necessarily lead to more unfavorable features over a 2-year period in young individuals. Conflicting results in the literature concerning the impact of psychiatric disorders PRS on clinical outcomes can be observed. While several studies have reported significant associations between psychiatric disorders PRS and various clinical parameters, such as symptom severity, cognitive performance, treatment resistance and functioning (Chen et al., 2018; Jonas et al., 2019; Mistry et al., 2018a, 2018b; Pignon et al., 2022; Santoro et al., 2018; Werner et al., 2020; Zhang et al., 2019), others have failed to detect such associations (Ahangari et al., 2023; Mas-Bermejo et al., 2023; Nenadić et al., 2022; Segura et al., 2022; Shafee et al., 2018; Smigielski et al., 2021; Sørensen et al., 2018; Wimberley et al., 2017). It is worth noting that our study may not have detected associations between PRS_{SZ} and the sub-clinical status due to the moderated sample size, potentially limiting our ability to identify small effects. If such effects do exist, they are likely smaller than those found for the other PRS.

4.4. PRS_{MDD} and PRS_{Neu} link with prodromal psychotic symptoms and functioning

The analyses of PRS_{MDD} and PRS_{Neu} differed from those of schizophrenia and bipolar disorder PRS. They exhibited an association with prodromal psychotic symptoms and functioning, suggesting that these PRS might capture genetic liability to nonspecific features commonly manifested in the prodromal phases of psychotic and mood disorders.

The mediation analyses indicated that the effect of PRS_{MDD} on s prodromal psychotic symptoms and global functioning was direct, while the effect of PRS_{Neu} on both scales of functioning was entirely mediated by the prodromal psychotic symptoms. Although neuroticism is a well-established personality trait and thus seemingly more distal to the

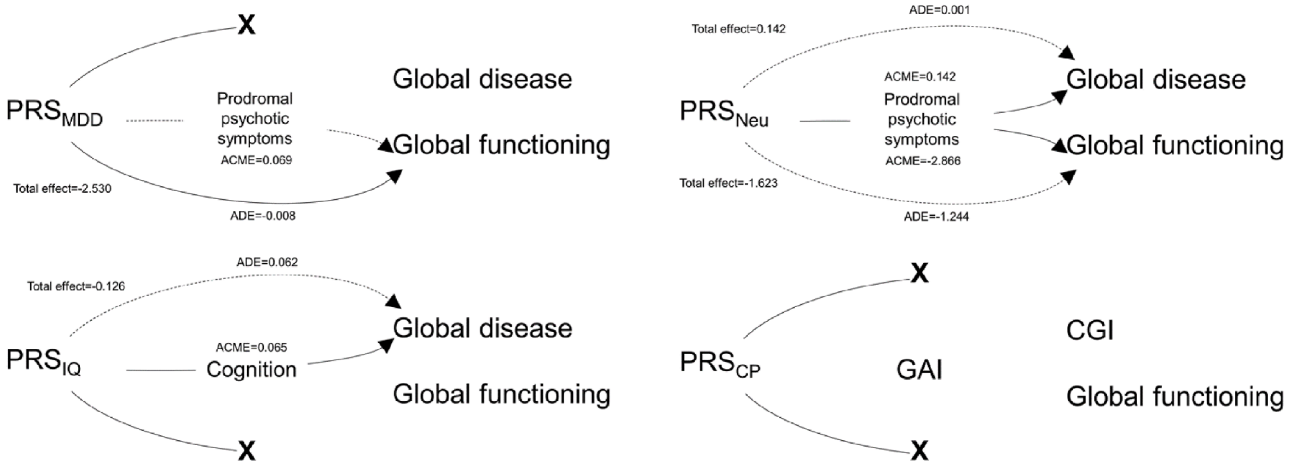

Fig. 1. Summary of mediation models illustrating the mediating effect of prodromal psychotic symptoms and cognitive performance between PRSMDD, PRSNeu, PRSIQ and PRSCP with global disease and functioning. Models with non-significant total effects are denoted with an X.
Major depressive disorder (MDD); neuroticism (Neu); general intelligence (IQ); cognitive performance (CP); average causal mediation effect (ACME); average direct effect (ADE)".

manifestation of severe mental disorders, it has been proposed as a predictor of overall quality of life (Lahey, 2009; Widiger and Oltmanns, 2017). The influence of genetic susceptibility for neuroticism on the clinical presentation of severe mental disorders remains an ongoing topic of debate (Coombes et al., 2020; Fanelli et al., 2022; Li et al., 2020). While some studies have focused on severe outcomes in the later stages of severe mental disorders, such as the risk of hospitalization (Balbuena et al., 2023), suicide attempts (Su et al., 2022) and comorbidity of internalizing and externalizing disorders (Khan et al., 2005), others have explored the early clinical manifestations in young individuals. These investigations have yielded inconclusive results concerning the connections between neuroticism PRS and behavior (Ensink et al., 2020) or psychotic symptoms (Jones et al., 2018; Kwong et al., 2021; Maxwell et al., 2023).

4.5. Cognitive PRS link with cognition and functioning

PRS_{IQ} and PRS_{CP} demonstrated significant associations with cognition, consistent with prior findings in patients with psychosis (Richards et al., 2019; Segura et al., 2022). Our findings suggest that elevated cognitive PRS_{IQ} and PRS_{CP} influence increased cognition and more favorable functioning outcomes in young individuals, without critically altering prodromal psychotic symptoms. The mediation analysis revealed that the effect of PRS_{IQ} on global disease was entirely mediated by the cognitive status. However, when examining the mediation effect of cognitive status on the relationship between PRS_{CP} and global disease, our analysis did not yield a statistically significant total effect. While a noticeable trend was observed, it is plausible that larger sample sizes are required to detect this mediation effect conclusively. This observation aligns with the high correlation between PRS_{IQ} and PRS_{CP}, both representing the genetic liability for a very similar phenotype. Considering the mediation analysis results of PRS_{IQ} and PRS_{Neu}, it becomes increasingly apparent that genetic factors of diverse natures may jointly influence cognitive and psychopathological traits, consequently affecting functional outcomes.

4.6. Limitations of the study

The results of this study must be considered in the context of its limitations. The study was constrained by a limited sample size, posing a critical challenge for conducting independent analyses for the three FHR groups. Consequently, group-specific associations could not be discerned, and some associations might have been masked due to the heterogeneity of the sample. Nonetheless, all statistical models in the study accounted for the variance associated with FHR membership. Additionally, the onset of severe mental disorders is expected in late adolescence and therefore longer follow-up periods will be necessary to conduct case-control analyses with stable diagnostic categories. Consequently, extended follow-up durations are required to provide a more comprehensive understanding of the role of PRS in the progression of cognitive performance, prodromal psychotic symptoms, and functioning, as well as their associations with illness onset.

5. Conclusions

The mechanisms underlying the continuum from sub-threshold clinical outcomes to the manifestation of mental disorders are crucial for understanding the onset and prognosis of schizophrenia and bipolar disorder. Previously reported sub-threshold psychopathological differences between familial risk groups could not be explained by the increased genetic liability for schizophrenia found in the offspring of schizophrenia patients. Instead, the genetic liabilities for neuroticism and cognition were found linked with cognitive and clinical features which, in turn, influenced downstream functioning outcomes. This study provides novel evidence of the genetic complexity involved in the early manifestation of sub-threshold clinical features and suggests a putative causal relationship between genetics, psychopathological features and functioning. Further investigation in this area are necessary to emphasize the importance of developing personalized tools for the detection and early intervention in young individuals at risk of developing a mental disorder.

CRediT authorship contribution statement

Alex G Segura: Formal analysis, Writing – original draft. **Elena de la Serna:** Data curation, Writing – review & editing. **Gisela Sugranyes:** Conceptualization, Funding acquisition, Writing – review & editing. **Inmaculada Baeza:** Data curation, Writing – review & editing. **Isabel Valli:** Investigation, Writing – review & editing. **Irene Martínez-Serrano:** Formal analysis, Writing – review & editing. **Covadonga M Díaz-Caneja:** Data curation, Writing – review & editing. **Álvaro Andreu-Bernabeu:** Data curation, Writing – review & editing. **Dolores M Moreno:** Data curation, Writing – review & editing. **Patricia Gassó:** Investigation, Writing – review & editing. **Natalia Rodríguez:**

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Declaration of competing interest

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Supplementary materials

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Epigenetic signatures in children and adolescents at familial high risk: linking early-life environmental exposures to psychopathology

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Abstract

Background This study investigates the relationship between environmental risk factors and severe mental disorders using genome-wide methylation data. Methylation profile scores (MPS) and epigenetic clocks were utilized to analyze epigenetic alterations in a cohort comprising 211 individuals aged 6–17 years. Participants included offspring of schizophrenia (n = 30) and bipolar disorder (n = 82) patients, and a community control group (n = 99). The study aimed to assess differences in MPS indicative of intrauterine stress and epigenetic aging across familial risk groups, and their associations with cognition, prodromal psychotic symptoms, and global functioning through statistical models.

Results Individuals at high familial risk demonstrated significant epigenetic alterations associated with pre-pregnancy maternal overweight/obesity, pre-eclampsia, early preterm birth and higher birth weight ($p.adj \leq 0.001$) as well as decelerated epigenetic aging in the Horvath and Hannum epigenetic clocks ($p.adj \leq 0.005$). Among offspring of schizophrenia patients, more severe positive and general prodromal psychotic symptoms correlated with MPS related to maternal pre-pregnancy BMI and overweight/obesity ($p.adj \leq 0.008$) as well as with accelerated epigenetic aging across all examined epigenetic clocks ($p.adj \leq 0.012$).

Conclusions These findings underscore the potential of methylation analysis to quantify persistent effects of intrauterine events and their influence on the onset of psychotic symptoms, particularly in high-risk populations. Further research is essential to elucidate the underlying biological mechanisms during critical early stages of neurodevelopment.

1. INTRODUCTION

Understanding the etiopathogenesis of severe mental disorders requires untangling the intricate relationship between genetic predisposition and environmental influences. Although both factors play essential roles, neither can fully explain the complex phenotypes observed (1). The study of environmental influences poses significant challenges due to the diverse range of factors involved and their dynamic effects across different life stages. Comprehensive measurements of environmental exposures, referred to as the "exposome", present notable methodological challenges due to their inherent subjectivity and the difficulty in accurately assessing their impact (2). Schizophrenia and bipolar disorder, exemplify this complexity, as their onset and prognosis are strongly affected by environmental events during critical periods of intrauterine neurodevelopment (3, 4). Exploring the biological impact of early-life environmental factors is essential for elucidating the mechanisms underlying the manifestation of mental disorders and for identifying individuals at risk.

Understanding the link between environmental risk factors and the onset of severe mental disorders presents a significant challenge due to the limited knowledge of the biological processes that may mediate this association (5, 6). Epigenetic modifications, defined as DNA changes that do not alter sequence, are promising candidates for studying the biological effects of environmental stressors and the mechanisms by which organisms cope with external inputs that may disrupt physiological homeostasis. Among various epigenetic processes, CpG methylation stands out due to its association with the modulation of gene expression (7) and its responsiveness to environmental inputs, making it essential for understanding the biological effects of these factors. Efforts to identify the risk of severe mental health disorders through methylation data have highlighted methylation abnormalities in genes implicated in the pathophysiology of schizophrenia and bipolar disorder as well as in genes implicated in the immune system and inflammatory responses (8).

Transitioning from candidate gene approaches to genome-wide methodologies offers a broader scope for studying complex phenotypes (9). Various methods exist for investigating genome-wide changes, with the earliest approach involving the selection of CpGs associated with undergoing methylation changes over time. These estimators of biological age are known as epigenetic clocks and can be used to detect discrepancies with the individual's chronological age. The accelerated aging hypothesis emerged due to the prevalence of age-related comorbidities among individuals with mental disorders (10, 11); however, inconsistent results have been reported regarding epigenetic age acceleration in these patients (12–14), possibly attributed to complexity and variety of mechanisms involved in aging processes (6). Based on findings in epigenome-wide association studies (EWAS), epigenetic profile score (MPS) analysis offers a novel method to summarize the methylation changes associated with a specific condition, such as environmental factors or health conditions. Although their construction resembles that of polygenic risk scores (PRS), two key distinctions emerge: MPS may exhibit variability across tissues and over time (15), and its causal relationship with the environmental factors cannot be straightforwardly presumed (16). Several studies have shown associations between MPS and metabolic, inflammatory and mental health outcomes (17–21).

The objectives of this study stem from previous findings within the study sample, which consists of child and adolescent individuals who are offspring of patients diagnosed with schizophrenia and bipolar disorder. Previous research has shown elevated rates of psychopathology (22–24), an increased genetic predisposition to schizophrenia (25) and epigenetic age deceleration (26) among individuals at familial high risk compared to offspring of community controls. These findings underscore the interconnected nature of familial antecedents of severe mental disorders, biological factors and subthreshold clinical features. The principal objective of this study was to analyze the epigenetic profile of the sample by employing the two aforementioned epigenetic constructs: MPS and epigenetic clocks. First, our goal was to summarize the epigenetic imprint resulting from exposure to stressful prenatal conditions. Second, we aimed to employ epigenetic clocks to quantify asynchronicities between chronological and biological ages, as previously investigated in a subset of this sample (26). We hypothesized that individuals at familial high risk, particularly those reporting more elevated rates of psychopathology subclinical features (i.e., offspring of schizophrenia patients), would exhibit greater MPS and epigenetic age deceleration. Our hypothesis posited that these abnormal epigenetic patterns would be associated with cognition, prodromal psychotic symptoms and the global functioning.

2. METHODS

The present study is part of the Bipolar and Schizophrenia Young Offspring Study (BASYS), which is a multicenter, longitudinal, naturalistic study that aims to compare the clinical, neuropsychological, neuroimaging, genetic and epigenetic characteristics of child and adolescent offspring of patients diagnosed with schizophrenia or bipolar disorder and of a community control group. This study was conducted in the Child and Adolescent Psychiatry Departments of two hospitals in Spain: the Hospital Clinic in Barcelona and the Hospital Gregorio Marañón in Madrid. The methodology and the clinical and cognitive characteristics of the sample have been described previously in detail (27).

2.1 *Sample*

The individuals at familial high risk were identified through their parents, who were recruited from the adult psychiatry units of both hospitals. The inclusion criteria were (a) age between 6 and 17 years and (b) a parent diagnosed with schizophrenia or bipolar disorder. The exclusion criteria were (a) intellectual disability with an impact on functioning and (b) significant head injury or a current medical or neurological condition. Community control parents were recruited through advertisements posted in primary health care centers and other community locations in the same geographical area as the patients. The only inclusion criterion for the offspring of the community controls was an age between 6 and 17 years, while the exclusion criteria were the same as those for the offspring of schizophrenia or bipolar disorder patients plus a family history of psychotic disorders in first- or second-degree relatives. BASYS included 69 offspring of parents with schizophrenia (SZoff), 143 offspring of parents with bipolar disorder (BDoff) and 155 offspring of community controls (CCoff). Given the focus on epigenetic data in this study, only the 211 individuals who had provided biological samples for DNA methylation analyses and had passed the quality controls (30 SZoff, 82 BDoff and 99 CCoff) were included.

2.3 *Assessments*

2.3.1 *Cognitive assessment*

The intelligence quotient was assessed using the Spanish version of the Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV) (28) and Fifth Edition (WISC-V) (29), which evaluates intellectual abilities in children and adolescents aged between 6 and 16 years. The WISC-IV provides four composite scores: the Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index and the Processing Speed Index. Previous research has shown that the Working Memory Index and Processing Speed Index may be impaired in SZoff (30) and BDoff (31, 32). To avoid the influence of each of these indices on the full-scale IQ, the General Ability Index (GAI), derived from the Verbal Comprehension Index and Perceptual Reasoning Index, was used as an index of cognition (33).

2.3.2 *Clinical assessment*

A trained psychiatrist or psychologist performed a mental health assessment of all the parents using the Spanish version of the Structured Clinical Interview for DSM-IV Disorders (SCID-I) (34, 35). Parents or primary caregivers were also interviewed about their children. Psychopathology was evaluated by child psychiatrists who were blinded to the parental diagnoses using the Spanish version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime version (K-SADS–PL) (36, 37).

Participants were assessed with the Scale of Prodromal Symptoms (SOPS) within the Structured Interview for Prodromal Symptoms (38). The reliability of the SOPS was calculated by the team members who performed the clinical assessments (Kappa statistic for both the SOPS total score and the subscales > 0.8). The SOPS is a 19-item scale that contains four subscales for positive, negative, disorganization and general symptom constructs. Higher scores indicate more severe prodromal psychotic symptoms.

Measures of global functioning capture the severity of psychotic symptoms and the level of occupational and social functioning with the Children's Global Assessment Scale (39). This measurement consists of a scale of 1–100, as evaluated by a clinician. Higher scores indicate better global functioning.

2.3.3 *Assessment of obstetric complications*

Information about obstetric complications (OC) was collected using the Lewis-Murray scale (40). This scale rates 15 OC as absent or definitely present, while 9 of the exposures can also be rated as equivocally present. OC can be grouped into three categories: complications of pregnancy (class A), abnormal fetal growth and development (class B), and difficulties in delivery (class C). All variables were categorized as dichotomous variables (present/absent), considering a positive history of OC when at least one exposure was definitely present.

2.4 *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 I and a MagNA Pure LC 2.0 instrument (Roche Diagnostics GmbH, Mannheim, Germany). Saliva samples were collected using an Oragene DNA Saliva Collection Kit (OG-500, DNA Self-Collection Kit, Genotek, Ottawa, Ontario, Canada), and DNA was extracted according to the manufacturer's instructions. DNA concentration and quality were measured spectrophotometrically using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Epsom, Surrey, UK). DNA methylation β-values were obtained at GenomeScan using the Illumina Infinium MethylationEPIC BeadChip Kit (n = 117) and the Illumina Infinium MethylationEPIC v2.0 Kit (n = 94) (Illumina, San Diego, CA, USA).

2.5 *Methylation data collection*

Raw intensity data (.IDAT) files were generated and parallel bioinformatics analyses were conducted in-house using the Chip Analysis Methylation Pipeline (*ChAMP*) Bioconductor package (41). We processed methylation data separately for each type of methylation platform and biological sample: MethylationEPIC blood (n = 79) and saliva (n = 38), as well as for MethylationEPIC v2.0 blood (n = 61) and saliva (n = 33). In total, four parallel analyses were conducted for each platform and tissue. The raw .IDAT files were used to load the data into the R environment with the *champ.import* function, which also enabled the undertaking of probe quality control 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. 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). The epigenetic measures discussed in the upcoming sections were derived from methylation sites found in all MethylationEPIC platforms and tissues, totaling 709,670 CpGs available for analysis.

2.2 *Methylation profile score calculation*

Seven EWAS were selected for the construction of MPS reflecting stressful prenatal conditions. The constructed MPS included pre-conception maternal body-mass index (BMI) (42), pre-conception maternal overweight/obesity (42), hypertensive disorders of pregnancy (43), pre-eclampsia (43), gestational diabetes, early preterm birth (44) and birth weight (45). For their construction, we selected methylation sites that (a) had reported $p \leq 0.050$ in the EWAS summary statistics and (b) were quantified and passed the quality control in the study sample. The individual MPS were calculated as the sum of all methylation site methylation values, weighted by the estimated effect associated with the environmental exposure:

$$MPS_i = \sum_j^{m_{MPS}} \widehat{\mathrm{b}_j} x \; CpG_{ij}$$

where:

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

The MPS were computed using the package methylscore for R, created by our research group and available on GitHub at the following URL: https://github.com/agonse/methylscore. The MPS were standarized by subtracting the mean and dividing by the standard deviation (SD). Further details about the MPS and the referenece EWAS can be found in **Table S1**.

2.3 *Epigenetic clock calculation*

The *methylclock* R package (46) was used to estimate the intrinsic epigenetic age acceleration (IEAA) for the epigenetic clocks used in the present study: Horvath (47), Hannum (48), Levine (49), PedBE (50) and Wu (51) (**Table S2**). The detailed procedure for IEAA estimation can be found in our previous study (26).

2.4 *Polygenic risk score calculation*

The genotyping data was processed through the Michigan Imputation Server (52), adhering to stringent quality control measures and utilizing reference panels tailored to European populations. GWAS summary results were employed to construct PRS for schizophrenia, bipolar disorder, major depressive disorder, neuroticism, intelligence, educational attainment, and cognitive performance. Detailed methods can be found in our previous study (25).

2.5 *Statistical analysis*

Familial risk group differences in sociodemographic, cognitive, prodromal psychotic symptoms and functioning scales at study entry were calculated by generalized linear mixed-effects models, using family ID as a random effect. The correlation between epigenetic constructs was tested using Pearson's product-moment correlation.

Differences in epigenetic constructs among the familial risk groups were evaluated using generalized linear mixed-effect models. Family ID was included as a random effect, and the analysis was adjusted for biological tissue, methylation array, and sex. When MPS was a fixed effect, age was also included as a covariate.

The associations between the epigenetic constructs and measures of cognition, prodromal psychotic symptoms (including subscales) and functioning were examined using independent linear mixed-effects models for each familial risk group. Family ID was included as a random effect, and the analysis was adjusted for the same covariates as in the previous analysis. To assess the association between epigenetic constructs and OC in the entire sample, generalized linear mixed-effect models were employed, utilizing the same random effects and covariates.

For the analyses including PRS, a genetic principal component analysis (PCA) was performed to control for population stratification (53) by means of the *SNPRelate* package. Associations between PRS and epigenetic constructs were examined using linear mixed-effects models, where family ID was treated as a random effect. The analysis was adjusted for familial risk group, biological tissue, methylation array, sex and the first 10 components of the genetic PCA. Additionally, for MPS, age was included as a covariate.

All the analyses were performed in the RStudio version 4.3.1 (54). The variance explained was defined by the marginal pseudo-R^2 (R^2). The reported R^2 values reflect the variance of the PRS on the outcome variable and were calculated as the difference between the R^2 of the full model (including the epigenetic constructs and the covariates) minus the model excluding the epigenetic constructs. Multiple testing correction was applied in all the analyses by means of the FDR method, and the threshold of significance of the adjusted p value (p.adj) was set at $\alpha < 0.05$.

3. RESULTS

3.1 Descriptive statistics

The sample consisted of 211 children and adolescents, 30 SZoff (14.2%), 82 BDoff (38.9%) and 99 CCoff (46.9%). Table 1 provides information on sociodemographics, cognition, prodromal psychotic symptoms, global functioning and OC as well as a comparison between familial risk groups. Consistent with previous studies in this sample, the SZoff and BDoff participants reported higher prodromal psychotic symptom scores and poorer global functioning as well as a greater proportion of class B OC (abnormal fetal growth and development) (p.adj < 0.05 for all analyses). Additional information on these analyses can be found in **Table S3**.

Table 1
Sociodemographic data, cognitive measures, prodromal psychotic symptom severity, functioning measures, obstetric complications and comparisons among familial risk groups.

Feature	SZoff n = 30 mean(SD) or n(%)	BDoff n = 82 mean(SD) or n(%)	CCoff n = 99 mean(SD) or n(%)	comparison*
Age	10.4(3.2)	12.6(3.2)	12.8(3.3)	
Sex - male	16(53.3%)	37(45.1%)	43(43.4%)	
Cognition	96.7(14.1)	105.3(12.5)	107.3(12.7)	
Total prodromal psychotic symptoms	7.2(9.6)	4.9(7.7)	1.8(2.4)	SZoff > BDoff > CCoff
positive prodromal psychotic symptoms	1.9(3.2)	1.1(2.2)	0.5(0.9)	SZoff > CCoff; BDoff > CCoff
negative prodromal psychotic symptoms	2.0(3.9)	1.3(2.8)	0.4(0.8)	SZoff > CCoff
disorganized prodromal psychotic symptoms	1.6(1.5)	1.2(1.9)	0.4(0.8)	BDoff > CCoff
general prodromal psychotic symptoms	1.6(3.7)	1.3(2.3)	0.5(1.1)	
Global functioning	76.9(12.2)	80.2(10.5)	87.1(7.3)	SZoff < CCoff; BDoff < CCoff
Class A OC present	2(7.1%)	5(6.3%)	4(4.2%)	
Class B OC present	6(21.4%)	9(11.4%)	5(5.1%)	SZoff > CCoff; BDoff > CCoff
Class C OC present	6(21.4%)	14(17.7%)	15(15.5%)	

SZoff: offspring of schizophrenia patients; BDoff: offspring of bipolar disorder patients; CCoff: offspring of community controls; OC: obstetric complications

* p.adj < 0.050

The correlation analyses revealed strong positive associations within MPS, except pre-pregnancy BMI MPS and the other MPS. Similarly, positive associations were observed among all IEAA. Furthermore, pre-pregnancy BMI MPS was correlated with the Hannum and Levine IEAA, while early preterm birth was negatively correlated with the Levine IEAA (Fig. 1).

3.2 Epigenetic profile of the familial high risk groups

In SZoff, MPS reflecting pre-pregnancy overweight/obesity, pre-eclampsia, early preterm birth and birth weight were greater than in CCoff (p.adj < 0.001 for all analyses). The BDoff group had elevated MPS for pre-pregnancy overweight/obesity, hypertensive disorders of pregnancy, gestational diabetes and higher birth weight, compared with the CCoff group (p.adj < 0.001 for all analyses). Regarding the IEAA, SZoff demonstrated a deceleration in the Horvath epigenetic clock compared to CCoff (p.adj < 0.001) and acceleration compared to BDoff (p.adj = 0.005). BDoff showed a deceleration in Hannum epigenetic clock compared to CCoff (p.adj < 0.001) (Table 2).

Table 2
Comparison of MPS and IEAA among familial risk groups. Significant results are marked in bold.

	Epigenetic construct	SZoff vs CCoff		BDoff vs CCoff		SZoff vs BDoff	
		beta	p.adj	beta	p.adj	beta	p.adj
MPS	pre-pregnancy BMI	2.055	0.513	0.347	0.835	-0.078	0.990
	pre-pregnancy overweight/obesity	1.018	**0.000**	8.642	**0.000**	-0.365	0.990
	hypertensive disorders of pregnancy	3.690	0.511	9.565	**0.000**	0.033	0.990
	pre-eclampsia	4.432	**0.000**	0.579	0.835	-0.248	0.990
	gestational diabetes	9.404	0.551	9.526	**0.000**	-0.162	0.990
	early preterm birth	0.064	**0.000**	0.224	0.835	-0.251	0.990
	birth weight	3.778	**0.000**	10.190	**0.000**	-0.360	0.990
epigenetic clock	Horvath IEAA	0.100	**0.000**	0.538	0.922	-2.364	**0.005**
	Hannum IEAA	0.218	0.967	0.469	**0.000**	-0.357	0.982
	Levine IEAA	-0.333	0.967	-0.071	0.922	-0.156	0.982
	PedBE IEAA	0.045	0.967	0.069	0.922	-0.027	0.982
	Wu IEAA	0.322	0.967	0.080	0.922	0.138	0.982

SZoff: offspring of schizophrenia patients; BDoff: offspring of bipolar disorder patients; CCoff: offspring of community controls; MPS: methylation profile score; IEAA: intrinsic epigenetic age acceleration

3.3 Association of epigenetic constructs with cognition, prodromal psychotic symptoms and global functioning

Prodromal psychotic symptoms in the SZoff group were positively associated with pre-pregnancy BMI and overweight/obesity MPS (p.adj = 0.023, p.adj = 0.001; respectively) and with accelerated Horvath (p.adj = 0.007), Hannum (p.adj = 0.007), Levine (p.adj = 0.038), PedBE (p.adj = 0.016) and Wu (p.adj = 0.018) IEAA (Table 3). Conversely, no epigenetic construct showed associations with cognition, prodromal psychotic symptoms or global functioning for the BDoff or CCoff groups (p.adj > 0.050 for all analyses).

Table 3
Stratified analysis of the association between MPS and IEAA with measures of cognition, prodromal psychotic symptoms, and global functioning in familial risk groups. Analyses were stratified for the SZoff, BDoff, and CCoff groups.

SZoff		Epigenetic construct	Cognition			Prodromal psychotic symptoms			Global functioning		
			beta	R^2	p.adj	beta	R^2	p.adj	beta	R^2	p.adj
	MPS	pre-pregnancy BMI	0.090	0.003	0.676	0.863	0.630	**0.023**	-0.456	0.351	0.370
		pre-pregnancy overweight/obesity	0.294	0.014	0.629	10.262	0.403	**0.001**	-0.198	0.084	0.976
		hypertensive disorders of pregnancy	0.584	0.055	0.629	0.154	-0.006	0.984	-0.015	0.068	0.976
		pre-eclampsia	0.424	0.025	0.629	1.630	0.007	0.750	0.021	0.074	0.976
		gestational diabetes	0.462	0.029	0.629	0.033	-0.007	0.984	-0.104	0.078	0.976
		early preterm birth	0.227	0.022	0.629	0.573	0.128	0.078	-0.256	0.042	0.976
		birth weight	0.275	0.010	0.629	9.423	0.127	0.078	-0.052	0.075	0.976
	epigenetic clock	Horvath IEAA	0.004	0.000	0.984	0.543	0.269	**0.007**	-0.156	0.097	0.907
		Hannum IEAA	0.015	0.000	0.984	0.548	0.345	**0.007**	-0.145	0.156	0.907
		Levine IEAA	0.006	0.000	0.984	0.394	0.136	**0.038**	0.017	0.009	0.931
		PedBE IEAA	-0.083	0.006	0.984	0.474	0.207	**0.016**	-0.081	0.066	0.907
		Wu IEAA	-0.036	0.001	0.984	0.452	0.187	**0.018**	-0.068	0.045	0.907
BDoff		**Epigenetic construct**	**Cognition**			**Prodromal psychotic symptoms**			**Global functioning**		
			beta	R^2	p.adj	beta	R^2	p.adj	beta	R^2	p.adj
	MPS	pre-pregnancy BMI	0.075	0.001	0.984	-0.092	-0.008	0.953	-0.166	0.000	0.275
		pre-pregnancy overweight/obesity	-0.027	0.011	0.984	0.018	0.010	0.953	-0.303	0.006	0.275
		hypertensive disorders of pregnancy	-0.081	0.001	0.984	-0.071	0.013	0.953	-0.214	-0.004	0.396
		pre-eclampsia	-0.058	0.010	0.984	0.036	0.009	0.953	-0.357	0.008	0.275
		gestational diabetes	-0.005	0.008	0.984	-0.033	0.009	0.953	-0.302	0.012	0.275
		early preterm birth	-0.064	-0.008	0.984	-0.186	0.004	0.953	0.125	-0.004	0.407
		birth weight	-0.072	0.012	0.984	0.013	0.010	0.953	-0.290	0.006	0.284
	epigenetic clock	Horvath IEAA	-0.023	-0.009	0.897	0.007	-0.002	0.953	0.174	0.122	0.342
		Hannum IEAA	-0.014	-0.009	0.897	-0.022	-0.006	0.953	-0.010	-0.007	0.942
		Levine IEAA	0.029	-0.010	0.897	0.178	0.025	0.733	-0.045	-0.015	0.942
		PedBE IEAA	-0.027	-0.012	0.897	0.104	0.036	0.854	-0.128	0.045	0.386
		Wu IEAA	-0.127	0.002	0.897	0.039	0.000	0.953	-0.007	-0.006	0.942
CCoff		**Epigenetic construct**	**Cognition**			**Prodromal psychotic symptoms**			**Global functioning**		
			beta	R^2	p.adj	beta	R^2	p.adj	beta	R^2	p.adj
	MPS	pre-pregnancy BMI	0.307	0.022	0.247	0.188	0.017	0.335	-0.081	-0.005	0.705
		pre-pregnancy overweight/obesity	0.475	0.012	0.247	0.345	0.017	0.335	-0.331	-0.004	0.401
		hypertensive disorders of pregnancy	0.487	0.048	0.247	0.392	0.019	0.335	-0.389	-0.016	0.401
		pre-eclampsia	0.402	0.020	0.300	0.310	0.010	0.335	-0.634	-0.001	0.401

SZoff: offspring of schizophrenia patients; BDoff: offspring of bipolar disorder patients; CCoff: offspring of community controls; MPS: methylation profile score; BMI: body mass index; IEAA: intrinsic epigenetic age acceleration

	gestational diabetes	0.628	0.053	0.247	0.253	0.009	0.335	-0.338	0.002	0.401
	early preterm birth	0.236	-0.004	0.247	0.177	0.012	0.335	-0.004	-0.003	0.977
	birth weight	0.431	0.015	0.279	0.305	0.011	0.335	-0.472	0.001	0.401
epigenetic clock	Horvath IEAA	-0.004	0.002	0.972	-0.103	0.010	0.406	0.150	-0.016	0.388
	Hannum IEAA	-0.053	-0.009	0.807	-0.107	0.010	0.406	0.036	0.003	0.906
	Levine IEAA	-0.091	-0.020	0.807	-0.138	0.016	0.406	0.159	0.043	0.388
	PedBE IEAA	-0.058	-0.002	0.807	-0.177	0.030	0.406	-0.010	-0.001	0.921
	Wu IEAA	-0.092	0.009	0.807	-0.084	0.006	0.417	0.065	-0.009	0.898

SZoff: offspring of schizophrenia patients; BDoff: offspring of bipolar disorder patients; CCoff: offspring of community controls; MPS: methylation profile score; BMI: body mass index; IEAA: intrinsic epigenetic age acceleration

In examining the prodromal psychotic symptom subscales in the SZoff group, pre-pregnancy BMI MPS exhibited an association with positive prodromal psychotic symptoms (p.adj = 0.004) and pre-pregnancy overweight/obesity MPS exhibited an association with positive and general prodromal psychotic symptoms (p.adj < 0.001; p.adj = 0.008; respectively). No other MPS showed associations with prodromal psychotic symptoms. Accelerated Horvath, Hannum, Levine, PedBE and Wu IEAA were associated with positive prodromal psychotic symptoms (p.adj < 0.002 for all analyses) and with general prodromal psychotic symptoms (p.adj < 0.012 for all analyses) (Table 4).

Table 4
Association of epigenetic constructs with prodromal psychotic symptom subscales in the offspring of schizophrenia patients. Significant results are marked in bold.

	Epigenetic construct	Positive prodromal psychotic symptoms			Negative prodromal psychotic symptoms			Disorganized prodromal psychotic symptoms			General prodromal psychotic symptoms		
		beta	R^2	p.adj	beta	R^2	p.adj	beta	R^2	p.adj	beta	R^2	p.adj
MPS	pre-pregnancy BMI	1.082	0.748	**0.004**	0.308	0.056	0.524	0.723	0.189	0.086	0.552	0.155	0.183
	pre-pregnancy overweight/obesity	11.049	0.464	**0.000**	4.468	0.017	0.524	8.464	0.442	0.064	9.621	0.337	**0.008**
	hypertensive disorders of pregnancy	0.307	-0.003	0.820	-0.907	0.037	0.524	-0.313	-0.030	0.954	0.528	0.002	0.701
	pre-eclampsia	3.228	0.047	0.326	-2.151	0.029	0.524	-0.163	0.000	0.954	2.933	0.039	0.406
	gestational diabetes	-1.253	0.016	0.527	1.111	-0.075	0.524	0.872	0.163	0.858	-0.708	0.003	0.701
	early preterm birth	0.447	0.074	0.245	0.349	0.018	0.524	0.279	0.173	0.790	0.665	0.172	0.060
	birth weight	9.712	0.134	0.110	2.474	0.004	0.618	4.074	0.158	0.790	11.440	0.189	0.060
epigenetic clock	Horvath IEAA	0.677	0.427	**0.000**	0.057	0.005	0.963	0.409	0.430	0.103	0.626	0.359	**0.002**
	Hannum IEAA	0.696	0.471	**0.000**	0.210	0.051	0.963	0.296	0.335	0.176	0.644	0.464	**0.002**
	Levine IEAA	0.580	0.310	**0.002**	-0.065	0.002	0.963	0.256	0.328	0.218	0.488	0.213	**0.012**
	PedBE IEAA	0.604	0.344	**0.001**	0.028	-0.010	0.963	0.452	0.698	0.103	0.542	0.271	**0.005**
	Wu IEAA	0.609	0.349	**0.001**	0.009	-0.004	0.963	0.320	0.582	0.176	0.551	0.280	**0.005**

MPS: methylation profile score; BMI: body mass index; IEAA: intrinsic epigenetic age acceleration

We conducted a similar analysis within the SZoff group, taking into account whether the affected parent was the mother. We observed consistent associations between MPS and the IEAA, mirroring those identified in the previous analysis. Further details are provided in **Table S4**.

3.4 Epigenetic constructs association with obstetric complications and polygenic risk scores

Pre-pregnancy BMI MPS showed a positive association with class B OC (p.adj < 0.001) and pre-eclampsia MPS demonstrated a positive association with both class B and class C OC (p.adj < 0.001 for both analyses) (**Table S5**).

No associations were detected between any of MPS or the IEAA and the PRS indicative of susceptibility to psychiatric disorders, neuroticism or cognition in the entire sample (p.adj > 0.050 for all analyses) (**Table S6**).

4. DISCUSSION

This study explored various aspects of genome-wide methylation patterns in a cohort enriched with offspring of schizophrenia and bipolar disorder patients. We utilized methylation data to create two epigenetic constructs – methylation profile scores and epigenetic clocks. Our aim was to examine these constructs, both as a consequence of exposure to early-life stress and as potential modulators of sub-clinical features in children and asolescents. Indeed, these epigenetic constructs provided evidence of a greater impact of stressful intrauterine events and a delay in biological aging in the offspring of patients with schizophrenia and bipolar disorder. Furthermore, these changes in methylation patterns exhibited specific associations with the manifestation of prodromal psychotic symptoms, although solely in the schizophrenia offspring group. Collectively, the findings of this study contribute to a deeper understanding of epigenetic methylation as a potential biological process linking the impact of environmental factors to the emergence of subthreshold clinical manifestations of mental health disorders.

The groups at familial high risk reported greater epigenetic scores indicative of maternal overweight/obesity, hypertensive disorders of pregnancy, pre-eclampsia, gestational diabetes, early preterm birth and higher birth weight. These altered methylation patterns align with large epidemiological studies that have demonstrated an elevated frequency of perinatal complications in mothers diagnosed with schizophrenia, schizoaffective and bipolar disorders (55–58). Within this cohort, 73.3% of SZoff individuals were born to affected women, and despite adjusting for this confounding factor, we still observed associations of MPS and IEAA with prodromal psychotic symptoms. However, we found no associations between genetic susceptibility to several psychiatric disorders and MPS reflecting intrauterine stress. Research indicates that women with mental disorders are more likely to experience greater incidence and severity of perinatal events due to unhealthy lifestyles and inadequate monitoring of pregnancy (59), rather than due to biological traits related to the disorder itself. In contrast, Ursini and colleagues proposed that genetic variants associated with schizophrenia risk may influence early neurodevelopmental processes through the placental response to stress, suggesting a shared genetic susceptibility for schizophrenia and intrauterine complications (60). These findings suggest that adverse events during pregnancy may be more prevalent in families with mental disorders, independent of the genetic background or the polygenic basis of the disorder. Noticeably, individuals at familial high risk exhibited epigenetic patterns associated with increased birth weight. Although this finding may seem contradictory, given that low birth weight is interpreted as a proxy for unspecific complications during pregnancy that restrict fetal growth (4), we observed a strong positive correlation between MPS in the prenatal environment and birth weight in our sample. The epigenetic patterns in individuals at high familial risk suggest that intrauterine sustained exposure to higher glucose levels, such as in cases of maternal obesity and gestational diabetes, may not only contribute to preterm deliveries but also potentially result in higher birth weight (61–63). Notably, gestational diabetes stands as one of the risk factors with higher odds ratios for schizophrenia (3, 4).

Epigenetic age acceleration, estimated through epigenetic clocks, provides insights into the biological aging pace of individuals exposed to various intrauterine and early-life environmental factors. In the current study, encompassing a larger sample size that included individuals from the previous study, we replicated previous findings indicating deceleration of the Horvath and Hannum epigenetic clocks among individuals at familial high risk (26). Our findings further evidence the complexity and dynamism of aging mechanisms, suggesting not only that each epigenetic clock may capture different aspects of aging, but also their sensitivity to external inputs (6, 64, 65). Notwistanding, the deaccelerations in Horvath and Hannum clocks challenge the accelerated aging hypothesis of schizophrenia, which is often inferred from the higher prevalence of age-related conditions in younger schizophrenia patients (10, 11). A recent review proposed that prenatal events may prompt abnormal fetal development, intricately associated with a slower pace of biological aging in epigenetic clocks estimating chronological age (e.g., Horvath) and a faster pace in those capturing mortality-associated phenotypes (e.g., Levine), ultimately linked to schizophrenia (64). Age acceleration may vary throughout the lifespan (66–68), adding complexity to the understanding of epigenetic aging dynamics, its interplay with early-life stressors and its role in the manifestation of mortality-associated phenotypes (69) and clinical symptoms later in life (70).

Analyses examining the associations between epigenetic constructs and clinical outcomes revealed that pre-pregnancy BMI and overweight/obesity MPS, as well as accelerated epigenetic aging were linked to the manifestation of positive and general prodromal psychotic symptoms exclusively in SZoff individuals. These findings suggest a potential connection between specific prenatal conditions and later-life prodromal psychotic features, mediated by epigenetic alterations and consistent with the developmental hypothesis of schizophrenia (71). Notably, this association appears unique to individuals raised in a family with a parent diagnosed with schizophrenia, emphasizing the interplay of the pre- and postnatal environment in triggering prodromal psychotic symptoms within this specific group. Previous studies have found associations between MPS for C-reactive protein and tobacco smoking with cognitive performence (20, 21, 72). Two studies found increased MPS for schizophrenia in schizophrenia patients (73) and but not with age at onset, clozapine use, cognitive status or global functioning (74). Regarding epigenetic age acceleration, it is intriguing to note that SZoff individuals exhibited deaceleration compared to controls, yet acceleration was associated with more severe prodromal psychotic symptoms. Studies on this subject are scarce, and their results are conflicting, reporting epigenetic age acceleration in schizophrenia patients with more severe prodromal psychotic symptoms or no acceleration in in psychiatric and healthy populations (20, 64, 67, 75–77).

The findings of this study should be interpreted within the scope of its limitations. First, the sample size, particularly when conducting independent analyses for the three study groups, may constrain the statistical power of association analyses (78). Additionally, epigenetic methylation is a dynamic process modulated by factors such as time, environmental conditions and sample tissue (16, 79). Therefore, the range of ages in our sample and the two tissues used to obtain methylation data may have contributed to heterogeneity in the epigenetic constructs. Finally, this study focused solely on prodromal psychotic symptoms and did not encompass prodromal symptoms of other mental conditions, such as affective disorders, thereby limiting its scope. Despite these limitations, we included a study sample of individuals at familial high risk in a critical stage for the development of mental

disorders, complemented by a comprehensive battery of clinical assessments. The simultaneous use of these two epigenetic constructs is highly innovative, representing a promising approach to capturing long-lasting epigenetic patterns associated with severe mental disorders. 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 (80). In this study, we implemented a thresholding method for CpG selection, building upon previous studies (19, 81, 82) and publicly shared the code for replication and refinement, in https://github.com/agonse/methylscore.

Genetic and environmental factors critically influence the onset and prognosis of severe mental disorders; however, neither is sufficient. Building upon previous genetic and epigenetic findings in this sample (25, 26), our study suggested that changes of specific methylation patterns may pose as key biological mechanisms linking external stress with the clinical manifestation of these disorders. Epigenetic constructs offer a promising solution to certain limitations of retrospective assessments, such as the Lewis-Murray scale for obstetric complications (2, 83), by quantifying the long-lasting biological repercussions of environmental inputs in peripheral tissues. If validated, methylation constructs could yield novel insights into the etiopathological mechanisms underlying the manifestation of severe mental disorders. Integrating genetic and epigenetic measures could provide a more comprehensive understanding of the dynamic interplay between the genetic architecture of disorders and environmental exposures (15). Ultimately, the integration of epigenetic data into prediction models in personalized psychiatry could enhance the detection of individuals at high risk, thereby facilitating the formulation of preventive policies.

Declarations

Ethics approval and consent to participate: All procedures contributing to this work complied 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. The study was approved by the Ethical Review Board of each participating hospital. Written informed consent was obtained from one of the parents or legal guardians, with the other parent been informed, together with written assent from the participant if 12 years of age or older.

Consent for publication: not applicable

Availability of data and materials: All data supporting the findings of this study are available within the paper and its Supplementary Information. EWAS data used for the calculation of MPS are publicly available and can be downloaded from https://www.ewascatalog.org/.

Competing interests: The authors declare no competing interests.

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Authors' contributions: AGS, SM, JCF designed the study. AGS, IMS and LJ analyzed the data. AGS, IMS, EdlS, GS, IB, DMM, PG, NR, AMP, LJ, CT, CGR, SM and JCF interpreted the data. AGS and IMS wrote the manuscript. AGS and LJ prepared figures and tables. IMS, EdlS, GS, IB, MDP, SP, DMM and contributed to the datasets used in the study. All authors reviewed and approved the manuscript prior to submission.

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Figures

Figure 1

Correlations among various epigenetic constructs. Significant correlations are marked with an asterisk.

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5. Discussion

5.1 Main results and general discussion

Understanding the biological mechanisms underlying the onset and progression of psychotic disorders is crucial for developing effective prevention tools, identifying potential drug targets and personalizing early treatment strategies. This thesis focused on analyzing biological data from patients experiencing first episode of psychosis (FEP), individuals at familial high risk (FHR) and community controls. Through the analysis of genetic variability and epigenetic patterns, two key constructs were developed: polygenic risk scores (PRS) and epigenetic scores. The primary aim of this doctoral thesis was to uncover distinct genetic and epigenetic signatures associated with psychosis and to assess their impact on the subclinical manifestation and early clinical progression. By doing so, the research sought to contribute valuable insights into the biological underpinnings of psychosis, which could potentially guide future therapeutic approaches.

Across four studies, the additive risk of common genetic variants was explored using PRS [Articles 1,2,3,4]. Collectively, these findings suggested that the genetic architecture of psychosis involves distinct genetic liabilities. Specifically, genetic susceptibility to schizophrenia was higher in individuals with psychosis and their offspring compared to community control groups. However, these genetic factors did not appear to influence the clinical severity and progression. In contrast, genetic factors related to depression, cognition, cannabis use and neuroticism exhibited a stronger association with clinical outcomes [Articles 1,3,4]. The use of explanatory models based on mediation analyses offered a deeper understanding of how these PRS are linked to clinical measures, both in individuals at FHR and in FEP patients [Articles 2,4].

Two studies focused on the epigenetic profiles of individuals at FHR by estimating the epigenetic imprint that reflect the pace of epigenetic aging and exposure to intrauterine stress [Articles 5,6]. First, the findings revealed decelerated epige-

netic aging of individuals at FHR, indicating a discrepancy between epigenetic and chronological aging [Articles 5,6]. Second, the analysis of methylation profile scores suggested increased intrauterine stress in the FHR group. Notably, in the offspring of schizophrenia patients, both epigenetic clocks and methylation profile scores were associated with the manifestation of prodromal psychotic symptoms [Article 6].

The conclusions derived from the studies included in this doctoral thesis are discussed in detail in the subsequent sections, highlighting the implications for understanding the genetic and epigenetic contributions to psychosis and their potential impact on clinical practice.

5.2 Genetic architecture

The studies of the genetic architecture of psychotic disorders combined multiple PRS, representing the genetic underpinnings of schizophrenia, bipolar disorder and major depressive disorder as well as cognition, cannabis use and neuroticism. The rationale behind simultaneously analyzing PRS from different domains is grounded in consistent evidence of the genetic overlap among mental disorders (118–120) as well as their genetic overlap with cognitive performance (121), cannabis use (122,123) and neuroticism (54,124). This approach aimed to describe genetic factors associated not only with the psychotic disorders but also with their clinical manifestation in early stages.

The following subsections detail the results of distinct genetic architectures explored in this thesis: The following subsections detail the results of distinct genetic architectures explored in this thesis:

- Psychopathological genetic architecture: Based on the results of the PRS for schizophrenia, bipolar disorder, and major depressive disorder (subsection 5.2.1)

- Cognitive genetic architecture: Based on the results of the PRS for intelligence, cognitive performance, and educational attainment (subsection 5.2.2)
- Other genetic architectures: Based on the results of the PRS for lifetime cannabis use, cannabis use disorder, and neuroticism (subsection 5.2.3)

5.2.1 Psychopathological genetic architecture

Numerous genetic studies describe an association of PRS for schizophrenia with schizophrenia and the broader spectrum of psychotic disorders, including FEP (35, 38,41–45,125,126). Increased genetic susceptibility has also been observed in individuals at clinical and familial risk for psychosis (34,127,128). The clinical overlap among psychiatric disorders suggests a shared genetic background that influences the overlapping features. In FEP, clinical manifestations often include a combination of psychotic and affective symptoms (129).

Our findings in the PEPs cohort [Article 1] align with with previous genetic studies, showing more disadvantageous PRS for schizophrenia and bipolar disorder in individuals experiencing FEP (130). In the BASYS cohort, offspring of schizophrenia patients showed increased PRS for schizophrenia, while offspring of bipolar disorder patients showed no differences in the PRS for bipolar disorder or any other PRS compared to controls [Article 4].

In the PEPs cohort, we observed stronger correlations between PRS for schizophrenia and bipolar disorder, as well as between PRS for schizophrenia and major depressive disorder, compared to the BASYS cohort. This highlights the idea that individuals experiencing FEP may also carry genetic factors associated with mood disorders, which are not as pronounced in FHR groups, where not all individuals transition to clinical psychosis. The smaller sample size of the BASYS cohort could contribute to lower statistical power to detect small effects, and methodological differences in PRS estimation between the cohorts (PRSice vs PRS-CS methods) could

also explain some of the observed discrepancies. Addittionally, the use of more recent reference genome-wide association study (GWAS) data for some PRS could partially account for the discrepancies in findings.

Contrary to our hypothesis and despite evidence from heterogeneous studies suggesting a role for psychopathological genetic factors in psychiatric and high-risk populations (30,31,33,36,39,51,52,54,55,57–59,131–134), the PRS for schizophrenia and bipolar disorder did not significantly influence subclinical and clinical outcomes in either the PEPs or BASYS cohorts [Articles 1,4]. An exception was found for the PRS for schizophrenia, which was associated with the early evolution of leisure time activities subscale in the Functioning Assessment Short Test (FAST) scale among FEP patients. It is noteworthy that these results, specifically in this domain, could be influenced with by negative symptoms such as abulia or anhedonia. No associations were found for the PRS for schizophrenia or bipolar disorder with cognitive, symptom, or other functioning features in either the PEPs or BASYS cohorts.

The PRS for major depressive disorder exhibited a distinct pattern, correlating with symptom severity and cognition rather than being elevated in FEP and FHR groups. In the PEPs cohort, it was associated with the overall cognitive function and executive function, while in the BASYS cohort, it was linked with prodromal psychotic symptoms and psychosocial functioning. The broad association of the PRS for major depressive disorder with various outcomes suggests that the genetic factors contributing to depression may influence a relatively unspecific psychopathological profile (54,56). This is consistent with clinical studies indicating that depression plays a significant role in both the onset and the distress associated with psychotic symptoms and is often used as a predictor for transitioning to psychosis (135,136).

5.2.2 Cognitive genetic architecture

Three cognitive PRS were constructed using GWAS data published from two large-scale studies, each with sample sizes ranging from approximately 250,000 to 1,100,000

individuals. Although these PRS were derived from related cognitive phenotypes, they each reflect distinct aspects of cognitive functioning. The GWAS for cognitive performance derived from cognitive scales, while the GWAS for educational attainment was based on years of schooling (137). Both PRS derived from this GWAS were based on the same sample and were included in studies with the PEPs and BASYS cohorts [Articles 1,2,4]. Additionally, a PRS for intelligence (138), reflecting fluid cognitive functioning, was included in the studies using the BASYS cohort [Article 4].

In the PEPs cohort, FEP individuals exhibited disadvantageous PRS for cognitive performance compared to controls, although no differences were found for the PRS for educational attainment [Article 1]. Previous research has shown that higher PRS for educational attainment and general cognitive ability are typically negatively associated with schizophrenia (52,60,126), suggesting that individuals with schizophrenia might have a lower genetic predisposition for these cognitive traits. However, in a FEP sample, the PRS for intelligence constructed from the same reference GWAS (138) did not differ from the control group (38). In the BASYS cohort, no differences were observed in cognitive PRS among the FHR groups [Article 4]. This finding is notable as there is limited research on cognitive PRS in individuals at FHR for schizophrenia and bipolar disorder, making this study one of the first to explore this relationship. Evidence of disadvantageous PRS for different cognitive constructs in FEP and schizophrenia patients is limited and appears to be more prominent in individuals with chronic schizophrenia. The diagnosis instability in FEP and FHR groups may mask any potential cognitive genetic factors specifically associated with schizophrenia.

Beyond diagnostic implications, cognitive PRS were also linked to cognitive performance in both the PEPs and BASYS cohorts. Detailed analysis in the PEPs cohort revealed that PRS for cognitive performance and educational attainment were particularly associated with the progression of working memory performance.

This finding is consistent with previous studies in schizophrenia patients and general young and adult population samples (40,61,126,139), where cognitive PRS have been shown to influence cognitive abilities such as working memory. Moreover, the impact of cognitive PRS extended beyond cognitive measures, influencing clinical outcomes such as the progression of prodromal and clinical psychotic symptoms, global disease severity and functioning, although the latter was only nominally significant in the BASYS cohort. These findings echo previous studies that have linked cognitive PRS with negative symptoms and subclinical psychopathology (53,54).

In the BASYS cohort, mediation models indicated that the effect of PRS for intelligence on global disease ratings was fully mediated by its impact on cognitive performance. This finding aligns with previous studies that have described cognition as a mediator between genetic susceptibility and psychotic-like experiences as well as brain morphology (61,139). Analyses using cognitive PRS further support the concept of a genetic architecture of psychosis built upon partially independent genetic factors. Various cognitive processes influenced by genetic factors likely contribute significantly to modulating clinical manifestation in terms of symptom severity and overall functioning. Thus, our findings provide genetic evidence supporting clinical studies linking impaired cognition with poor prognosis in FEP (140).

Cognitive reserve—a concept describing the brain's ability to cope with pathology through pre-existing cognitive processes and compensatory mechanisms (141–143)—emerged as a promising framework for understanding the role of cognition in psychosis. Higher cognitive reserve has been linked to better clinical outcomes, including less severe illness, later onset of symptoms and improved prognosis (144–146). Additionally, other studies have linked lower cognitive reserve with FHR and with poorer clinical and cognitive outcomes during relapse (147,148).

Given the correlation of cognitive PRS with cognitive reserve and functioning observed in the FEP group [Article 1], and considering the potential role of cognitive reserve as a mediator between cognition and clinical and functioning outcomes

(149,150), we proposed more complex explanatory models based on mediation analysis [Article 2]. A serial model showed that the association between PRS for educational attainment and functioning was mediated by cognitive reserve, which subsequently influenced negative symptoms and ultimately functioning. These findings suggested that cognitive reserve may serve as an endophenotype strongly influenced by genetics and closely associated with negative symptoms.

While clinical interventions aimed at enhancing cognitive reserve have shown some benefits, their long-term effectiveness remains uncertain (151,152). Nonetheless, these findings underscore the importance of considering cognitive reserve in the development of personalized treatment strategies for psychosis.

5.2.3 Other genetic architectures

Psychosis is often accompanied by various epiphenomena—features that, while not directly indicative of psychotic disorders, can serve as predictors of poor prognosis. Unlike core psychotic symptoms or cognitive decline, these traits are not exclusive to psychotic disorders but may share a common genetic substrate. In the PEPs cohort [Article 3], two PRS related to cannabis use were estimated : one for cannabis initiation, representing the genetic predisposition for lifetime cannabis use and another for cannabis use disorder, which reflects a genetic tendency toward substance dependence and abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (8). In the BASYS cohort, a PRS for neuroticism—a personality trait characterized by emotional instability and a predisposition toward anxiety and stress—was studied alongside other PRS related to psychiatric disorders and cognitive traits.

The analysis in the PEPs cohort revealed that genetic predisposition for cannabis use is intricately linked with the early progression of psychosis, albeit in distinct ways for each PRS. The PRS for cannabis initiation did not show an association with current cannabis use or frequency of consumption. However, it was associated with

the early progression of negative and general psychotic symptoms. Interestingly, there was no association with positive psychotic symptoms, suggesting that the genetic factors captured by this PRS might primarily affect unspecific symptoms such as affective or depressive states. This finding is significant, as it implies that the genetic predisposition for cannabis initiation assessed in the general population may influence mood-related symptoms, which could, in turn, contribute to the initiation of cannabis use, especially in the context of environmental risk factors.

The PRS for cannabis use disorder showed a more straightforward relationship with cannabis consumption patterns. Individuals with higher scores on this PRS were more likely to be cannabis users and reported higher levels of use at study entry, aligning with previous research (153,154). However, despite these associations, there were no significant links were found between the PRS for cannabis use disorder and changes in cannabis use over the 12-month period. This suggests that despite a genetic predisposition, cessation of cannabis use may still be achievable, potentially through effective intervention strategies. Medical counseling interventions are typically provided to FEP individuals who use cannabis, although current strategies are often considered insufficient (89). These findings underscore the critical importance of monitoring and carefully addressing cannabis use in individuals at risk of FEP, particularly since initiation frequently occurs during sensitive periods of neurodevelopment (155,156). Thus, prevention efforts aimed at educating and intervening early could potentially mitigate the risk associated with cannabis use during these vulnerable stages.

In the BASYS cohort [Article 4], the inclusion of a PRS for neuroticism was based on evidence linking this personality trait to psychiatric disorders, including schizophrenia and to various measures of of subjective well-being, anxiety, depression, mania, irritability and cognition (157–159). Studies involving young individuals, high risk groups and psychiatric populations underscore the significance of the genetic factors influencing personality traits as relevant endophenotypes with

predictive implications for quality of life (124,160).

Interestingly, the FHR groups in the BASYS cohort did not exhibit elevated PRS for neuroticism, suggesting that the genetic predisposition for this personality trait may not be inherited by the offspring of individuals with schizophrenia or bipolar disorder. However, neuroticism PRS was associated with prodromal psychotic symptoms, global disease severity and overall functioning. This finding is consistent with studies involving young individuals and psychiatric populations, where genetic factors related to neuroticism have been shown to influence quality of life and clinical outcomes (54,58,161,162).

Mediation models provided further insights, revealing that the effect of neuroticism PRS on global disease ratings and functioning was fully mediated by its impact on psychotic symptoms. This suggests that the genetic basis of neuroticism may primarily manifest through its influence on psychotic symptoms, rather than directly affecting functioning or overall disease severity. These results underscore the importance of considering personality traits like neuroticism in the broader genetic architecture of psychosis, as they may play a significant role in shaping the clinical trajectory and outcomes of FHR individuals.

Overall, these findings contribute to a more nuanced understanding of how genetic predispositions for traits like cannabis use and neuroticism intersect with the early development and progression of psychosis. They highlight the complexity of the genetic architecture underlying psychosis and suggest that addressing these epiphenomena through early interventions could potentially improve clinical outcomes for individuals at risk.

5.3 Epigenetic imprint of environmental factors

In the BASYS cohort, data from CpG methylation were used to create epigenetic scores, which are essential for examining how environmental factors shape

the epigenome and contribute to health outcomes (111,163). Various epigenetic clocks, which rely on specific CpG sites that exhibit time-dependent methylation patterns, were employed in this analysis. These include clocks such as Horvath, Hannum, PedBE and Wu epigenetic clocks. Additionally, other clocks like Levine and GrimAge focus on CpGs associated with age-related mortality and morbidity phenotypes, as well as telomere length. Methylation profile scores (MPS), which are particularly useful for identifying epigenetic imprints linked to external stressors and health conditions (95), were also utilized. These MPS often remain stable over time (164,165), thus defining a persistent epigenetic profile that can provide insights into health outcomes.

This section is divided into two subsections, each addressing a specific aspect of the epigenetic profile:

- Epigenetic age acceleration: based on measuring epigenetic age through epigenetic clocks (subsection 5.3.1)
- Cognitive genetic architecture: Based on the results of the PRS for intelligence, cognitive performance, and educational attainment (subsection 5.2.2)
- Epigenetic marks of intrauterine stress: based MPS reflecting prenatal conditions (subsection 5.3.2).

5.3.1 Epigenetic age acceleration

The potential link between schizophrenia and accelerated aging has been suggested by epidemiological studies that highlight the increased prevalence of age-related comorbidities among individuals with schizophrenia (166–168). However, the use of epigenetic clocks to measure biological age offers a more nuanced understanding of this relationship. A recent meta-analysis concluded that epigenetic age alterations in schizophrenia vary significantly depending on the specific epigenetic clock and

other contributing factors (100). Young adults with schizophrenia exhibited decelerated epigenetic aging according to the Horvath clock, whereas older adults and women showed accelerated aging with the Levine clock. Additionally, in a recent study including FEP individuals, epigenetic age acceleration was observed using the DunedinPACE method (169) in four out of five independent detests, while other clocks (Horvath, Hannum, Levine, GrimAge) did not show robust associations (101).

Our studies are among the first to assess epigenetic aging in individuals at FHR for psychotic disorders. We observed epigenetic age deceleration in FHR individuals using the Horvath, Hannum and PedBE clocks, with no aging alterations detected for the Levine, Wu or telomere length clocks [Article 5]. Specifically, the Horvath clock indicated decelerated epigenetic aging in the offspring of schizophrenia and bipolar disorder patients, while the Hannum clock showed similar deceleration exclusively in the offspring of bipolar disorder patients [Article 6]. These findings underscore the complexity of aging as assessed through epigenetic data, where not all clocks uniformly indicate aging alterations in FHR groups. Aging is a multifaceted and dynamic process encompassing numerous mechanisms and its progression is not consistently linear across the lifespan due to external factors (99,102,104,170). Therefore, cross-sectional analysis of age acceleration may not comprehensively capture the trajectory of aging, complicating the interpretation of results. Despite these challenges, there is growing evidence supporting alterations in aging processes among schizophrenia patients, even from the early stages of the disorder (100–104).

Early life stressors are known to significantly disrupt epigenetic aging (130, 170–174), with such disruptions potentially originating as early as early prenatal stages (175). It has been hypothesized that alterations in epigenetic aging are linked to the manifestation of subclinical features in young individuals, particularly those at high risk for psychosis (176). Consistent with this hypothesis, our findings indicate associations between all the epigenetic clocks analyzed (Horvath, Hannum, Levine, PedBE, Wu) and positive and general prodromal psychotic symptoms. Notably,

these associations were observed only in the offspring of schizophrenia patients, but not for the offspring of bipolar disorder patients or community controls.

Interestingly, while the offspring of schizophrenia patients exhibited slower aging overall, those with accelerated epigenetic aging within this group also showed more pronounced psychotic symptoms. Studies using epigenetic clocks to analyze clinical severity have shown mixed results in both psychiatric and healthy populations, indicating either positive or null associations of epigenetic aging with psychotic symptoms and cognition (104,105,107,177), as well as positive or negative associations with internalizing and externalizing behavioral problems (108,178).

These inconsistent results underscore the intricate interplay between epigenetic changes driven by the environment and the development of clinical features later in life. A detailed analysis of the roles of different epigenetic clocks—whether they are based on chronological age or age-related phenotypes—is essential for advancing our understanding of this interplay (99). Moving beyond simplistic assumptions, epigenetic clocks offer the potential to provide deeper insights into how an individual's psychosocial context influences their health outcomes (179). When combined with demographic factors, these clocks could also inform preventive strategies aimed at mitigating the risks associated with altered aging processes (163,180).

5.3.2 Epigenetic marks of prenatal stress

In our study, we leveraged methylation data to generate MPS that capture epigenetic alterations associated with seven prenatal conditions: pre-pregnancy maternal body mass index, pre-pregnancy maternal overweight/obesity, hypertensive disorders of pregnancy, pre-eclampsia, gestational diabetes, early preterm birth and birth weight. These MPS reflect epigenetic changes linked to obstetric complications or intrauterine stressors affecting fetal growth and gestational duration (181–183). Our selection of was guided by the hypothesis that methylation patterns established during early neurodevelopment are be associated with clinical phenotypes manifesting

later in life. Although our statistical models did not prove causality, the considerable time gap between intrauterine stress and the eventual emergence of symptoms strongly suggests a plausible causal relationship.

To our knowledge, this was the first study [Article 6] to characterize the epigenetic profiles related to prenatal stress of individuals at FHR for schizophrenia and bipolar disorder. We found that the offspring of patients with schizophrenia and bipolar disorder showed elevated MPS for maternal pre-pregnancy overweight/obesity, hypertensive disorders of pregnancy, pre-eclampsia, early preterm birth and birth weight. These findings corroborate epidemiological studies linking obstetric complications with increased risk of schizophrenia, schizoaffective disorder and bipolar disorder in pregnant patients (184–186).

Obstetric complications are well-established risk factors for psychosis, yet the underlying factors contributing to their higher prevalence in psychiatric populations are still under debate. One theory, proposed by Ursini et al. (2018), suggests that the genetic liability for schizophrenia might also predispose individuals to experience obstetric complications (187). However, another study by Vassos et al. (2022) concluded that the co-occurrence of schizophrenia and obstetric complications was not fully explained by the PRS for schizophrenia (188). In the BASYS cohort, offspring of individuals with schizophrenia showed elevated PRS for schizophrenia as well as MPS for intrauterine stress, but these scores did not show a correlation. Molecular studies indicate that common genetic variants have a modest influence on DNA methylation, with their effects typically being independent and additive to those of methylation (189–191). These findings align with of Vassos et al. (2022) and underscore the significant role of sociodemographic determinants—mediated by epigenetic changes—in the occurrence and severity of obstetric complications (192).

Similar to the analyses involving epigenetic clocks, two MPS were linked to prodromal psychotic symptoms in the offspring of schizophrenia patients. Specifically, individuals with higher MPS related to maternal pre-pregnancy body mass

index and overweight/obesity displayed more severe positive and general psychotic symptoms. Studies investigating the clinical implications of MPS are limited and predominantly focus on the epigenetic patterns associated with factors such as smoking or inflammation and their effects on cognition (107,193,194). A recent study in a schizophrenia cohort (110) linked MPS for schizophrenia and treatment-resistant schizophrenia with clozapine treatment, though it did not find associations with age at onset, cognitive performance or overall functioning.

5.4 Translational applicability: limitations and future perspectives

5.4.1 General limitations

Several limitations must be acknowledged in the studies conducted for this doctoral thesis. The limited sample size in the PEPs and BASYS cohorts may reduce the statistical power to detect subtle effects, especially when stratified analyses are conducted across different FHR groups. This limitation also extends to the availability of specific scales for assessing clinical features, such as negative symptomatology and cognitive reserve. Another significant limitation is the relatively short follow-up period. A 2-year follow-up is insufficient to capture long-term outcomes, including the progression to clinical or chronic stages of psychotic disorders or the full impact of early interventions. The homogeneity of the sample, predominantly consisting of individuals of European ancestry, further restricts the generalizability of the findings. The genetic architecture and epigenetic modifications observed may not fully apply to populations of different ethnic backgrounds, limiting the broader applicability of the results. Additionally, the young age of participants in the BASYS cohort constrains the ability to categorize subjects based on their eventual conversion to schizophrenia or bipolar disorder. Epigenetic methylation, which is a central

focus of these studies, is inherently dynamic and influenced by a variety of temporal, environmental and tissue-specific factors. The heterogeneity of biological samples used for methylation analysis adds complexity to the interpretation of the data.

Despite these limitations, the cohorts employed in this thesis are among the largest and most thoroughly characterized FEP and FHR samples in Spain. The naturalistic design of the studies ensures that the findings are representative of both general and psychiatric populations, enhancing their relevance for clinical practice. The PRS were calculated using data from the largest international GWAS, providing a robust foundation for capturing genetic susceptibility linked to the phenotypes under investigation. Similarly, the epigenetic clocks employed in the analysis were established using advanced methodologies and data from the most extensive EWAS databases available. Rigorous quality control measures were applied to both genetic and epigenetic data, including stringent significance thresholds for multiple testing. These measures help to mitigate methodological biases and statistical inaccuracies, thereby strengthening the reliability and validity of the results presented in this thesis.

5.4.2 Methodological considerations for genetic scores

The shift from candidate gene analysis to GWAS has marked a significant advancement in understanding genetic susceptibility to complex traits, including psychotic disorders, allowing for the aggregation of risk from millions of loci into a single score (65). However, this approach inherently overlooks non-additive effects, such as gene-gene (epistatic) and gene-environment interactions (GxE). These interactions may play a crucial role in the development and progression of psychotic disorders, yet they are not accounted for in PRS calculations. This oversimplification might partially explain the "missing heritability" problem, where the heritability of psychotic disorders estimated from twin studies is substantially higher than the variance explained by PRS alone (195).

In this thesis, we employed statistical models to validate the association of PRS with psychosis and multiple clinical features across two extensively phenotyped cohorts. By utilizing multiple PRS, which were either highly or moderately correlated, our studies aimed to delineate specific and nonspecific genetic factors contributing to the heterogeneous clinical presentation and early progression of psychotic disorders. This approach was particularly valuable in analyzing subclinical and early clinical stages, where identifying genetic influences could provide critical insights into the disorder's trajectory and severity.

Moreover, the genetic landscape is continually evolving as genetic consortia release new and more powerful GWAS. This ongoing development enables the recalibration of PRS, enhancing their predictive power and relevance. For instance, in the studies involving the PEPs [Article 1] and BASYS cohorts [Articles 4,6], the PRS for bipolar disorder was based on different GWAS, reflecting the continuous improvement and refinement of genetic risk assessment tools. This highlights the importance of staying updated with the latest GWAS and methodological advancements to ensure that the findings remain reliable and applicable to contemporary clinical settings.

5.4.3 Methodological considerations for epigenetic scores

Epigenetic scores, much like PRS, present unique methodological challenges that must be carefully addressed. One of the primary issues with epigenetic data is its susceptibility to technical variability, such as batch effects and tissue heterogeneity. While stringent QC measures can help mitigate these issues, they cannot completely eliminate them (196).

Although PRS and epigenetic scores share conceptual similarities, the assumptions made in genetic modeling may not fully apply to epigenetic data. Age-related epigenetic scores, such as those derived from Horvath's clock, have been well-established and standardized for over a decade (163,197). However, methods

for estimating MPS are still in the early stages of development. In our study [Article 6], we utilized a thresholding method (https://github.com/agonse/methylscore), which is a straightforward approach but not without limitations. Emerging methods, such as the Co-Methylation with Genomic CpG Background (CoMeBack) approach (198), offer more sophisticated techniques including co-methylation pruning and evaluation of multiple p-value thresholds, similar to PRSice-2 tool used in PRS analysis. However, further advances towards methods that do not require thresholding, similar to PRS-CS used in PRS analysis, face challenges when applied to MPS. This is largely due to the reliance on linkage desequilibrium (LD) correlations in SNPs, which are not directly applicable to the structure of methylation data (95).

Interpreting epigenetic scores requires a nuanced approach to avoid potential misinterpretations. Unlike genotyping, which provides accurate data on the genetic information of nearly all cells of an individual, methylation data is more complex. It reflects a snapshot of the average methylation status of a CpG in a heterogeneous group of cells at a single time point. This temporal and cellular specificity complicates the causal interpretation of associations between epigenetic scores and clinical conditions. The CpGs included in an epigenetic score can represent a variety of factors: they may be causal in nature, a byproduct of a concurrent biological process, or a consequence of a particular environmental exposure or condition (111).

This complexity limits the predictive power of epigenetic scores compared to PRS. While PRS can be relatively straightforward in identifying genetic predispositions, epigenetic scores often require a deeper understanding of the underlying molecular mechanisms. This highlights the need for continued research into the biological implications of DNA methylation to better understand how these scores can be effectively used in predicting health outcomes and informing clinical practice.

5.4.4 Future perspectives

The integration of PRS and epigenetic scores into multiomic frameworks holds considerable promise for advancing our understanding of psychotic disorders. By combining genome-wide genetic and epigenetic data with other omics data, such as transcriptomics, proteomics and metabolomics, researchers can create a more nuanced picture of the biological, environmental and social factors contributing to mental health outcomes (96,191). When integrated with social, clinical and neurobiological data, these approaches could revolutionize diagnostic and therapeutic strategies, leading to more personalized and effective mental health care solutions (63).

Recent technological advancements have made it increasingly feasible to collect large-scale, multi-modal data in both population-based and clinical settings. The development of high-dimensional statistical modeling techniques, alongside the growing emphasis on open science, support a cross-disciplinary approach. This holistic approach addresses the biopsychosocial complexity of mental disorders, incorporating diverse fields of study to offer a more integrated understanding of these conditions (199).

However, the challenge now lies in translating these research findings into practical, real-world applications within clinical settings. While advances in genetics and epigenetics have provided valuable insights into the biological underpinnings of mental disorders, the next step is to develop robust, explainable and reliable applications that can be used in clinical settings (200). This involves creating robust, explainable and reliable biomarkers and predictive models that can guide individualized treatment plans and early intervention strategies (201,202). These tools must undergo rigorous validation to ensure they are accurate, cost-effective and accessible. Only by bridging the gap between research and clinical practice can these innovations lead to more effective and precise healthcare solutions, ultimately improving outcomes for individuals with psychotic disorders.

6. Conclusions

1. Common genetic variability, as quantified by polygenic risk scores, is associated with the subclinical stages and early progression of psychotic disorders.

2. The polygenic risk score for schizophrenia is elevated in individuals experiencing their first episode of psychosis and in the offspring of schizophrenia patients, although it does not appear to directly influence the clinical severity or the progression of the disorder.

3. Polygenic risk scores related to depression, cognitive, cannabis use and neuroticism consistently correlate with symptom severity, cognitive performance and functional outcomes.

4. The impact of cognitive and neuroticism polygenic risk scores on overall functioning is mediated by their influence on symptom severity and cognitive performance, with this relationship varying depending on the specific polygenic risk score and cohort under study.

5. Individuals at familial high risk for schizophrenia and bipolar disorder show signs of epigenetic age deceleration in certain age-realted epiegentic scores, underscoring the complexity of aging processes in this populations.

6. Individuals at familial high risk show evidence of increased exposure to intrauterine stress, as measured by methylation profile scores.

7. Offspring of schizophrenia patients who show epigenetic markers of accelerated aging and increased prenatal stress tend to exhibit more severe prodromal psychotic symptoms.

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